RANDOMIZED CONTROLLED TRIALS IN PEDIATRIC CRITICAL CARE

RANDOMIZED CONTROLLED TRIALS IN PEDIATRIC CRITICAL CARE:

ADVANCING THE RESEARCH ENTERPRISE

By

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Lay abstract

Evidence from randomized controlled trials (RCTs) is required to guide treatment of critically ill children. Unfortunately such evidence is not always available. My objectives in this thesis are to describe the RCT research enterprise in pediatric critical care — the evidence and the process of creating it, along with problems and some solutions. To meet these objectives I undertook a series of 5 related studies: to identify and describe the RCTs, describe how researchers collaborate, understand how clinicians use RCTs, identify barriers and facilitators of conducting high quality RCTs, and understand how we can improve the evidence available from RCTs in pediatric critical care. We found that the number of RCTs is increasing but there are opportunities to improve the methods, outcome measures, and quality of reporting. We identified strategies that researchers can adopt to facilitate the rigorous RCTs that are needed to improve the care of critically ill children.

Abstract

Importance: Evidence from randomized controlled trials (RCTs) is required to guide treatment of critically ill children. Unfortunately such evidence is not always available.

Objectives: To describe the RCT research enterprise in pediatric critical care — the evidence and the process of creating it, along with problems and some solutions.

Methods: To meet these objectives I undertook a series of 5 related studies. First a scoping review to describe the output of the research enterprise. Second, a social network analysis of coauthorship patterns to describe the community of researchers who produce this evidence. Third, a survey to investigate the importance of RCTs in clinicians' decision-making. Fourth, a survey of trialists to identify barriers and facilitators of high quality RCTs. Fifth, a qualitative interview study to identify acceptable, feasible and effective strategies to improve the evidence available from RCTs in pediatric critical care.

Results and conclusions: The number of RCTs in pediatric critical care is increasing but there is a preponderance of small, single-centred RCTs focusing on laboratory or physiological outcomes that are often stopped early because of feasibility problems or futility. The research community is highly fragmented and highly clustered. Experienced trialists identified approaches to improve the pediatric critical care research enterprise, including building a sense of community and ensuring key training and relevant practical experiences for new investigators. Because of the barriers that researchers face and their ethical obligation to undertake trials that are feasible and make a meaningful contribution to advancing the care of critically ill children, individuals and groups must take an active role in building a healthy research community. Only by changing how we function as a research community can we train the next generation of investigators and undertake the type of trials needed to improve the care of critically ill children.

Acknowledgements

This program of research would not have been possible without the large number of people who have given me their help, their advice, their time, and their expertise. Most importantly, I would like to thank the clinicians and researchers who participated in these studies for their generosity and enthusiasm for this topic. Thanks to my advisor, Deborah Cook, who has been an outstanding mentor to me since long before I began to write this thesis and continues to inspire and encourage. Thanks also to the other members of my thesis committee, Melissa Brouwers and Maureen Meade, for their wise counsel. I am also indebted to my many collaborators on each of these studies.

Table of contents

List of figures

List of tables

List of abbreviations

ALI	Acute lung injury
ATS	American Thoracic Society
ARDS	Acute respiratory distress syndrome
CCCTG	Canadian Critical Care Trials Group
CI	Confidence interval
ESICM	European Society of Intensive Care Medicine
ESPNIC	European Society of Pediatric and Neonatal Intensive Care
GEE	Generalized estimating equations
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
ICC	Intracluster correlation factor
ICU	Intensive care unit
IQR	Interquartile range
NICU	Neonatal intensive care unit
PALISI	Pediatric Acute Lung Injury and Sepsis Investigators
PICU	Pediatric intensive care unit
REB	Research Ethics Board
RCT	Randomized controlled trials
SCCM	Society of Critical Care Medicine
SD	Standard deviation
THAPCA	Therapeutic Hypothermia After Pediatric Cardiac Arrest
VIF	Variance inflation factor
WFPICCS	World Federation of Pediatric Intensive and Critical Care Societies

Declaration of academic achievement

The 5 studies included in this thesis are original research designed and conducted by Mark Duffett.

Chapter 1: Mark Duffett wrote this chapter.

Chapter 2: This chapter is an expanded and updated version of a published manuscript. Mark Duffett conceived of and led the design of this study, acquired funding, completed the literature searches, coordinated the study selection and data collection, performed the analysis, and drafted the manuscript. Karen Choong, Deborah Cook, Lisa Hartling, and Kusum Menon contributed to the design and data collection and helped to draft the manuscript. Lehana Thabane contributed to the design and helped draft the manuscript. This study was conducted between 2011 and 2016.

Chapter 3: This chapter is an expanded version of a manuscript that will be submitted for publication. Mark Duffett conceived of and designed this study, coordinated the data collection, performed the analysis, and drafted the manuscript. This study was conducted in 2015 and 2016.

Chapter 4: This chapter is based on a published manuscript. Mark Duffett conceived of and led the design of this study, acquired funding, coordinated the survey administration, and drafted the manuscript. Thuva Vanniyasingam helped to design the analysis, conducted the analysis, and helped draft the manuscript. Lehana Thabane contributed to the design of the analysis and helped draft the manuscript. Karen Choong and Deborah Cook contributed to the design and helped draft the manuscript. This study was conducted in 2012 and 2013.

Chapter 5: This is an expanded version of a manuscript that has been submitted for publication. Mark Duffett conceived of and led the design of this study, coordinated the survey administration, performed the analysis, and drafted the manuscript. Karen Choong, Deborah Cook, Jennifer Foster, Maureen Meade, Kusum Menon, and Melissa Parker contributed to the design and helped to draft the manuscript. This study was conducted in 2015.

Chapter 6: This is an expanded version of a manuscript that will be submitted for publication. Mark Duffett conceived of and led the design of this study, conducted the interviews, performed the analysis, and drafted the manuscript. Marilyn Stanton contributed to the interview guide, performed the analysis, and helped draft the manuscript. Deborah Cook contributed to the design and helped draft the manuscript. This study was conducted in 2015 and 2016.

Chapter 7: Mark Duffett wrote this chapter.

Chapter one:
Introduction

> *"The time has come to protect children and young people through research not from research…It will always be easier to say 'no' to research with children on the grounds that it's too difficult, but we should challenge the idea that it is acceptable to continue to offer health care to children without seeking to improve the evidence base for many of the treatments provided"*
>
> — Bobbie Farsides, Chair of the Working Party for the Nuffield Council on Bioethics.[1]

How can we improve the evidence base in pediatric critical care? This is the primary question I address in this program of research. It is an important question because fundamental aspects of the management of both common and life-threatening conditions are not supported by high-quality evidence from RCTs.

Three of the most influential guidelines in pediatric critical care highlight the limited amount and quality of the evidence available to support clinical decision-making. First, the Surviving Sepsis Campaign's International guidelines for management of severe sepsis and septic shock provided 76 recommendations for adults, but only 22 pediatric-specific recommendations.[2] Not only are there fewer pediatric recommendations, but the quality of the evidence informing these recommendations is lower; 3 (14%) of the pediatric recommendations were supported by high/moderate quality evidence as compared to 41 (54%) of those for adults. Second, the Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents[3] used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group's approach to categorize the strength of their conclusions and the quality of the evidence supporting those conclusions.[4] They categorized all 15 recommendations as

weak and 12 were based on low quality evidence. The remaining 3 were based on moderate quality evidence. Finally, The American College of Critical Care Medicine's Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock made 27 recommendations.[5] None of the 27 recommendations were categorized as Level 1 (Convincingly justifiable on scientific evidence alone).

The frequency of off-label medication use (prescribing outside of the terms of the product licence) in pediatric critical care also highlights the deficiency in evidence. Off-label use itself may not be problematic, but rather illustrates that population-specific research evidence is missing, as regulatory approval and product labelling are usually contingent on evidence from RCTs. A retrospective review in a Canadian PICU found that 65% of prescriptions were off-label and 96% of children received at least one off-label prescription during their stay in the PICU.[6] In similar studies, 50% of prescriptions in a Brazilian PICU[7] and 71% in an Indian PICU[8] were off-label. Even when approved for use in children, medications are not often approved for use in critically ill children. In a single-centre observational study from the United States, while 11 of the 25 most frequently dispensed medications in the PICU were approved for use in children, none was used for the indication or age group for which they were approved.[9]

Clearly, we need to improve the state of RCT research so we can improve clinical care, but there is also an ethical dimension. For clinical research studies to be ethically justified, they must provide social or scientific value and be scientifically valid.[10] I will focus on 3 potential explanations for the limited role that RCTs play in pediatric critical care, each with its own ethical implications and potential remedies. The research program outlined in this PhD thesis will provide data to help assess the roles of these 3 factors. The first potential explanation is that few or no relevant RCTs have been completed. The most obvious solution to this is to increase the number of RCTs completed, but not all RCTs are feasible. In those cases strategies may include using alternative designs and considering which data from other populations such as critically ill adults may be generalizable. The second potential explanation is that although relevant RCTs have been

performed, they fail to adequately answer the clinical question because their quality is too low, the results are imprecise, or other characteristics of the study preclude them from being clinically useful. Improving how RCTs are performed is the obvious solution, but we must also consider the possibility of doing fewer RCTs. Trials that are not feasible or that contribute little are not ethically supportable if they waste valuable resources or expose children to the potential for harm without the potential for individual or societal benefit. Such studies are fundamentally disrespectful to the children and their parents in the study. Parents who provide consent for their children to participate in a research study expect that they are making a meaningful contribution to advancing the care of other critically ill children. The third potential explanation is that clinicians do not apply the results of relevant, high-quality RCTs that have been performed, for example if they they are unaware of the RCTs or don't value these RCTs in their decision-making process.

In this thesis I have focused on RCTs for 3 reasons. First, from a clinical perspective, they are generally the least biased design to address questions about the efficacy and effectiveness of preventive or therapeutic interventions in many situations. Thus, they are likely to be of interest to clinicians and patients and their families. Second, the state of RCT research is likely a good indicator of the state of research in a particular field. These studies are often the most complex of research designs and require substantial collaboration and resources. They are usually preceded by substantial scientific preparatory work such as bench research, applied physiology, mechanistic studies, observational studies in humans, and systematic reviews. Because of this, any efforts that improve the state of RCT research will likely improve state of other research designs — many of the challenges are likely the same. Third, from a methodologic perspective, focusing on RCTs allows me to examine one type of study design for an entire field without being constrained to a particular time period or subset of journals, 2 approaches that are typically employed in this type of methodologic research.[11,12] There are also well developed techniques to identify,[13] assess risk of bias,[14] and report[15] RCTs.

My overarching objectives in this thesis are to describe the RCT research enterprise in pediatric critical care — the evidence and the process of creating it, along with problems and some solutions. To meet these objectives I undertook a series of 5 related studies, outlined in the following 5 chapters. Figure 1.1 shows the structure of the research program.

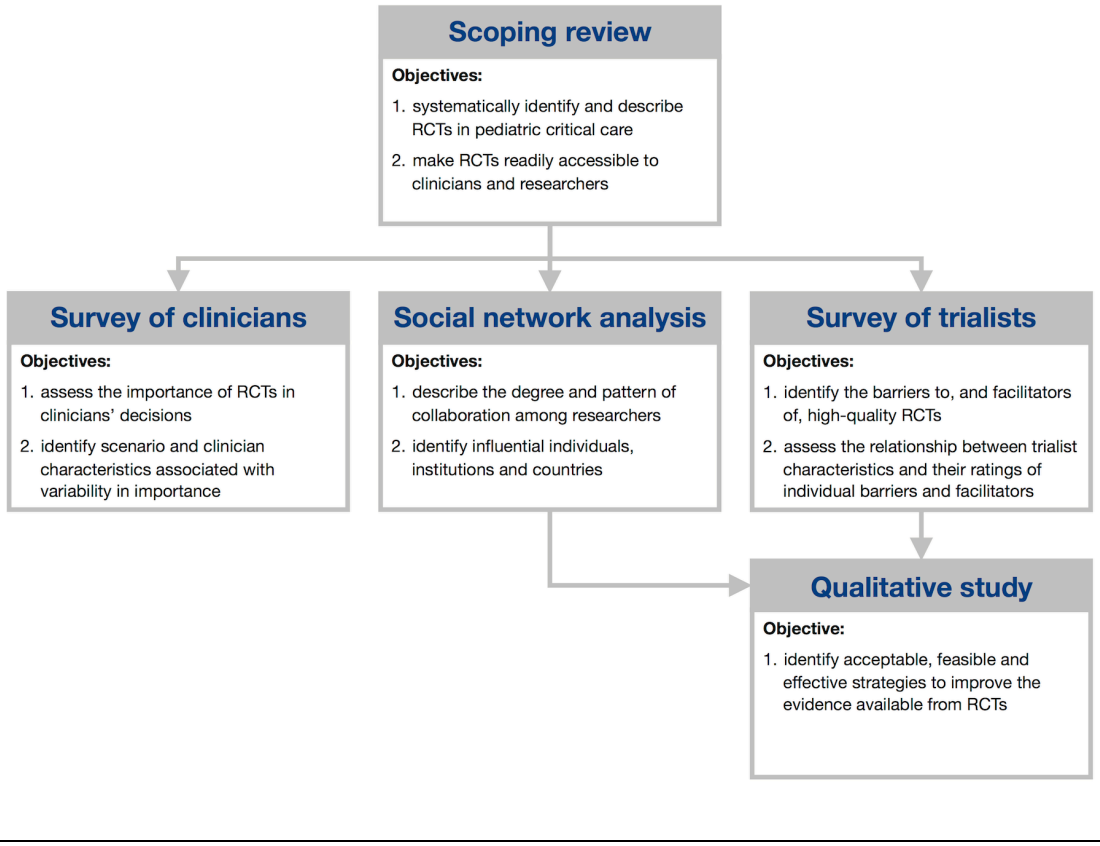

Figure 1.1. Overview of research program.

Chapter 2: Scoping review

First, I conducted a scoping review to describe the output of the RCT research enterprise in pediatric critical care. Scoping reviews systematically map a broad and diverse body of research evidence.[16] They can examine the extent, range, and nature of research activity, determine the value of undertaking a full systematic review, summarize and disseminate research findings, or identify gaps in the existing literature.[17] My purpose in conducting

this scoping review was to examine the extent, range, and nature of RCTs in pediatric critical care and to aid dissemination by making them more available to clinicians and researchers.

In this review I used comprehensive search strategies to identify published RCTs in pediatric critical care. I updated the searches quarterly, adding any newly published RCTs. Pairs of reviewers screened studies for eligibility and abstracted data independently. This review provides a summary of key methodologic and reporting characteristics of RCTs in the field and a publicly-accessible, regularly-updated, online database of RCTs. Although not the part of this research program, I also designed this scoping review to be used by other researchers to assess the feasibility of systematic reviews, identify research gaps, and inform potentially useful future methodologic research.

The first step in any effort to improve the state of RCT research is to identify the problems. I undertook this review to provide a clear understanding of the scope and scale of the problems — identifying opportunities to improve the design, conduct, and reporting of RCTs in pediatric critical care. My primary focus was on methodological gaps, rather than clinical gaps, in the evidence. Data on the methodological gaps will be relevant to all researchers conducting RCTs in pediatric critical care and solutions will be relevant for many, if not all, areas of research. Clinical gaps in the evidence are, by their very nature, only relevant to those studying that particular clinical problem and defining clinical gaps is dependent on the context and nuances of particular topics.

Since publishing this review in 2013, we have continued to update the review every 3 months. With each update we add newly published RCTs to the website PICUtrials.net so that the review continues to be relevant. Chapter 2 of this thesis includes all RCTs published in 2015 or earlier — the most recent update. Subsequent chapters refer to the scoping review or use it to identify potential participants. The number of trials and researchers varies among the chapters because we conducted the research described in

Chapters 3 to 6 between 2013 and 2016 using the most current scoping review update at the time.

Chapter 3: Social network analysis

Second, I used social network analysis to describe the community of researchers who produced the evidence that I identified in the scoping review — describing the individual researchers and the degree and patterns of their collaboration. Social networks are "a set of nodes (or network members) that are tied by one or more types of relations."[18] In this study, the nodes are individual researchers, institutions, and countries. The relationships that connect them are research collaboration as demonstrated by coauthorship in the published RCTs. Social network analysis is an approach to studying social structure, focusing primarily on the patterns and characteristics of relationships among individuals rather than the attributes of those individuals.[19]

For this study we manually extracted the name of each of the authors of the published RCTs identified in the scoping review. I then used this data to build a coauthorship network where researchers were linked when they shared authorship in a publication.

Science is a social enterprise — collaboration is fundamental to it. A full description of the research enterprise must acknowledge that these RCTs are the products of not just individual researchers, but collaboration among these individuals. This social network analysis builds on the scoping review to provide this perspective. It also provides insight into the social structure of the community that may be important to undertake any interventions to improve the output of the research.

Chapter 4: Survey of clinicians

Third, I conducted a survey to better understand the importance of RCTs in clinicians' decision-making. I sent a self-administered postal survey to physicians and pharmacists working in Canadian PICUs. Respondents used 7-point scales to rate the importance of 13 specific factors that may influence their decisions in the 4 clinical scenarios. I also

examined the relationship between respondents' ratings of the importance of the specific factors and the scenario and respondents' practice, views, and demographics.

This survey expanded the scope of this research program to include the application of the evidence I identified in the scoping review. This is a critical and often overlooked aspect of methodologic research. The underlying goal of all of these RCTs is to improve the care of patients. Any consideration of how RCTs can be improved has to consider how this evidence is interpreted and applied by clinicians. This survey assessed the relative importance of RCTs and other factors and also assessed how higher-quality evidence and other factors were associated with increased importance of RCTs in clinical decision-making. The results of the scoping review informed the survey design, specifically the development of clinical scenarios with varying number and size of the RCTs testing the intervention in each scenario.

Chapter 5: Survey of trialists

Fourth, I conducted a survey of pediatric critical care trialists to better understand the barriers they face in undertaking RCTs in pediatric critical care. I sent a self-administered online survey to authors of the RCTs identified by the scoping review. Respondents used 7-point scales to rate the importance of 41 barriers to, and the effectiveness of 42 facilitators of, conducting high-quality RCTs in pediatric critical care. I also assessed the relationship between respondent characteristics and differences in their ratings of individual barriers and facilitators.

After using the scoping review to describe some of the deficiencies in the design, conduct, and reporting of the published RCTs, I then used this survey to investigate some of the reasons for these deficiencies. With a clearer understanding of the barriers that successful pediatric critical care researchers face and the strategies they use to overcome these I could begin to identify effective initiatives to improve evidence from RCTs in the field.

Chapter 6: Qualitative interview study

Finally, I conducted a qualitative interview study of pediatric critical care trialists to better understand their perspectives on strategies to improve the evidence available from RCTs in pediatric critical care. A qualitative approach acknowledges that context is important for many facilitators, that any strategy for improvement is likely to include more than one facilitator, and that balancing acceptability, feasibility and effectiveness is a complex process requiring a more nuanced approach than a survey.

In this qualitative study I conducted individual semi-structured interviews with pediatric critical care trialists to explore and understand their multiple perspectives and experiences. I then used a qualitative descriptive approach to analyze the interview transcripts.[20] We coded the interview transcripts then organized the codes into meaningful categories.

This study builds on the results of prior studies in this research program: the survey of trialists, the social network analysis, and the scoping review. I used the results of the survey of trialists to inform the design of the interview guide: focusing on facilitators that either respondents rated most highly or for which there was the most variability amongst the respondents. I used the results of the social network analysis as one criterion in my sampling strategy: including researchers with a range of influence in the social network. We also used the results of the scoping review to inform the selection of participants: including researchers with who had completed trials with a range of characteristics.

Chapter 7: Discussion and conclusions

I begin the final chapter with a brief summary of the results and conclusions of the individual studies. Then I make some overall conclusions based on the results of my PhD thesis research program as a whole. Finally I discuss the strengths and limitations of the research program, provide come context and present some suggestions for future avenues of research.

Chapter two:
Randomized controlled trials in pediatric critical care:
A scoping review

This chapter is an expanded and updated version of a published manuscript: Duffett M, Choong K, Hartling L, Menon K, Thabane L, Cook DJ. Randomized controlled trials in pediatric critical care: A scoping review. Crit Care 2013; 17: R256. The most important change is the number of included RCTs; with searches updated in January 2016, this version includes an additional 72 RCTs.

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Abstract

Importance: Evidence from randomized controlled trials (RCTs) is required to guide treatment of critically ill children, but the number of RCTs available is limited and the publications are often difficult for clinicians to find.

Objective: The objectives of this review were to systematically identify RCTs in pediatric critical care and describe their methods and reporting.

Design: Scoping review.

Study selection: We searched MEDLINE, EMBASE, LILACS and CENTRAL (from inception to January 4, 2016) and reference lists of included RCTs and relevant systematic reviews. We included published RCTs administering any intervention to children in a pediatric ICU. We excluded trials conducted in neonatal ICUs, those enrolling exclusively preterm infants, and individual patient crossover trials.

Data extraction: Pairs of reviewers independently screened studies for eligibility, assessed risk of bias, and abstracted data. Discrepancies were resolved by consensus.

Main outcome and measures: We described key methodological features of the trials and provide an online database of trials (PICUtrials.net) for clinicians and researchers .

Results: We included 320 RCTs: 63 (20%) were multicentred and 24 (8 %) were multinational. Trials most frequently enrolled both medical and surgical patients (42%) but postoperative cardiac surgery was the single largest population studied (22%). The most frequently evaluated types of intervention were medications (59%), ventilation (7%), devices (6%) and nutrition (6%). Laboratory or physiological measurements were the most frequent type of primary outcomes (18%). Half of the trials (52%) reported blinding. Of the 152 (48%) trials that reported an a priori sample size, 45 (30%) were stopped early. The median number of children randomized per trial was 50 and ranged

from 6 to 4 947. The frequency of RCT publications increased at a mean rate of 0.8 RCTs per year ($p<0.001$, $r^2=0.77$) from 1 to 27 trials per year.

Conclusions: This scoping review identified the available RCTs in pediatric critical care and made them accessible to clinicians and researchers. Most focused on medications and intermediate or surrogate outcomes, were single-centred and were conducted in North America and Western Europe. The results of this review underscore the need for trials with rigorous methodology, appropriate outcome measures, and improved quality of reporting to ensure that high quality evidence exists to support clinical decision-making in this vulnerable population.

Introduction

Evidence from randomized controlled trials (RCTs) is required to guide treatment of critically ill children. There are fewer RCTs in pediatrics when compared to adult medicine; in reviews of RCTs published in general and specialist medical journals only 14% of trials enrolled exclusively children.[21,22] Moreover, while the methodological quality of pediatric RCTs appears to be improving, 37 to 59% were still at high risk of bias.[23-25] Finally, the focus of published pediatric RCTs may not align with the frequency or importance of the conditions seen in clinical practice. For example, in pediatric primary care there is discordance between the conditions studied and the frequency seen in clinical practice: 23% of Cochrane systematic reviews relevant to pediatrics focused on asthma, which represents 3 to 5% of children's primary care visits.[26]

The extent of these challenges in pediatric critical care has not previously been examined. An example from critical care is the Surviving Sepsis Campaign's International Guidelines for Management of Severe Sepsis and Septic Shock.[2] These guidelines highlight the limited quality of evidence available in pediatric critical care to support clinical decision-making. The consensus committee was able to make 76 recommendations for adults, but only 22 pediatric-specific recommendations. Not only are there fewer pediatric recommendations, but the quality of the evidence informing these pediatric

recommendations is lower; 3 (14%) of the pediatric recommendations were supported by high/moderate evidence as compared to 41 (54%) of those for adults.

To effectively apply the results of pediatric critical care RCTs, it is imperative that clinicians can easily and efficiently find these publications. However, clinicians are not typically trained to conduct the complex literature searches required to find pediatric RCTs; even a highly specific search strategy yielded only 56% of citations relevant to children.[27] Challenges in locating relevant pediatric RCTs are likely to increase as the number of adult RCTs increases faster than the number of pediatric RCTs in both general medical journals (4.7 RCTs per year vs. 0.4 RCTs per year) and in specialist journals (91 RCTs per year vs. 17 RCTs per year).[21,22] There also are few tools, resources or reviews to help clinicians quickly access or identify the available RCTs in pediatric critical care.

A scoping review systematically maps a broad and diverse body of research evidence.[16] We conducted this scoping review to systematically identify and describe RCTs in pediatric critical care and make them readily accessible to clinicians and researchers.

Methods

Trial eligibility

We included RCTs and quasi-randomized trials that reported the effect of any intervention on children or their families in a pediatric intensive care unit. We used the authors' definitions of pediatric and only included trials in which critically ill children were a subgroup if the demographic and outcome data for the critically ill children were reported separately. We considered a unit to be an intensive or critical care unit if the authors described it as such and if it had the capacity to provide mechanical ventilation. We included trials in all languages. We excluded trials enrolling exclusively preterm infants or infants in a neonatal intensive care unit, individual patient crossover trials and those only published as abstracts. For trials reported in multiple publications, we used the most recent publication. We excluded substudies and secondary publications of included RCTs.

Searching

We searched MEDLINE, EMBASE, LILACS and CENTRAL from inception to January 4, 2016. To identify RCTs we used previously tested search strategies for MEDLINE (the Cochrane Highly Sensitive Search Strategy, sensitivity- and precision-maximizing version[13]) EMBASE[28] and LILACS[29]. To identify studies enrolling children in MEDLINE we used a previously tested strategy[27] and adapted for the other databases. We then added search terms related to pediatric critical care. Appendix A contains the full search strategies. To identify other potentially relevant trials, we also examined the reference lists of all included RCTs, systematic reviews identified by our searches, and the researchers' personal files.

Study selection and data extraction

We developed an electronic data collection tool using DistillerSR™ (Evidence Partners Incorporated, Ottawa, Canada) and an accompanying screening and data extraction manual. To increase consistency among reviewers, all reviewers screened the same 50 publications, discussed the results and amended the screening and data extraction manual before beginning screening for this review. Nine reviewers working in pairs sequentially evaluated the titles, abstracts and then full text of all publications identified by our searches for potentially relevant publications. Reviewers then worked in pairs to independently and in duplicate extract data from the included trials using a pretested electronic data collection tool. We recruited other individuals with a clinical or research methodology background to screen and extract data from non-English trials. We were not able to complete duplicate data extraction for 3 trials because of the language of publication. We resolved disagreements on study selection and data extraction by consensus and discussion with other reviewers if needed. We extracted data from the main trial publication and also any referenced published protocols and supplemental materials.

Risk of bias assessment

We used the Cochrane Risk of Bias Tool to describe the risk of bias for the included trials.[14] This tool rates each trial as low, unclear, or high risk of bias for each of the following factors: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. We then classified the overall risk of bias for each trial as low (low risk of bias in all domains), high (high risk of bias in at least one domain), or unclear.

Statistical analysis

We used the kappa statistic to assess agreement between reviewers and considered values of 0.6 or greater to indicate substantial agreement.[30] In summarizing the characteristics of included systematic reviews and RCTs we reported continuous data as medians (interquartile range [IQR]), and binary data as count (percent). We used linear regression to evaluate the changes over time in the number of trials published. We used the Mann-Whitney *U* test to compare the number of children randomized in trials that reported early stopping and those that did not and those that reported funding and those that did not, hypothesizing that sample sizes would not be statistically different. We used Fisher's exact test to compare the proportion of trials that were stopped early among those reporting funding with those that did not, hypothesizing that funded trials would be less frequently stopped early. We used alpha=0.05 as the criterion for statistical significance. We used R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) to perform the statistical analysis.

Results

Trial publication

We included 320 RCTs randomizing a total of 37 173 children. Appendix A: Figure A1 shows the flow of studies through the review process and Appendix B lists all of the included trials. Chance-corrected agreement for study inclusion was almost perfect (kappa=0.93, 95% CI 0.91 - 0.96). The included RCTs were published in 114 different journals. The five journals that published the highest number of trials: *Pediatric Critical Care Medicine* (40), *Critical Care Medicine* (33), *Intensive Care Medicine* (25), *Journal of Pediatrics* (11) and *The New England Journal of Medicine* (9) published 37% of the included trials. Forty percent were published in the 15 journals with a specific critical care focus and 36% were published in the 34 journals with a specific pediatric focus. Eighteen trials (6%) were published in 7 languages other than English. Figure 2.1 shows the number of trials published per year. The number of trials published per year increased at a mean rate

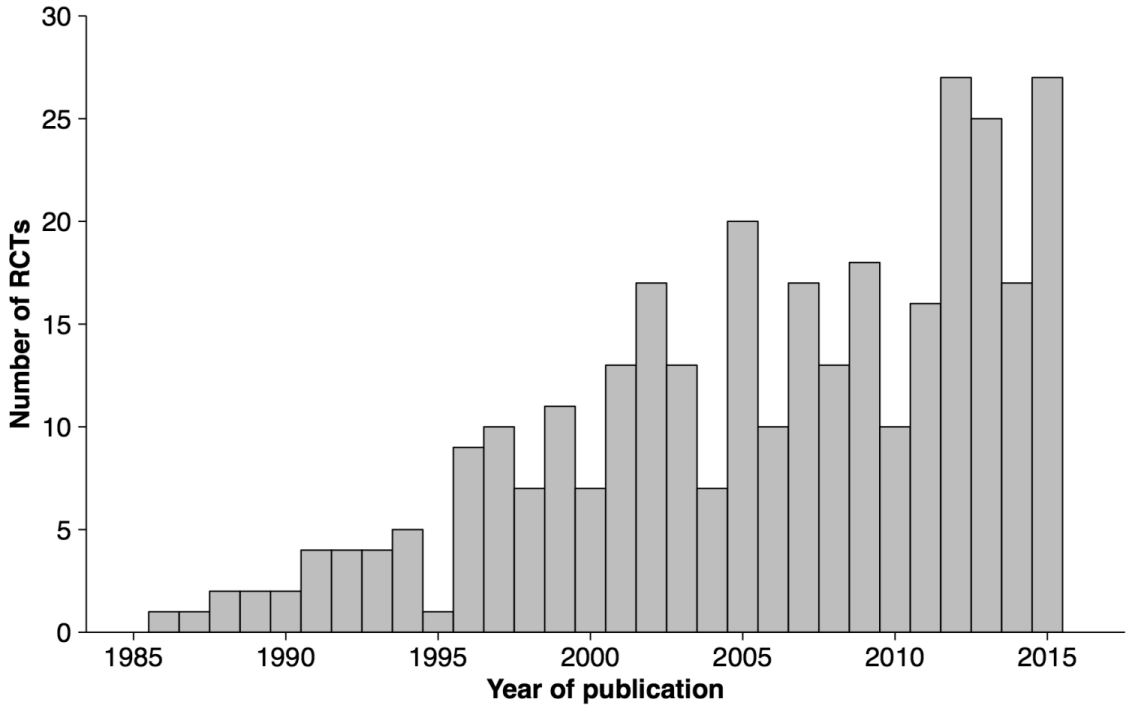

Figure 2.1. Number of pediatric critical care RCTs published per year.

of 0.8 RCTs per year (95% CI=0.6 - 0.9, p<0.001, r^2=0.77), from 1 in 1986 to 27 in 2015.

Description of included trials

Table 2.1 shows the characteristics of included trials. The majority (80%), were single-centred and the median (IQR) number of centres participating in the multicentred trials was 6 (2 to 15) and varied from 2 to 104. Trials were conducted in 37 different countries (Figure 2.2), the majority, 225 (70%), high-income countries. With respect to the number of trials conducted, the top 4 countries (United States, Brazil, India, and The Netherlands) conducted the majority (52%) of the RCTs. All trials randomized individual children except 2 cluster RCTs. These randomized 10 PICUs in 5 centres[31] and 31 centres.[32] In the 223 (70%) RCTs that reported their duration of enrolment, the median (IQR) was 1.9 (1.1, 2.9) years.

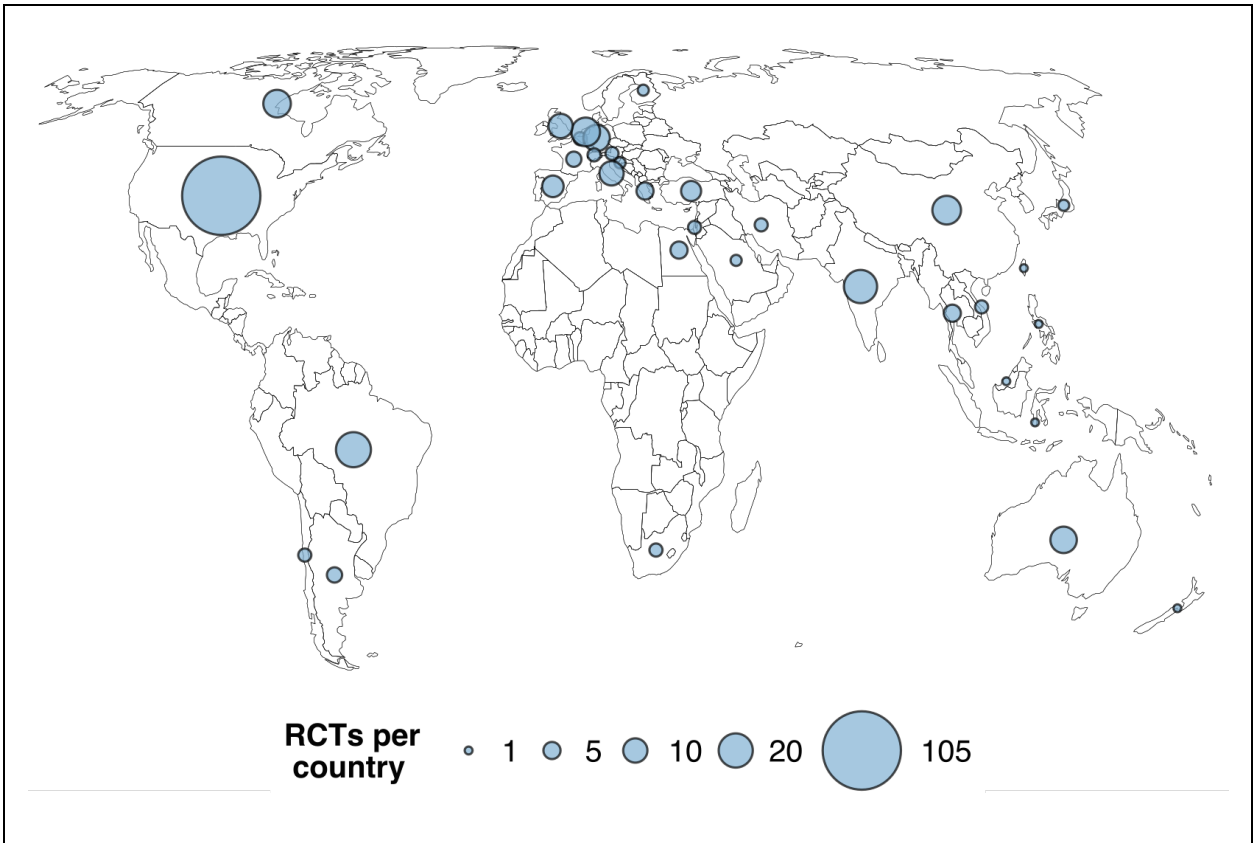

Figure 2.2. Number of published pediatric critical care randomized controlled trials per country. This map shows the country where each trial was conducted. We used the country of the primary author for multinational trials.

Table 2.1. Methodological characteristics of pediatric critical care RCTs

Trial characteristics	RCTs (n=320)
Design	
Pilot trial	38 (12%)
Medication intervention	189 (59%)
Blinding reported	166 (52%)
High risk of bias	138 (43%)
Centres	
Multicentred	63 (20%)
Centres in multicentred RCTs	6 (2, 15) (min=2, max=104)
Multinational	24 (8%)
Funding	
Any funding reported	162 (52%)
Any commercial funding reported	45 (14%)
None	13 (4%)
Results	
Children randomized per RCT[a]	50 (32, 97) (min=6, max=1 369)
Stopped early[b]	45 (30%)
Reason for stopping early[c]	
Futility	18 (40%)
Recruitment or funding	11 (24%)
Benefit	8 (18%)
Funding	2 (4%)
Harm	2 (4%)
Unclear	4 (9%)
Results statistically significant[d]	79 (41%)
Impact	
Citations per year	1.7 (0.7, 3.3) (min=0, max=37.5)
Journal impact factor	3.8 (2.3, 6.3) (min=0.2, max=55.9)

Data are n (%), median (IQR), unless otherwise specified. [a]This includes just the individually-randomized trials. The 2 cluster RCTs randomized 10 PICUs in 5 centres[31] and 31 centres[32] and enrolled 4 947 and 2 459 children respectively. [b]We could determine if the trial had been stopped early for the 152 (48%) RCTs that reported their planned sample size. [c]Reported as a percentage of the 45 RCTs that were stopped early. [d]For the primary outcome only. Reported as a percentage of the 194 two-arm RCTs reporting their primary outcome.

Overall, 50 trials (16%) reported in the publication that the trial had been registered. This was 32% in the trials published since 2010. A significant proportion of trials (43%) did not report their funding source and 14% had at least some industry funding.

Figure 2.3 shows the categories of patients studied. Families were the target of the intervention in two trials: the remainder focused on individual children. Cardiac surgery patients represented the commonest single group of patients studied (22%). Figure 2.4 shows the types of conditions studied. The majority of trials evaluated medications (Figure 2.5).

We could determine the primary outcome in 210 (67%) trials (Table 2.2). Of these, laboratory and physiological primary outcomes were the most frequently reported. Mortality was the primary outcome measure in only 4% of trials. Of the 195 trials (61%) reporting mortality, the median (IQR) mortality was 8% (1 to 15%), varying from 0% to 94%. The mortality was 0% in 37 trials (12%). We could assess the statistical significance of the primary outcome (using the authors' definitions or $p<0.05$ if not defined) in 282 RCTs that compared two interventions. In 79 (28%) of trials, the results were statistically significant: 74 (94%) of these favoured the experimental intervention.

Table 2.2. Type of primary outcome of pediatric critical care RCTs

Type of primary outcome	**RCTs (n=320)**
Laboratory or physiological	57 (18%)
Clinical complications	35 (11%)
Duration of ventilation	24 (8%)
Process of care	18 (6%)
Clinical success	16 (5%)
Mortality	14 (4%)
Severity of illness score	13 (4%)
Other	40 (13%)
Not reported	103 (32%)

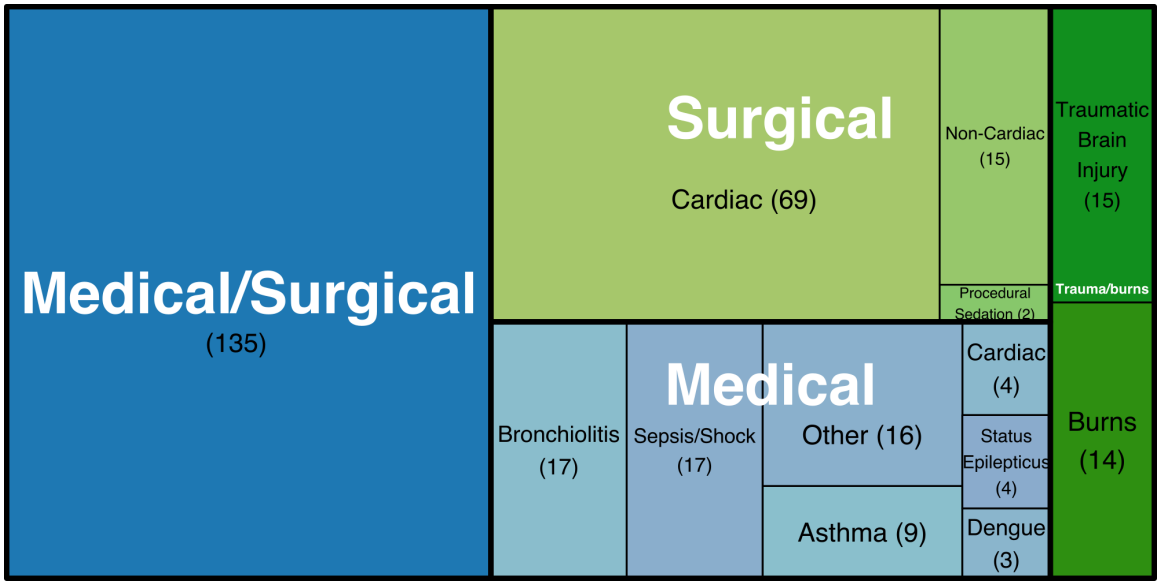

Figure 2.3. Category of patients enrolled in pediatric critical care RCTs. The area of each rectangle is proportional to the number of RCTs in each category. The number in parenthesis is the number of trials in each category.

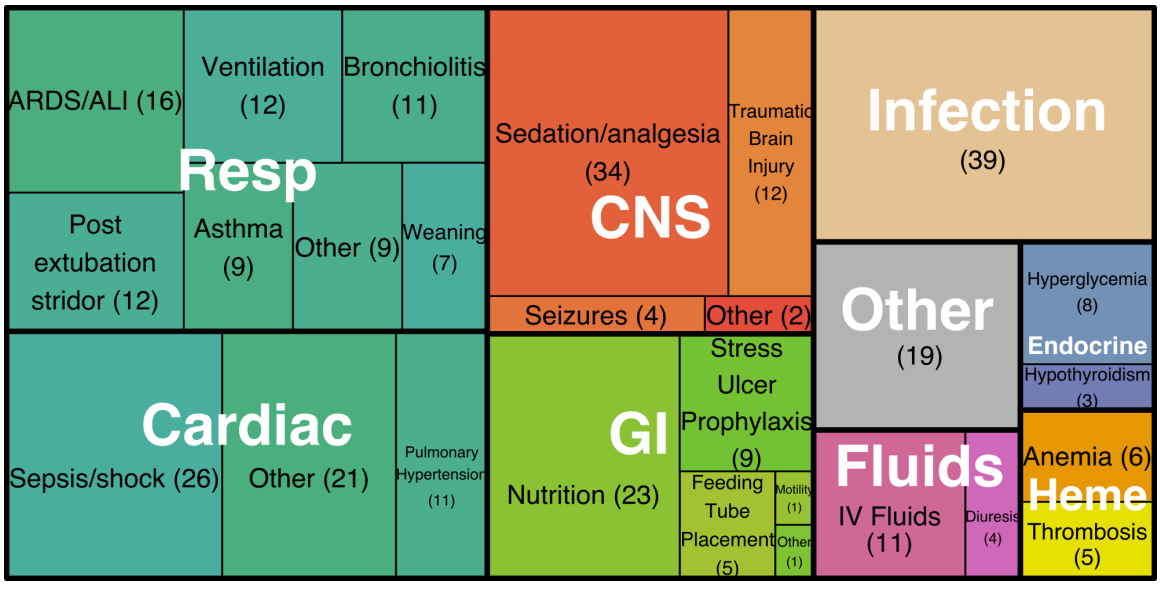

Figure 2.4. Type of conditions studied in pediatric critical care RCTs. The area of each rectangle is proportional to the number of RCTs in each category. The number in parenthesis is the number of trials in each category.

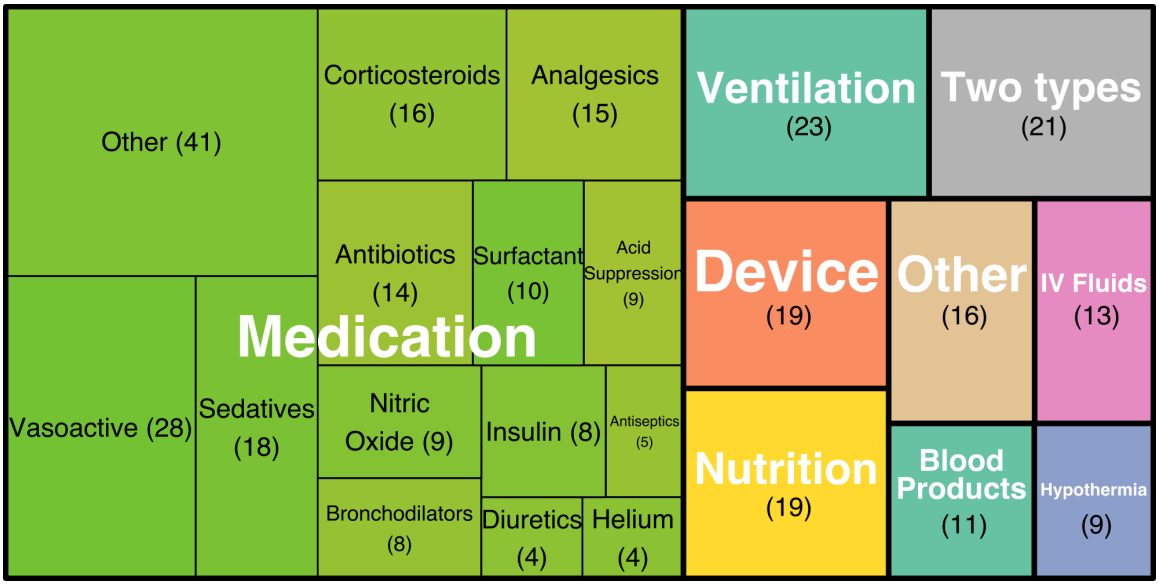

Figure 2.5. Type of intervention studied in pediatric critical care RCTs. The area of each rectangle is proportional to the number of RCTs in each category. The number in parenthesis is the number of trials in each category.

Sample size

The number of children randomized in individual-patient RCTs varied from 6 to 1 369 (Figure 2.6). The 2 cluster RCTs — randomizing PICUs — included 4 937 and 2 449 children. There were 6 trials randomizing more than 500 (including 3 randomizing more than 1 000) children, all published since 2001. The total number of children randomized increased from 40 in 1986 to a maximum of 6 326 in 2013. The mean rate of increase was 133 children per year (95% CI=86 - 180; p0.001; r^2=0.53). The number of children randomized per trial, also increased in the same time period. The mean rate of increase was 6 children per RCT per year (95% CI=1 - 11; p=0.02; r^2=0.01). The number of children randomized in the 162 RCTs that reported a funding source compared to trials that did not was not significantly different: median (IQR) of 51 (32 to 110) compared to 50 (30 to 82), p=0.22. The number of children randomized in the 45 RCTs that reported a

commercial funding source compared to trials that did not was not significantly different: median (IQR) of 51 (33 to 110) compared to 50 (30 to 94), p=0.64.

We also evaluated the completeness of follow-up and early stopping among these RCTs. The mean proportion of randomized children who were not included in the analysis was 5% and the maximum was 59%. A total of 170 trials (53%) included all randomized children in the analysis. Of the 152 trials that reported a planned sample size, 45 (30%) were stopped early, most frequently for futility or recruitment problems (Table 2.1). The median (IQR) number of children randomized in trials that were stopped early was 77 (40 to 129) and 74 (40 to 142) in those that were not reported to be stopped early (p = 0.70). Among the trials that reported a planned sample size: A total of 35% of the trials

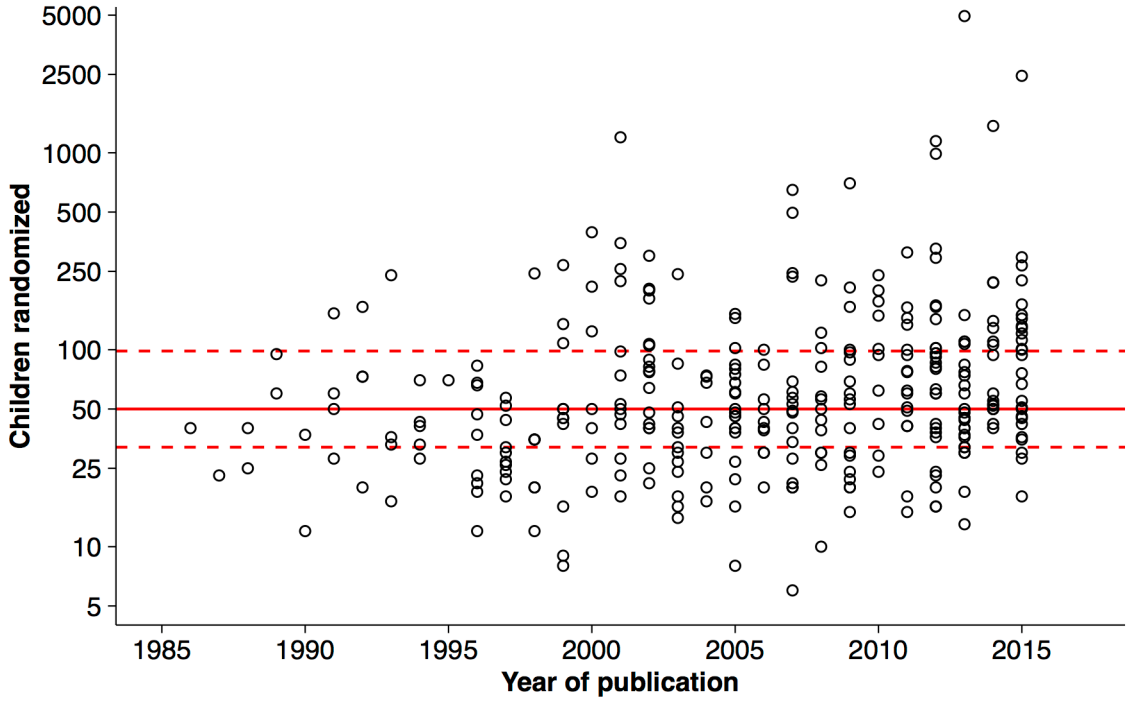

Figure 2.6. Number of children randomized in pediatric critical care randomized controlled trials. The solid red line indicates the median and the dashed red lines indicate the 1st and 3rd quartiles.

reporting any funding were stopped early, compared to 20% of those who did not report funding (p = 0.04).

Risk of bias

Figure 2.7 presents the risk of bias assessments for the individual domains of the Cochrane Risk of Bias tool. The overall risk of bias was low for 21 (7%) trials, high for 141 (44%) and unclear for the remaining 158 (49%). All trials at low risk of bias were published since the year 2000. Blinding was only reported in half the trials (167, 52%). 9 (3%) trials were quasi-randomized trials: using a process such as alternation or date of admission to assign participants to treatment groups.

Discussion

Scoping reviews can be used 'to examine the extent, range, and nature of research activity; to determine the value for undertaking a full systematic review; to summarize and disseminate research findings; and to identify research gaps in the existing literature.[17] In this scoping review we found 248 pediatric critical care RCTs, from 31

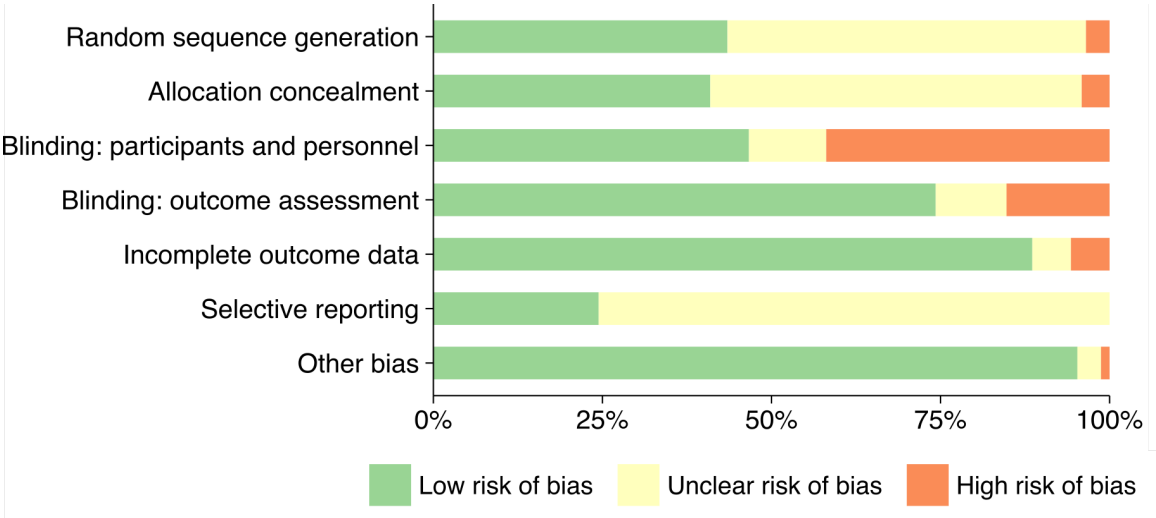

Figure 2.7. Risk of bias in pediatric critical care RCTs. We used the Cochrane Risk of Bias Tool to describe the risk of bias for the included trials.[14]

countries, published in 7 languages over 28 years. The majority of these RCTs were single-centred, focused on intermediate or surrogate outcomes and were small in sample size. Important aspects of their methodology and reporting remain less than optimal. As part of this review we have created a publicly accessible online database of these trials including key methodological features and links to the original reports (PICUtrials.net).

There are gaps in the body of pediatric critical care RCT research. For example, rehabilitation and the needs of parents coping with their child's illness are relevant for almost all critically ill children, yet there are only two trials focusing on each of these. Similarly, pharmacological interventions were studied in the majority of RCTs; although 27% of RCTs studied devices, there were no trials focused on renal replacement therapy or extracorporeal membrane oxygenation. Pediatric critical care clinicians, researchers and decision-makers can use the results of this review as part of a process to evaluate unmet needs and set research priorities, both in terms of the focus and design of additional RCTs and other research designs. There are also important limitations to the reporting of these trials; for example, only two-thirds reported the primary outcome and less than half reported the planned sample size or the funding source.

When compared to the findings of a random sample of 300 pediatric RCTs published in 2007, pediatric critical care RCTs were less frequently multicentred (18% vs. 35%), randomized fewer children (median 49 vs. 83), and had a lower proportion assessed as having a low risk of bias (4% vs. 8%).[33] Pediatric critical care RCTs are also smaller and less common than adult critical care RCTs. A systematic review of adult critical care RCTs with clinical or economic primary outcomes published in 16 prominent journals included 127 RCTs published between 2007 and 2012.[11] We identified 79 pediatric RCTs over the same time period. Compared to these adult RCTs, pediatric RCTs randomized fewer participants (mean 109 vs. 519), and were less frequently multicentred (18% vs. 60%). Another systematic review of RCTs evaluating nutritional interventions in critically ill adults included 207 RCTs randomizing a mean of 112 adults in the period 1980 to 2008.[34]

Using similar criteria, we found 17 trials randomizing a mean of 48 children in the same time period.

We found that pediatric RCTs are generally small, single-centred, and primarily measured short-term laboratory and physiological outcomes. This raises two important issues for clinicians, researchers and funding agencies to consider. The first question is whether or not the small sample size matters: were these studies able to definitively answer the question posed? This is unclear for many trials included in this review as 57% did not report the planned sample size. The second question is did these trials use appropriate outcome measures? Trials focusing on surrogate or intermediate outcomes can be used to inform the design and conduct of future studies using patient-important outcomes or when a trial with patient-important outcomes is not feasible.[35] Further research should focus on assessing if these RCTs lead to subsequent trials focusing on patient-important outcomes or if the outcomes used are indeed appropriate surrogates for more patient-important outcomes.[36] If many trials are indeed too small to generate clear results, further research needs to be done to identify the barriers to conducting larger trials and methods to overcome this limitation. A previous mixed-methods study of pediatric trialists identified a lack of research training, negative research culture and logistical challenges as barriers to conducting methodologically rigorous pediatric RCTs.[33] One important factor we identified is certainly feasibility, as 27 trials in this review (11% of all trials, 22% of those reporting an *a priori* sample size) were stopped early for reasons such as enrollment challenges or futility.

Strengths include the comprehensive search strategy to identify relevant trials and incorporation of trials published in any language. For each study we assessed the clinical and methodological features, and the completeness and transparency of reporting. We have also made publicly available data from the included trials and links to the full-text publications (PICUtrials.net). This is updated quarterly. The public availability of the results of this scoping review increases the ability of clinicians and pediatric critical care researchers to easily access pre-appraised, relevant RCTs. Finally, by synthesizing the

methodological features of, and identifying gaps in, the body of pediatric critical care research, it will allow researchers and funding agencies to prioritize trial designs to fill the gaps we identify in the conditions studied, trial methods, interventions, and the outcomes assessed.

This scoping review has some limitations. The relevance of this review to clinicians in some resource-limited areas may be limited, as *a priori*, we excluded trials that were conducted in settings where mechanical ventilation was not available. We limited this review to RCTs conducted in a pediatric ICU and acknowledge that that some trials conducted in other populations such as critically ill adults or neonates, or in other settings such as prehospital, the emergency department, or the operating room may also inform the care of children in the ICU. Our objective in this review was to identify and describe pediatric critical care RCTs. Other research designs are also relevant to pediatric critical care practice, but are beyond the scope of a single review to include all the potentially relevant research. To focus on trials most likely to inform clinical practice and to improve the feasibility of this review we also excluded individual patient crossover trials.

Conclusions

This pediatric critical care scoping review identified the available RCTs and made them accessible to clinicians and researchers. Most RCTs focused on medications and intermediate or surrogate outcomes, were single-centred and were conducted in North America and Western Europe. While the number of published trials is increasing over time, the sample size is not. The results of this review underscore the need for trials with rigorous methodology, appropriate outcome measures, and improved quality of reporting in pediatric critical care. Such trials on a broad range of topics relevant to pediatric critical illness are required to ensure that more rigorous evidence exists to support clinical decision-making in this vulnerable population.

Chapter three:

Research collaboration in pediatric critical care:

A social network analysis

Abstract

Importance: Clinical research is a collaborative enterprise: individual researchers have access to expertise, experience, and resources through their collaborators.

Objectives: To describe the extent and patterns of collaboration among researchers who have published a pediatric critical care RCTs and to identify the most important individuals, centres, and countries.

Design: Social network analysis of coauthorship.

Data sources: Publications of the 320 pediatric critical care RCTs published between 1986 and 2015.

Data extraction and synthesis: We manually extracted the names of all authors and their affiliations from the trial publications.

Main outcome and measures: We used network density, measures of clustering, and the number and size of isolated components to describe the patterns of collaboration. To identify influential individuals, we used productivity (the number of published RCTs), influence (citations), and measures of centrality (degree, closeness, betweenness, Eigenvector centrality).

Results: We included 1 711 individual researchers and 17 group authors. A minority of researchers (245 [14%]) coauthored more than 1 RCT (maximum 13). Researchers coauthored publications with a median (IQR) of 7 (5, 11), and a maximum of 89 other researchers. We identified a large cluster of 629 (36%) researchers publishing 105 (33%) of the RCTs. There were 22 smaller disconnected clusters of researchers publishing a median of 3 (minimum 2, maximum 13) RCTs each. There were also 125 (39%) RCTs published by groups of researchers who published a single RCT and were not connected by co-authorship to any other researchers. The proportion of RCTs published by groups of researchers with experience (a member has previously published an RCT) has plateaued. The network is highly clustered, particularly geographically. Most researchers'

collaboration occurs within countries rather than between countries (modularity=0.66) and international collaboration does not appear to be increasing.

Conclusions: The research enterprise in pediatric critical care RCTs is highly clustered and highly fragmented. Most researchers' collaborations occur within countries rather than between countries. Important measures of the network structure have not dramatically changed since the year 2000. The most important individuals and centres were most often from the USA and Canada.

Introduction

Clinical research in pediatric critical care is, like all of science, a social enterprise. RCTs are the products of the collaboration among individuals rather than of isolated researchers. Insight into the social structure — the patterns of collaboration — in the community of researchers is an important step towards understanding the state of the science.

Social structure is relevant in many aspects of human life. A particular individual's relationships with others provide opportunities — but also place constraints on them — and patterns of relationships are important for the spread of disease, information, and behaviours. Social network analysis is an approach to studying social structure. It focuses primarily on the patterns and characteristics of relationships among individuals rather than the attributes of those individuals.[19] There are many types of personal and professional relationships. Our focus in this study is on scientific collaboration. Studying coauthorship of scientific publications provides a unique perspective on the patterns of scientific collaboration. Coauthorship documents a collaboration between 2 or more researchers. Although not the only type of relationship, coauthorship likely indicates a particularly strong or important type of collaboration. Publication dates allows examination of the evolution of scientific social structures as new researchers enter the field and new collaborations are formed. Other researchers have used social network analysis of coauthorship to study collaboration in a variety of contexts including large-

scale analysis of bibliographic databases[37] and, on a smaller scale, research in particular countries[38], institutions[39], and clinical specialties[40]as well as specific clinical[41] and methodological topics.[42]

Collaboration facilitates sharing knowledge, expertise, and/or other resources needed to successfully complete an RCT. These relationships may also strengthen group norms or, conversely, facilitate change and innovation. Social network analysis of coauthorship networks can identify opportunities to improve collaboration and identify influential individuals and groups who can facilitate change. Our objectives in this study were to describe the extent and patterns of collaboration among researchers who have published one or more pediatric critical care RCTs and to identify potentially important individuals, centres, and countries.

Methods

Data sources

We used coauthorship of a published RCT to indicate collaboration. We used 320 RCTs that were identified in a scoping review of pediatric critical care RCTs.[43] We extracted the names of all authors and their affiliations from the trial publications. We considered research networks, consortia, and other group authors to be a single author unless the trial publication listed all the group members. For authors with multiple affiliations, we selected the most recent or the first listed. We considered a university and its departments, affiliated research institutes, and hospitals to be a single centre. One reviewer extracted the data from the trial publications and de-duplicated the lists of author names and affiliations. A second reviewer checked the data and disagreements were resolved by consensus. We searched the Science Citation Index Expanded™ (Thomson Reuters) on Feb 22, 2016 to determine the number of times each publication was cited.

Analysis

From the list of researchers and their publications, we constructed 3 separate networks: 1 each for researchers, centres, and countries. In the researcher network the nodes are individual researchers and they are connected to other researchers by ties representing coauthorship of at least one publication. In the centre network the nodes are centres and they are connected to other centres by ties representing coauthorship of at least one publication by researchers affiliated with those centres. In the country network the nodes are countries and they are connected to other countries by ties representing coauthorship of at least one publication by researchers affiliated with centres in those countries. Each tie between a pair of researchers is weighted by the number of publications coauthored by that pair. After constructing the network, we used a variety of techniques to explore the properties of the network. Hawe et al. provides a useful glossary of terms.[44]

Network structure

To describe the overall structure of the resulting coauthorship network and the interconnectedness of the individual researchers, we reported:

- **Network components** — isolated subgroups of researchers who are connected to each other, directly or indirectly, by coauthorship, but not to other researchers. Information and resources cannot flow between isolated components. We calculated the number of components, their size, and the number of RCTs published by each component of the network.
- **Mean distance** — the mean number of ties on the shortest route between pairs of connected researchers. Shorter mean distances (or degrees of separation) indicate that, on average, researchers are closer to other researchers and more able to access their information and resources.
- **Network diameter** — the largest number of ties in the shortest route between a pair of researchers in the largest component of the network. The network diameter is a measure of the size of the network.

- **Density** — the total number of ties in the network as a proportion of the total possible number of ties. The density of a given network ranges from 0 to 1. Dense networks are more efficient for the spread of information and coordination of activities. Dense networks may also hinder change as the many connections may entrench societal norms.
- **Clustering coefficient** — the mean probability that two of an individual's coauthors have in turn coauthored a publication.[45] The clustering coefficient ranges from 0 to 1 and higher values indicate more tightly clustered networks.
- **Modularity** — measures of the extent to which the network is divided into communities or clusters. The modularity for a given network ranges from -0.5 to 1. Higher modularity indicates that there are more connections within the community or cluster than would be expected if the connections were distributed randomly. To test the effects of geography on the patterns of collaboration we calculated the modularity for country, city, and centre levels.

Important individuals

We used productivity, impact, and 4 measures of network centrality to identify the most important researchers in pediatric critical care:

- **Productivity** — the total number of RCTs coauthored by each researcher.
- **Impact** — the total number of citations of all of the RCTs coauthored by each researcher.
- **Degree centrality** — the total number of researchers with whom a researcher has coauthored a publication. Researchers with a high degree — more collaborators — would presumably have access to more expertise, experience and resources than those with a lower degree — fewer collaborators. Researchers with a high degree may also be more able to influence many others.
- **Betweenness centrality** — the number of times each researcher connects pairs of researchers who have not directly collaborated. Researchers with high betweenness act as intermediaries, connecting different groups within the network.

- **Closeness centrality**— the mean distance (measured in the number of ties on the shortest path) from a researcher to all other researchers in the network. Closeness measures an individual's influence on whole network and indicates how long it takes information to spread to or from others. Individuals with high closeness may also be more independent, as they are less dependent on intermediaries to reach other members of the network .
- **Eigenvector centrality** — measures the influence of a researcher in the network. It considers not only the number of connections to other researchers, but the importance of those connections. Researchers with connections to prominent researchers will have a higher eigenvector centrality than those who have connections to less prominent researchers.

Important centres and countries

We used the number of researchers, productivity, impact, and degree centrality to identify the most important centres and countries in pediatric critical care:

- **Number of researchers** — the total number of researchers from each centre and country.
- **Productivity** — the total number of RCTs coauthored by researchers from each centre and country.
- **Impact** — the total number of citations of all of the RCTs by researchers from each centre and country.
- **Degree centrality** — the number of other centres with which researchers from a particular centre have coauthored a publication, and the number of other countries with which researchers from a particular country have coauthored a publication.

We used R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and the igraph software package[46] to perform the analysis and Gephi version 0.8.2 (gephi.github.io) to construct the network diagrams.

Results

We identified 1 733 researchers (including 17 group authors) from 290 centres in 39 countries who co-authored a total of 320 RCTs between 1986 and 2015.

Network structure: individuals

Figure 3.1 shows the coauthorship network diagram for individual researchers. The coauthorship network is highly disconnected and dominated by a single large component publishing 33% of the RCTs. There are 147 other components that are all much smaller; the second-largest component published 4% of the RCTs and 125 of the components published a single RCT each. Figure 3.2 shows how the number of RCTs published by the components has changed over time. Figure 3.3 shows how the percentage of RCTs conducted by groups of researchers with previous experience (defined as a least 1 researcher having previously coauthored an RCT in pediatric critical care) has changed over time. This percentage increased until 2005 and appears to have plateaued at approximately 60%.

Table 3.1 shows the summary statistics for the network. The large component is denser than the network as a whole, but the clustering coefficient is similar. Pairs of researchers have a 78% probability of collaborating if they have both collaborated with a third researcher. The coauthorship network is divided into local communities with many connections among the members and fewer with individuals outside the immediate community. The modularity at each of the 3 levels (institution, city, and country) shows the extent of geographical clustering. Higher modularity indicates that more of each individual's collaborations are with other researchers from the same institution, city, or country. Compared to the whole network, there is less geographic clustering in the large component. Those researchers more often collaborated with other researchers in other institutions, cities, and countries — the modularity for all of these 3 levels is lower in the large component than the network as a whole.

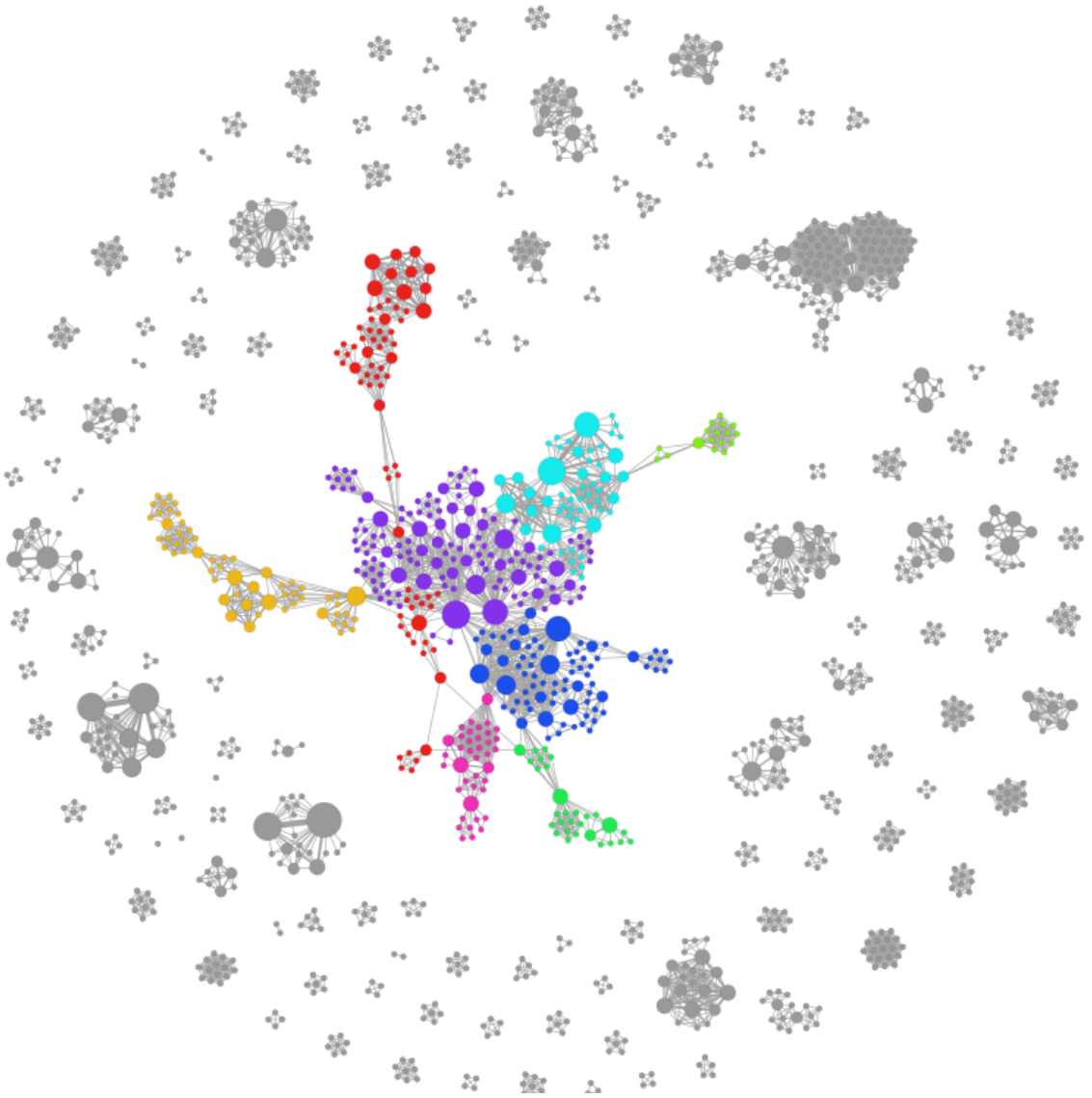

Figure 3.1. Coauthorship network diagram in pediatric critical care RCTs. Each circle represents a researcher who has published an RCT in pediatric critical care. The area of each circle is proportional to the number of RCTs that each researcher has published. A line connecting two researchers indicates that they have co-authored at least one published RCT. The width of each line is proportional to the number of RCTs that each pair of researchers has coauthored together. The colours in the large component indicate communities of researchers detected using the Louvain method.[47]

Table 3.1. Pediatric critical care RCT coauthorship network statistics

Characteristics	Whole network	Large component
Researchers		
Number of researchers	1 733	632
Researchers from high-income countries	1 321 (78%)	548 (89%)
Number of countries	39	17
RCTs per researcher	1 (1, 1) (max=13)	1 (1, 1) (max=8)
Researchers publishing >1 RCT	249 (14%)	149 (24%)
Collaborators per author	7 (5, 11) (max=89)	10 (6, 15) (max=89)
RCTs		
Number of RCTs	320	105
Researchers per RCT	6 (4, 8) (max=46)	7 (5, 10) (max=46)
Components		
Number of components	148	
Size of largest component		
Researchers	632 (37%)	
RCTs	105 (33%)	
Size of other components		
Researchers	6 (4, 9) (max=46)	
RCTs	1 (1, 1) (max=13)	
Network characteristics		
Density	0.0055	0.021
Clustering coefficient	0.78	0.74
Mean distance	4.7	4.8
Maximum distance	15[a]	15
Modularity		
Country	0.66	0.43
City	0.47	0.26
Institution	0.36	0.17

[a]Measured for the large component only.

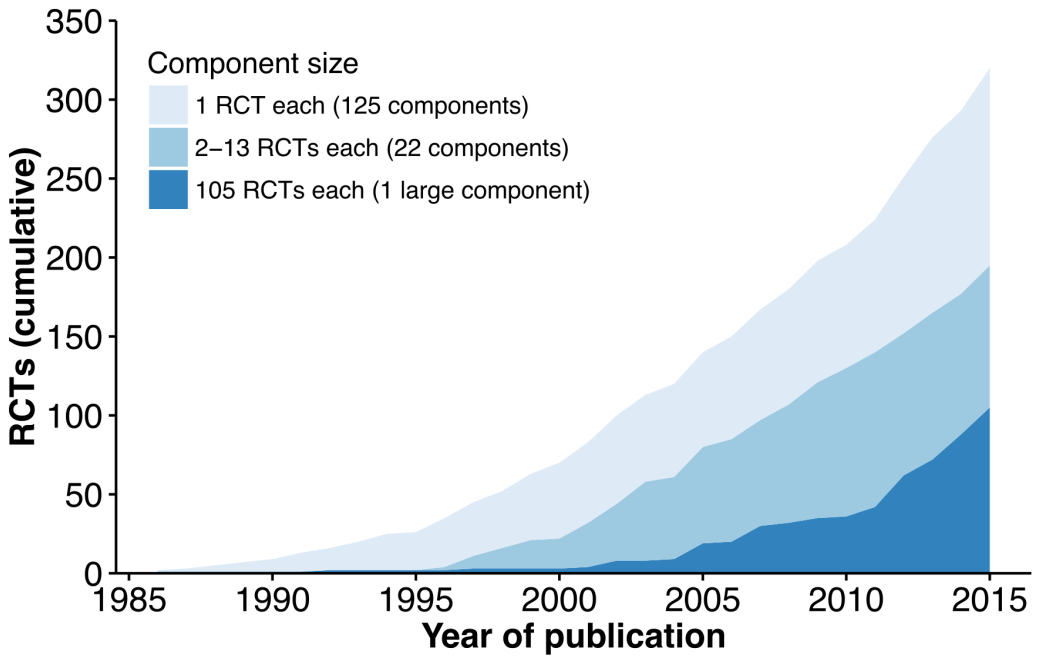

Figure 3.2. Productivity of coauthorship network components over time

Figure 3.4 shows how the size and structure of the network has evolved over time. The size of the network (measured by both the number of researchers and the number of RCTs) is increasing along with the mean number of collaborators for each researcher. There are not, however, any important changes in the patterns of collaboration; in particular collaboration with a wider range of individuals — the network density and clustering coefficient have remained relatively stable over time.

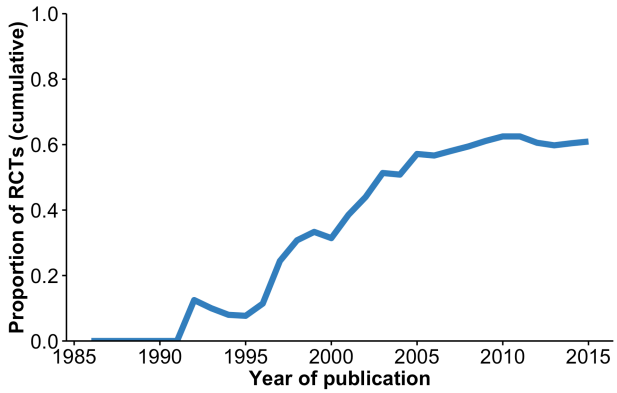

Figure 3.3. RCTs by experienced groups of researchers over time. We considered a group to be experienced if at least 1 coauthor had previously published an RCT in pediatric critical care.

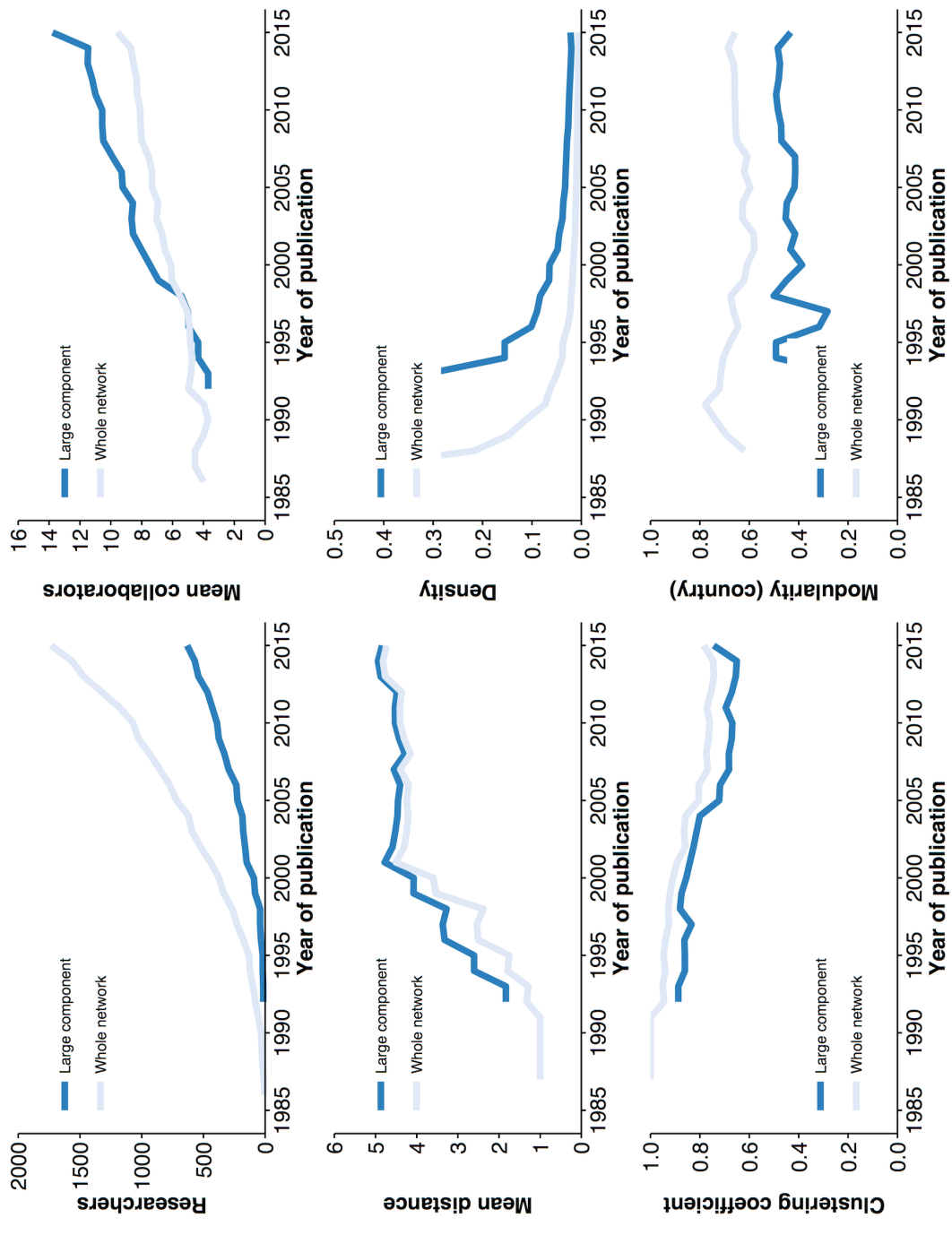

Figure 3.4. Change in individual coauthorship network statistics over time. The largest network component first emerged in 1992.

Network structure: centres and countries

The overall structure of the centres network is similar to the individual researcher network with 71 disconnected components and a single large component including 194 (67%) of the centres. The smaller components range in size from 1 to 4 centres and 53 (18%) of the centres have not collaborated with another centre. Figure 3.5 shows the coauthorship network diagram for countries. The single large component includes 30 (77%) of the countries and the 8 other components are each composed of a single country that has not collaborated with another country.

Important individuals

Table 3.2 shows the 25 most important researchers (and their country of origin) ranked by the number of RCTs they have published, the total number of times their RCTs have been cited and 4 measures of network centrality (degree, betweenness, closeness, and eigenvector centrality). The number of publication per researchers range from 1 to 13 and is highly skewed; 1 484 (86%) of the researchers have published a single RCT and only 82 (5%) have published more than 2 RCTs. Each researcher's RCTs have been cited a median (IQR) of 24 (6.5, 60) times. Figure 3.6 shows that most individuals in the network have relatively few collaborators, but a few have a very high number of collaborators. This is a typical pattern in many social networks. Table 3.3 shows the individuals who rank highly in all 6 measures of prominence. Three researchers (Heidi Dalton, Kathleen Meert, James Hutchison) rank in the top 25 for all measures. An additional 10 researchers, all from the United States or Canada, rank in the top 100 for all measures.

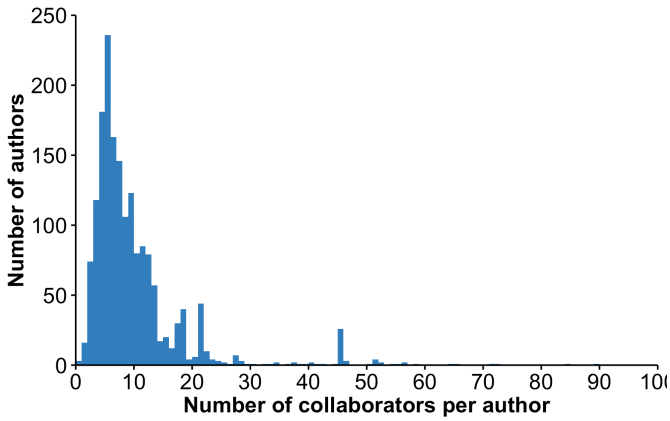

Figure 3.6. Histogram of total number of collaborators per author. Three authors were group authors who published a single RCT and thus have zero collaborators in this figure.

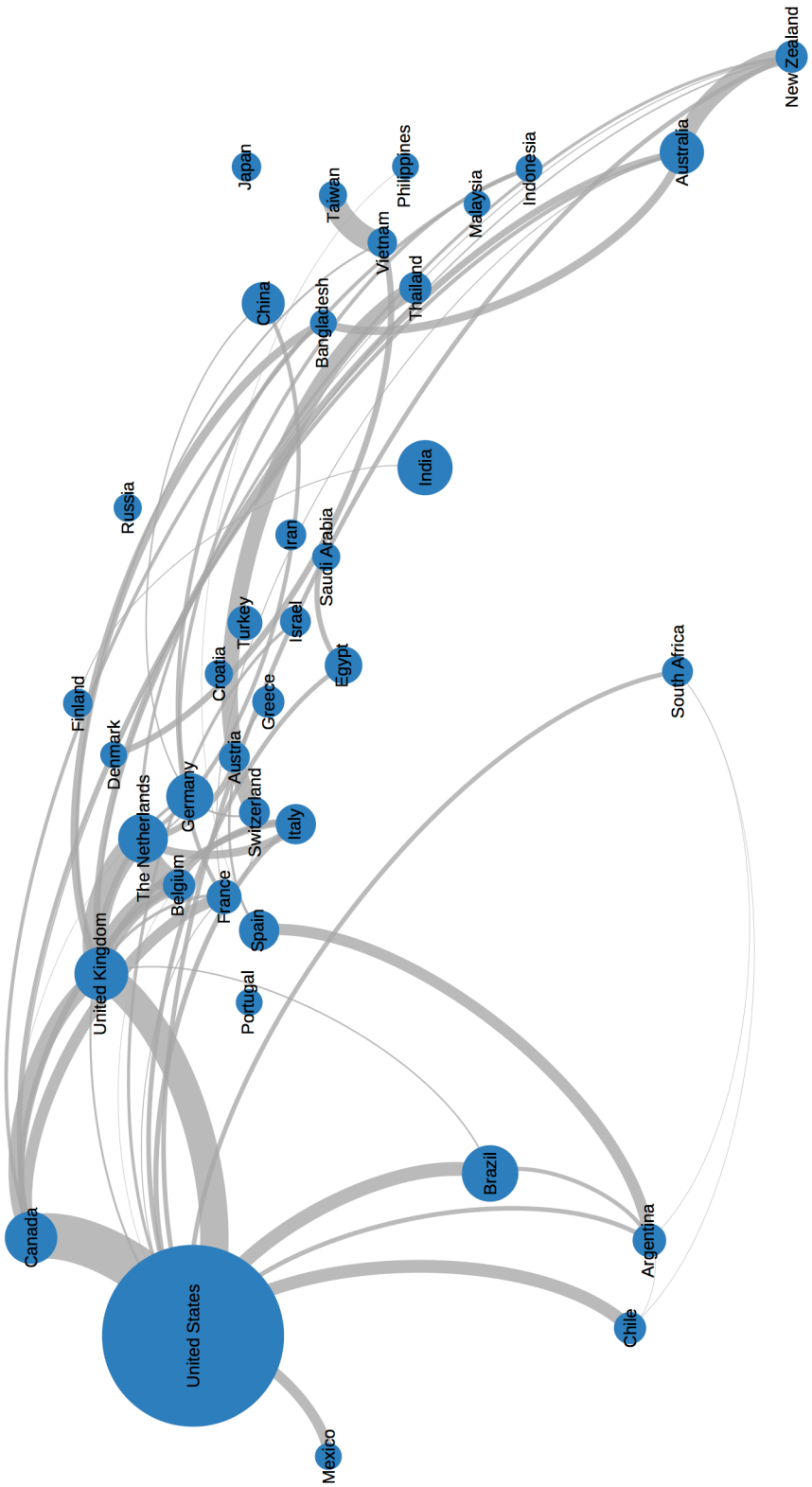

Figure 3.5. Country coauthorship network diagram in pediatric critical care RCTs. Each circle represents a country with researchers who have published an RCT in pediatric critical care. The area of each circle is proportional to the number of RCTs that researchers from that country have coauthored. A line connecting two countries indicates that researchers at those centres have co-authored at least one published RCT. The width of each line is proportional to the number of RCTs that researchers from each pair of countries have coauthored together.

Important centres and countries

Table 3.4 shows the 25 most important centres ranked by the number of researchers affiliated with each centre, the number of published RCTs, the total number of times their RCTs were cited, and the number of centres they have collaborated with. Children's Medical Centre, Dallas, USA ranks first in all 4 measures of prominence and with Cincinnati Children's Hospital, is one of the only 2 centres ranking in the top 10 for all 4 measures.

Table 3.3. Researchers ranking in the top 100 for all 6 prominence measures

Rank	Researcher
1	Meert, Kathleen - USA
2	Hutchison, James - CAN
3	Dalton, Heidi - USA
4	PALISI
5	Thomas, Neal - USA
6	Lacroix, Jacques - CAN
7	Joffe, Ari - CAN
8	CCCTG
9	Jacobs, Brian - USA
10	Willson, Douglas - USA
11	Wypij, David - USA
12	Arnold, John - USA
13	Goldstein, Brahm - USA
14	Luckett, Peter - USA

Researchers are ranked by the sum of their ranks in the 6 measures of prominence: the number of RCTs they have published, the total number of times their RCTs have been cited and 4 measures of centrality (degree, betweenness, closeness, and eigenvector centrality). The 3 letter code after each researcher's name indicates their country of origin.

Table 3.5 shows the 25 most important centres ranked by the number of researchers from each country, the number of published RCTs, the total number of times their RCTs were cited, and the number of countries they have collaborated with. The United States ranks first in all 4 measures of prominence and with Canada, Germany, The Netherlands, The United Kingdom, and Australia, is one of the 6 countries ranking in the top 10 for all 4 measures.

Table 3.2. Twenty-five most prominent researchers

Rank	Published RCTs	Total times RCTs cited	Degree centrality (Number of collaborators)
1	Singhi, Sunit - IND (13)	PALISI (813)	Meert, Kathleen - USA (89)
2	Jayashree, M - IND (9)	Meert, Kathleen - USA (797)	Hutchison, James - CAN (84)
3	Herndon, David - USA (8)	Lacroix, Jacques - CAN (729)	Dalton, Heidi - USA (72)
4	Jacobs, Brian - USA (8)	Hutchison, James - CAN (721)	Thomas, Neal - USA (71)
5	Meert, Kathleen - USA (8)	CCCTG (694)	PALISI (65)
6	Jeschke, Marc - USA (7)	Joffe, Ari - CAN (685)	Nadkarni, Vinay - USA (64)
7	PALISI (7)	Peters, Mark - GBR (630)	Theodorou, Andreas - USA (58)
8	Brilli, Richard - USA (6)	Hebert, Paul - CAN (621)	Dean, J Michael - USA (56)
9	Lacroix, Jacques - CAN (6)	Giroir, Brett - USA (610)	Newth, Christopher - USA (56)
10	Tibboel, Dick - NLD (6)	Arnold, John - USA (532)	Wheeler, Derek - USA (55)
11	Butt, Warwick - AUS (5)	Goldstein, Brahm - USA (491)	Meyer, Michael - USA (54)
12	de Carvalho, Werther - BRA (5)	Hanson, James - USA (400)	Christensen, James - USA (52)
13	Hutchison, James - CAN (5)	Ducruet, Thierry - CAN (399)	Slomine, Beth - USA (52)
14	Lopez-Herce, Jesus - ESP (5)	Tucci, Marisa - CAN (399)	Berger, John - USA (51)
15	Shann, Frank - AUS (5)	Biarent, Dominique - BEL (388)	Harrison, Rick - USA (51)
16	Thomas, Neal - USA (5)	Gauvin, France - CAN (384)	Holubkov, Richard - USA (51)
17	Barton, Phil - USA (4)	Collet, Jean-Paul - CAN (375)	Zimmerman, Jerry - USA (51)
18	Bos, Albert - NLD (4)	Hume, Heather - CAN (375)	Alten, Jeffrey - USA (50)
19	Bousso, Albert - BRA (4)	Robillard, Pierre - CAN (375)	Browning, Brittan - USA (46)
20	Carcillo, Joseph - USA (4)	Toledano, Baruch - CAN (375)	Moler, Frank - USA (46)
21	Dalton, Heidi - USA (4)	TRIPICU Investigators (375)	Pemberton, Victoria - USA (46)
22	Dean, J Michael - USA (4)	Dalton, Heidi - USA (369)	Silverstein, Faye - USA (45)
23	Giroir, Brett - USA (4)	Wypij, David - USA (365)	Clark, Amy - USA (45)
24	Piva, Jefferson - BRA (4)	Adelson, P - USA (365)	Page, Kent - USA (45)
25	Willson, Douglas - USA (4)	Beers, Sue - USA (365)	Shankaran, Seetha - USA (45)

Researchers are ranked in descending order in each column. Researchers with the same value are in alphabetical order. The 3 letter code after each researcher's name indicates their country of origin.

Table 3.2 (continued). Twenty-five most prominent researchers

Betweenness centrality ($x10^{-3}$)	**Closeness centrality** ($x10^{7}$)	**Eigenvector centrality**
Biarent, Dominique - BEL (49.6)	Meert, Kathleen - USA (5.23566)	Meert, Kathleen - USA (1.000)
Meert, Kathleen - USA (49.4)	Hutchison, James - CAN (5.2356)	Dean, J Michael - USA (0.979)
Newth, Christopher - USA (43.0)	Newth, Christopher. - USA (5.23537)	Newth, Christopher - USA (0.926)
Chang, Anthony - USA (39.1)	Thomas, Neal - USA (5.2353)	Holubkov, Richard - USA (0.924)
Carcillo, Joseph - USA (36.0)	Nadkarni, Vinay - USA (5.23528)	Zimmerman, Jerry - USA (0.924)
Hutchison, James - CAN (35.3)	Dalton, Heidi - USA (5.23526)	Harrison, Rick - USA (0.924)
Hirtz, Deborah - USA (32.2)	Biarent, Dominique - BEL (5.2352)	Berger, John - USA (0.924)
van Woensel, Job - NLD (31.8)	Theodorou, A. - USA (5.23518)	Hutchison, James - CAN (0.892)
Beca, John - NZL (23.7)	Meyer, Michael - USA (5.23518)	Moler, Frank - USA (0.841)
PALISI (21.5)	Wheeler, Derek - USA (5.23517)	Pemberton, Victoria - USA (0.841)
Wernovsky, Gil - USA (18.9)	Christensen, James - USA (5.23517)	Browning, Brittan - USA (0.841)
Spray, Thomas - USA (18.9)	Slomine, Beth - USA (5.23517)	Thomas, Neal - USA (0.833)
Troster, Eduardo - BRA (16.8)	Alten, Jeffrey - USA (5.23516)	Dalton, Heidi - USA (0.807)
Morris, Kevin - GBR (16.0)	Silverstein, Faye - USA (5.23514)	Christensen, James - USA (0.806)
Farias, Julio - ARG (12.8)	Clark, Amy - USA (5.23514)	Slomine, Beth - USA (0.806)
Tibboel, Dick - NLD (12.5)	Page, Kent - USA (5.23514)	Nadkarni, Vinay - USA (0.798)
Nadkarni, Vinay - USA (11.9)	Shankaran, Seetha - USA (5.23514)	Wheeler, Derek - USA (0.796)
Dalton, Heidi - USA (11.5)	Bennett, Kimberly - USA (5.23514)	Theodorou, A. - USA (0.790)
Tasker, Robert - USA (11.5)	Topjian, Alexis - USA (5.23514)	Meyer, Michael - USA (0.788)
Wypij, David - USA (11.2)	Pineda, Jose - USA (5.23514)	Alten, Jeffrey - USA (0.786)
Wessel, David - USA (9.6)	Koch, Joshua - USA (5.23514)	van der Jagt, Elise - USA (0.784)
Shann, Frank - AUS (9.2)	Schleien, Charles - USA (5.23514)	Schwarz, Adam - USA (0.784)
de Weerd, W - NLD (8.7)	Ofori-Amanfo, G. - USA (5.23514)	Sanders, Ronald - USA (0.784)
Bos, Albert - NLD (8.6)	Goodman, Denise - USA (5.23514)	Nowak, Jeffery - USA (0.784)
Lacroix, Jacques - CAN (8.1)	Fink, Ericka - USA (5.23514)	THAPCA Investigators (0.784)

CCCTG, Canadian Critical Care Trials Group; PALISI, Pediatric Acute Lung Injury and Sepsis Investigators; THAPCA, Therapeutic Hypothermia After Pediatric Cardiac Arrest.

Table 3.4. Twenty-five most prominent centres

Rank	Researchers	Published RCTs	Total times RCTs cited	Collaborating centres
1	Children's Medical Center Dallas - USA (60)	Children's Medical Center Dallas - USA (27)	Children's Medical Center Dallas - USA (1835)	Children's Medical Center Dallas - USA (55)
2	Universidade de São Paulo São Paulo - BRA (37)	Mattel Children's Hospital Los Angeles - USA (18)	Hospital for Sick Children Toronto - CAN (1235)	Hospital for Sick Children Toronto - CAN (51)
3	Cincinnati Children's Hospital Cincinnati - USA (33)	Boston Children's Hospital Boston - USA (14)	Mattel Children's Hospital Los Angeles - USA (1229)	Mattel Children's Hospital Los Angeles - USA (49)
4	Sophia Children's Hospital Rotterdam - NLD (33)	Cincinnati Children's Hospital Cincinnati - USA (14)	Boston Children's Hospital Boston - USA (927)	Primary Children's Medical Center, Salt Lake City - USA (48)
5	Boston Children's Hospital Boston - USA (30)	Universidade de São Paulo São Paulo - BRA (14)	Texas Children's Hospital Houston - USA (915)	Children's Hospital of Michigan Detroit - USA (47)
6	Hospital Infantil La Paz Madrid - ESP (29)	Hospital for Sick Children Toronto - CAN (13)	Children's Hospital of Michigan Detroit - USA (796)	Phoenix Children's Hospital Phoenix - USA (47)
7	Royal Children's Hospital Melbourne - AUS (27)	Advanced Pediatrics Centre PGIMER, Chandigarh - IND (13)	Sainte-Justine Hospital Montreal - CAN (778)	Penn State Children's Hospital Hershey - USA (45)
8	Hospital Interzonal Neuquen - ARG (25)	Primary Children's Medical Center, Salt Lake City - USA (12)	Children's Hospital of Pittsburgh Pittsburgh - USA (767)	Children's Hospital of Philadelphia - USA (44)
9	Children's Hospital of Philadelphia - USA (24)	Children's Hospital of Michigan Detroit - USA (11)	Great Ormond Street Children's Hospital, London - GBR (739)	Cincinnati Children's Hospital Cincinnati - USA (42)
10	Children's Hospital of Pittsburgh Pittsburgh - USA (23)	Children's Hospital of Pittsburgh Pittsburgh - USA (11)	Cincinnati Children's Hospital Cincinnati - USA (735)	Duke Children's Hospital Durham - USA (41)
11	University of Rochester Rochester - USA (22)	Academisch Medisch Centrum Amsterdam - NLD (11)	Stollery Children's Hospital Edmonton - CAN (712)	Children's Hospital Los Angeles Los Angeles - USA (41)
12	Mattel Children's Hospital Los Angeles - USA (21)	Children's Hospital of Philadelphia - USA (10)	Children's Hospital of Philadelphia - USA (683)	Boston Children's Hospital Boston - USA (40)
13	Lucile Packard Children's Hospital, Stanford - USA (20)	Royal Children's Hospital Melbourne - AUS (9)	Primary Children's Med. Center, Salt Lake City - USA (677)	Children's Hospital of Pittsburgh Pittsburgh - USA (40)

14	Advanced Pediatrics Centre PGIMER, Chandigarh - IND (20)	Sophia Children's Hospital Rotterdam - NLD (9)	Children's Hospital of Eastern Ontario, Ottawa - CAN (670)	Children's National Medical Center, Washington - USA (40)
15	Hospital for Sick Children Toronto - CAN (19)	Texas Children's Hospital Houston - USA (8)	Phoenix Children's Hospital Phoenix - USA (670)	Children's Healthcare of Atlanta Atlanta - USA (38)
16	Central Hospital Cologne Cologne - DEU (19)	Children's Hospital Los Angeles Los Angeles - USA (8)	University of British Columbia Vancouver - CAN (623)	University of Michigan, Ann Arbor - USA (37)
17	Miami Children's Hospital Miami - USA (17)	Children's Hospital of Wisconsin Milwaukee - USA (8)	Montreal Children's Hospital Montreal - CAN (621)	NINDS Bethesda - USA (36)
18	Primary Children's Med. Center, Salt Lake City - USA (17)	Children's National Medical Center, Washington - USA (8)	St Mary's Hospital London - GBR (586)	Lurie Children's Hospital of Chicago, Chicago - USA (36)
19	Academisch Medisch Centrum Amsterdam - NLD (17)	Hospital Infantil La Paz Madrid - ESP (8)	Penn State Children's Hospital Hershey - USA (572)	Cornell University New York City - USA (36)
20	Sainte-Justine Hospital Montreal - CAN (16)	Sainte-Justine Hospital Montreal - CAN (7)	Children's Hospital Los Angeles Los Angeles - USA (503)	Children's Hospital Columbus - USA (35)
21	University Hospitals Leuven Leuven - BEL (16)	Penn State Children's Hospital Hershey - USA (7)	Children's Hospital of Wisconsin Milwaukee - USA (501)	Loma Linda University Children's Hospital, - USA (35)
22	University of Tennessee Health Science, Memphis - USA (15)	University of Tennessee Health Science, Memphis - USA (7)	Doernbecher Children's Hospital Portland - USA (491)	Children's Hospital of Wisconsin Milwaukee - USA (35)
23	University Children's Hospital Erlangen - DEU (15)	Phoenix Children's Hospital Phoenix - USA (7)	Children's National Medical Center, Washington - USA (419)	University of Tennessee Health Science, Memphis - USA (34)
24	Children's Hospital of Michigan Detroit - USA (14)	NINDS Bethesda - USA (6)	University of Michigan Ann Arbor - USA (417)	University of Washington School of Medicine, Seattle - USA (33)
25	Pediatric Hospital No. 1 Ho Chi Minh City - VNM (14)	Lurie Children's Hospital of Chicago, Chicago - USA (6)	Lucile Packard Children's Hospital, Stanford - USA (414)	University of Arizona Tucson - USA (33)

Centres are ranked in descending order in each column. Centres with the same value are in alphabetical order. We considered a university and its departments, affiliated research institutes, and hospitals to be a single centre. The 3 letter code after each centre indicates the country. PGIMER, Postgraduate Institute of Medical Education and Research; NINDS, National Institute of Neurological Diseases and Stroke.

Table 3.5. Twenty-five most prominent countries

Rank	Researchers	Published RCTs	Total times RCTs cited	Collaborating countries
1	United States (602)	United States (116)	United States (5693)	United States (14)
2	Germany (97)	Brazil (23)	United Kingdom (1541)	United Kingdom (12)
3	Canada (84)	India (22)	Canada (1332)	Canada (8)
4	The Netherlands (83)	United Kingdom (21)	Belgium (744)	The Netherlands (8)
5	Brazil (79)	Canada (20)	Germany (514)	France (6)
6	India (60)	The Netherlands (18)	Australia (500)	Germany (6)
7	United Kingdom (58)	Germany (16)	The Netherlands (474)	Argentina (5)
8	Italy (56)	Australia (14)	France (386)	Australia (5)
9	China (53)	China (13)	Brazil (317)	Belgium (5)
10	Australia (51)	Italy (11)	India (292)	New Zealand (5)
11	Spain (50)	Spain (11)	Switzerland (253)	Italy (4)
12	Argentina (35)	Egypt (9)	Spain (210)	Bangladesh (3)
13	Turkey (33)	France (7)	Austria (169)	Brazil (3)
14	Belgium (32)	Turkey (7)	Israel (156)	Chile (3)
15	Chile (31)	Argentina (6)	South Africa (152)	South Africa (3)
16	Egypt (27)	Belgium (5)	Chile (151)	Spain (3)
17	Thailand (24)	Chile (5)	Argentina (137)	Switzerland (3)
18	France (19)	Greece (5)	Vietnam (115)	Vietnam (3)
19	Greece (19)	New Zealand (5)	Greece (107)	China (2)
20	Japan (18)	Thailand (5)	Turkey (94)	Egypt (2)
21	Austria (17)	Austria (4)	Italy (86)	Indonesia (2)
22	Switzerland (17)	Iran (4)	Egypt (73)	Austria (1)
23	Taiwan (17)	Israel (4)	Mexico (64)	Denmark (1)
24	Iran (15)	South Africa (4)	China (44)	Finland (1)
25	Israel (16)	Switzerland (4)	Thailand (41)	Greece (1)

Countries are ranked in descending order in each column. Countries with the same value are in alphabetical order

Discussion

In this analysis of coauthorship patterns in pediatric critical care RCTs we found that the research enterprise is highly fragmented with 148 disconnected components and the largest component is relatively small (publishing only 33% of the trials). The network is highly clustered, particularly geographically — most researchers' collaboration occurs within countries rather than between countries. The size of the network, defined as the

number of researchers, and the researchers' mean number of collaborators have increased over time: other important measures of the network structure have not. The mean distance (degrees of separation), density (number of collaborations out of all possible collaborations), clustering coefficient (clustering of researchers), and modularity (a measure of international collaboration) have not dramatically changed since the year 2000. We also found that the most important individuals and centres — ranked using a variety of measures — were most often from the United States and Canada.

An important feature of this coauthorship network is the many small, disconnected components — most of the RCTs are conducted by groups of researchers with few connections to other groups of researchers. The pattern of a single large component far larger than the other components often develops in networks as the number of connections increases.[48] This coauthorship network fits this pattern, but the largest component is relatively small. In a coauthorship analysis of over 1.5 million publications indexed in Medline, the largest component included 92% of the researchers.[49] The percentage in mathematics, physics and computer science ranged from 57% to 89%.[37,49] This pattern of collaboration in pediatric critical care has important implications. Conducting RCTs in pediatric critical care is challenging, and, as many are conducted by groups of researchers will little or no previous experience with RCTs in this population, we are missing potentially important opportunities to learn from the experience of other researchers. This pattern of collaboration is also relevant in 2 ways for any efforts to improve the research enterprise. First, it suggests that creating opportunities for collaboration, particularly international collaboration and collaboration between new and experienced investigators, may be important. Second, innovation dissemination may be hampered by the sparse connections among groups of researchers.

The patterns of collaboration among countries are complex and the reasons for these patterns are not entirely clear. Sharing a common language is one obvious potential factor in the frequent collaboration between countries such as the United States, Canada, and the United Kingdom, but this is clearly not the only factor. For example, even though

they share common languages and borders, there is limited collaboration between researchers in Argentina and Chile and between those in Germany and Austria. The absolute number of researchers and RCTs may contribute to the higher collaboration in some countries, but there are also countries such India and China with high productivity (measured by the number of published RCTs) but limited intentional collaboration. We hypothesize that personal connections between researchers in different countries may be an additional factor underlying the collaboration patterns, but this is not easily measured in this type of study.

The results of this study will also inform efforts to improve the state of RCTs in pediatric critical care. The pattern of collaboration we found in this study is likely a contributor to the preponderance of small, single-centred RCTs that are often stopped early because of feasibility problems or futility. Inexperienced trialists at a single centre are likely disadvantaged because of the complexity of clinical research in this environment and the relatively small number of critically ill children at most centres. The pattern of collaboration also highlights opportunities to encourage sharing of expertise through collaboration between new and experienced researchers. Steps to increase international collaboration may also be important and may be particularly relevant for middle-income countries. Researchers in those countries may face more — and different — challenges in conducting RCTs, and the extent to which results from RCTs in high-income countries can be generalized to their patients (and vice versa) varies. This study also helps provide insight into who is likely to lead or facilitate efforts to improve how RCTs are conducted. We identified prominent individuals, using a variety of metrics, who are likely to be opinion leaders globally. We can also use these results to identify prominent individuals in the smaller network components. These locally influential individuals may be important in efforts to encourage wider collaboration.

Strengths of this study include the high-quality data and the use of both researcher characteristics (productivity and impact) and their position in the social network to assess prominence. Rather than downloading the author information from bibliographic

databases – where multiple authors may have the same name and a single author may have multiple versions of their name – we manually extracted the author names and affiliations from the publications and manually de-duplicated the author list to ensure high-quality data. This ensured that each node in the network represents a single researcher (and not multiple researchers with the same or similar names) and that each researcher is represented by a single node in the network (and not a node for each variation in name spelling). This study also has some limitations. Coauthorship of an RCT is only one type of scientific collaboration, and acknowledging variable levels of engagement within a group of authors, likely reflects strong relationships because of the commitment and resources required to complete an RCT. Studies of coauthorship networks assume that all coauthorship links between pairs of researchers represent the same type and intensity of relationships, and that all coauthors have made substantial contributions to the publication. Coauthorship studies also cannot consider the type, magnitude, or dissolution of academic relationships. In our study we focused only on RCTs in pediatric critical care and our findings may not generalize to studies with different designs or in different populations. Finally, group authors and research networks or consortia may include influential individuals who are not listed as authors in the publications.

Conclusions

The research enterprise in pediatric critical care RCTs is highly fragmented. The network is also highly clustered, particularly geographically — most researchers' collaboration occurs within countries rather than between countries. The size of the network, defined as the number of researchers, and the researchers' mean number of collaborators have both increased over time: other important measures of the network structure have not dramatically changed since the year 2000. We also found that the most important individuals and centres — ranked using a variety of measures — were most often from the United States and Canada.

Chapter four:
The role of randomized controlled trials in clinical decision-making:
A survey of pediatric critical care clinicians

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This was a scenario-based survey to better understand the importance of RCTs — and other factors — in clinicians' decision-making. We anticipated that most readers would be interested in applying these results in a clinical context, so rather than focusing just on the importance of RCTs, the published manuscript emphasizes the utility of these results to inform the design of tailored knowledge translation interventions.

In this survey we found that clinicians are optimistic about the quality of the evidence: 43% to 62% rated the body of evidence in each scenario as moderate or high, despite the preponderance of small RCTs at high risk of bias. Despite this, clinicians rated RCTs in pediatric critical care as important in their decision-making process. They rated pediatric critical care RCTs as the fourth most important factor they consider — after severity of illness, physiological rationale, and adverse effects. Despite the gaps in the evidence, clinicians prefer to base their decisions on pediatric critical care-specific RCTs. They rated RCTs in other populations (critically ill adults, neonates, and non-critically ill children) as less important (6^{th}, 10^{th}, and 11^{th}, respectively). Respondents' ratings of the importance of

RCTs in pediatric critical care did not vary among the scenarios despite differences in the number and size of RCTs. This suggests that the quality of the available evidence is inadequate in all the scenarios. We also investigated which respondent characteristics were associated with increased importance of RCTs. We found that respondents who rated the level of evidence as moderate or high rated the importance of RCTs in critically ill children — and indeed all RCTs — as being more important in their decision-making process. This implies that high-quality RCTs are likely to have an effect on clinical practice.

Abstract

Importance: Changing clinician practice in pediatric critical care is often difficult. Tailored knowledge translation interventions may be more effective than other types of interventions.

Objective: To describe the importance of specific factors that influence physicians and pharmacists when they make decisions about medications in critically ill children.

Design: Postal survey.

Participants: One hundred and seventeen physicians and pharmacists practicing in 18 PICUs.

Interventions: None

Main outcome and measures: Respondents used 7-point scales to rate the importance of specific factors that influence their decisions in the following scenarios: corticosteroids for shock, intensive insulin therapy, stress ulcer prophylaxis, surfactant for acute respiratory distress syndrome, and sedation interruption. We used generalized estimating equations to examine the association between the importance of specific factors influencing decision making and the scenario and respondents' practice, views, and demographics.

Results: The response rate was 61%. The 3 factors reported to most strongly influence clinician decision making overall were: severity of illness (mean [SD] 5.8 [1.8]), physiologic rationale (5.2 [1.3]), and adverse effects (5.1 [1.9]). Factors least likely to influence decision making were drug costs (2.0 [1.5]), unit policies (2.9 [1.9]), and non–critical care randomized controlled trials (3.1 [1.9]). The relative importance of 8 of the 10 factors varied significantly among the five scenarios: only randomized controlled trials in critically ill children and other clinical research did not vary. Clinician characteristics associated with the greatest difference in importance ratings were: frequent use of the

intervention in that scenario (7 factors), profession (5 factors), and respondents' assessment of the quality of evidence (5 factors).

Conclusions: The relative importance of many factors that clinicians consider when making decisions about medications varies by demographics, and depends on the clinical problem. This variability should be considered in quality improvement and knowledge translation interventions in this setting.

Introduction

Changing clinician practice in pediatric critical care is often difficult. The effectiveness of specific quality improvement or knowledge translation interventions such as guidelines, protocols, education, and opinion leaders is often not clear.[50] Tailored interventions, in which the intervention is modified to address context-specific barriers, are appealing because of the heterogeneity among individual patients, clinicians, PICUs, and hospitals. In other clinical areas, tailored knowledge translation interventions are more likely than no intervention or dissemination of guidelines to result in practice change (odds ratio 1.52, 95% CI 1.27–1.82, p 0.001).[51]

A critical component of tailoring a knowledge translation intervention is a clear understanding of individual clinicians' decision-making processes, particularly what specific factors they consider, and their relative importance. Investigators can capitalize on this information to prioritize their choice and design of knowledge translation intervention. The interventions can also be further tailored when the importance of factors varies with the clinical context or individual clinician characteristics.

The primary objective of this survey was to assess the importance of specific factors that influence physicians and pharmacists when they make decisions about medications in critically ill children. Our secondary objectives were to determine whether the relative importance of specific factors was consistent across clinical scenarios, and to identify clinician characteristics associated with variability in the importance of specific factors.

Methods

Questionnaire Development and Testing

Using focus groups of adult and pediatric critical care clinician researchers with expertise in research methodology and survey design, we drafted a scenario-based questionnaire (Appendix C). We developed five clinical scenarios (Table 4.1) that PICU clinicians encounter frequently, that we considered important, and for which there is at least one randomized controlled trial (RCT) in critically ill children. In choosing the scenarios we aimed for diversity with respect to attributable mortality, prophylaxis versus treatment, the potential for adverse effects, the costs of the intervention, the extent of RCT evidence in children and adults, and the concordance between results of pediatric and adult RCTs.

Table 4.1. Characteristics of the questionnaire scenarios

Characteristic	**Scenario**				
	Corticosteroids for fluid refractory septic shock	**Intensive insulin therapy**	**Stress ulcer prophylaxis**	**Surfactant therapy for ARDS**	**Daily interruption of sedation**
Underlying risk of mortality	High	Low	Low	High	Low
Drug costs	Low	Low	Low	High	Low
Workload	Low	High	Low	Low	High
Pediatric critical care RCTs (number randomized)[43]	1 trial (n=40)	5 trials (n=2 059)	3 trials (n=405)	4 trials (n=400)	1 trial (n=102)
Adult critical care RCTs (number randomized)	17 trials (n=2 138)[52]	26 trials (n=13 567)[53]	17 trials (n=1 836)[54]	9 trials (n=1 441)[55]	5 trials (n=699)[56]

The questionnaire focused on four domains of interest: 1) respondents' self-reported practice, 2) factors that may influence their decisions to use or not use a particular intervention in that scenario, 3) their assessment of the overall body of evidence, and 4) respondent demographics. We asked respondents to rate the importance of the following 13 specific factors in each scenario, using 7-point Likert-type scales: RCTs in critically ill children, RCTs in adults, RCTs in neonates and RCTs in non–critically ill children, other

clinical research, the child's severity of illness, potential for adverse effects, drug cost, unit policies or protocols, clinical experience, opinion leaders, guidelines, and physiologic rationale.

After questionnaire development, we performed clinical sensibility testing using adult clinicians to avoid reducing the already limited number of potential respondents in our sample frame. Six physicians and six pharmacists used a six-item tool to evaluate the ease of use, content validity, and face validity of the questionnaire, which we then revised based on their assessments.

Sample Frame

We included pharmacists and physicians (including fellows) who practice in PICUs in Canada. We included both physicians and pharmacists to reflect the multidisciplinary nature of critical care clinical practice. We selected pharmacists who worked in PICUs providing clinical care rather than only supervising drug distribution as they are more often involved in making decisions about drug therapy. As in many countries, pharmacists in Canadian PICUs generally work in collaboration with physicians and other health professionals, are often major knowledge brokers and advisors, and do not have independent prescribing authority. They participate in decisions and make recommendations at both at the level of the individual patient (e.g., participating in patient-care rounds) and on a unit and hospital level (e.g., quality improvement initiatives, formulary decisions). We hypothesized that there may be differences in the factors that each professional group weighs in making decisions. We included any unit that was referred to as a PICU by the hospital, affiliated university or individual potential respondents. To identify potentially eligible units, we used the websites of the Canadian Association of Pediatric Health Centres (www.caphc.org) and the Royal College of Physicians and Surgeons of Canada (www.royalcollege.ca). We then contacted a representative at each site by e-mail or telephone to confirm the names and contact information for the potential respondents at that site. We did not estimate a target sample size a priori.

Survey Administration

We mailed a questionnaire and return envelope to all potential respondents. We sent up to two reminders with replacement questionnaires at approximately 4-week intervals to those who had not responded, randomly assigning nonresponders to receive a $5 incentive of either a coffee card or a charitable donation made on their behalf.

Statistical Analysis

In summarizing the characteristics of the survey respondents, we reported continuous data as medians (first quartile and third quartile), and binary data as counts (percent). For all analyses, we used the actual number of respondents for the denominator. We used SAS 9.3 (SAS Institute, Cary, NC) to conduct the statistical analysis.

The primary outcome variables were the importance of the 13 specific factors that respondents considered in making decisions in each of the scenarios. First, we selected factors with a mean response of greater than or equal to 3.5 on the 1–7 importance scale for further analysis. We then assessed the clustering in the data. Our data have two types of cluster pairs: 1) the centre-level and respondent-level data structure from correlation between individuals within each centre; and 2) the scenario-level and respondent-level data structure from the survey in which we asked the same questions within each scenario. To test the degree of relatedness between individuals in a cluster, we calculated the intraclass correlation coefficient (ICC) and the variance inflation factor (VIF). The VIF measures the extent of collinearity among the predictor variables in the model. It shows how much the variance of the estimated regression coefficients is increased by correlation among the predictor variables. The VIF is 1 if there is no correlation among the predictor variables. The ICC for both the scenario and centre variables for each outcome was very similar (Table C1). We thus used centre as our cluster variable for regression analysis as we anticipated more similarity among individuals within a centre than within a scenario, and a larger number of levels would improve statistical power.[57]

Finally, we used multivariate analyses to assess the independent relationship between importance of the specific factors and potential covariates: the scenario, the respondents' reported frequency of use of the intervention in each scenario, the respondents' rating of the overall quality of the body of evidence for the intervention in each scenario, and respondent demographics: profession (physician or pharmacist), number of years in pediatric critical care practice, any role in clinical research (as an investigator or research staff), and the centre in which they practiced. We grouped responses from centers with fewer than five responses with larger centers using the units' usual referral practice (or the closest centre if referral patterns were not known). To account for potential clustering among the centers, we used generalized estimating equations (GEE) for the multivariate analysis.[58] The GEE approach is a type of regression that can be used to analyze longitudinal and other correlated data. We used an exchangeable correlation matrix to test for within-group clustering by assuming the correlation between responses within a group was constant. We assumed the same correlation structure is across groups. We presented the results of the GEE analysis for each outcome of interest as the coefficients, 95% CIs, and p values.

Results

Survey respondents

We identified 19 academic PICUs. All are academic centres in urban settings, eight (42%) of which have fellowship programs. We identified a total of 202 potential respondents with a median (interquartile range [IQR]) of four (4–7) physicians and two (1–4) pharmacists per PICU. We received 122 responses, 117 of these indicated they were eligible and were included in the analysis. Figure 4.1 shows the survey flow diagram. The overall response rate was 61% (68% for intensivists, 41% for fellows, and 60% for pharmacists). There was no difference in the response rates between the two types of incentives; 20 (31%) of the 64 randomized to receive a coffee card replied compared with 14 (25%) of 57 randomized to a charitable donation made on their behalf (odds ratio 1.4; 95% CI 0.6–3.1; p=0.41). The number of questions not answered by respondents was 3.7% overall and the

question most often omitted by respondents was rating the quality of the body of evidence (5.3%).

We received responses from 18 (95%) of 19 PICUs and all nine Canadian provinces with a PICU. The median (IQR) number of responses per centre was 7 (1–8) and varied from 1 to 14. The median (IQR) response rate per centre was 65% (60–87%) and varied from 29% to 100%. Table 4.2 shows the characteristics of the survey respondents.

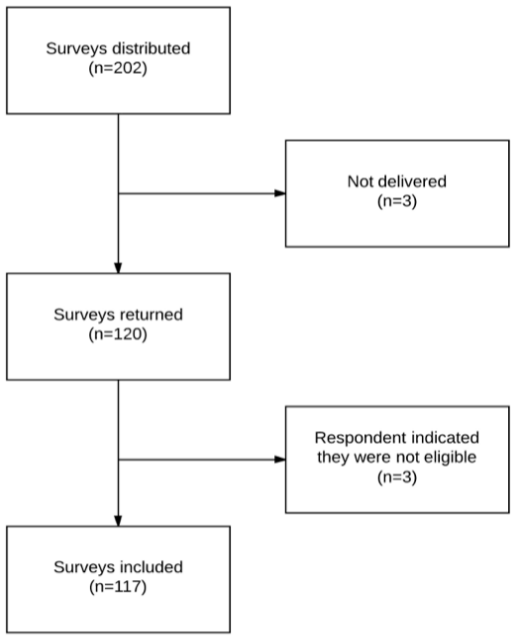

Figure 4.1. Survey flow diagram

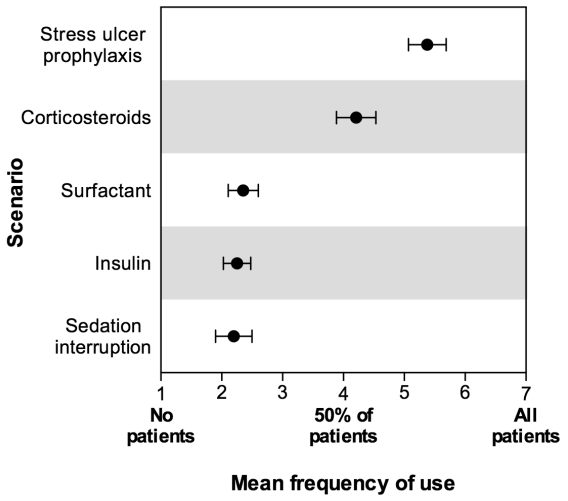

Figure 4.2. Respondents' reported use of the intervention in the five scenarios. Error bars show the 95% CI for the mean.

Practice Patterns and Ratings of the Evidence

Respondents used a 7-point scale to describe their usual practice pattern in each of the five scenarios: 1 indicated that they did not use the intervention in any patients and 7 indicated they used it in all patients without contraindications (Figure 4.2). They rated the overall quality of the body of evidence regarding the interventions in the five scenarios as high, moderate, low, very low, or unsure. The proportion of respondents who rated the body of evidence as moderate or high was similar in the five scenarios: corticosteroids (51%), intensive insulin therapy (46%), stress ulcer prophylaxis (62%), surfactant (45%), and sedation interruption (43%) (Figure 4.3).

Table 4.2. Characteristics of survey respondents

Characteristic	All respondents (n=117)	Intensivists (n=73)	Fellows (n=16)	Pharmacists (n=28)
Years in pediatric critical care	9 (3, 16)	12 (7, 16)	2 (1, 2)	6 (4, 14)
Role(s) in research				
principal investigator	54 (46%)	35 (48%)	9 (56%)	10 (36%)
site investigator	50 (43%)	50 (68%)	9 (56%)	14 (50%)
research staff	12 (10%)	3 (4%)	4 (25%)	5 (18%)
caring for patients in studies	80 (68%)	47 (64%)	14 (88%)	18 (64%)
other	5 (4%)	5 (7%)	0 (0%)	0 (0%)
none	18 (15%)	12 (16%)	0 (0%)	6 (21%)
Region[a]				
Atlantic	6 (5%)			
Quebec	33 (28%)			
Ontario	40 (34%)			
Manitoba and Saskatchewan	14 (34%)			
Alberta	14 (12%)			
British Columbia	11 (9%)			

[a]We have reported the region for all respondents only to avoid identifying respondents in regions with smaller numbers of clinicians.

Importance of Specific Factors: Overall

Respondents used a 7-point scale to rate how important each specific factor was in their personal decisions to use or not to use the intervention in each of the five scenarios: 1 indicated the specific factor was not important and 7 indicated it was very important (Figure 4.4). The three factors with the highest mean overall ratings were: the child's severity of illness, physiologic rationale, and the potential for adverse effects. The three factors with the lowest mean overall ratings were: drug costs, written unit policies or protocols, and RCTs in non–critically ill children. The mean score for these latter three factors was less than 3.5, so we did not include them in the multivariate analysis.

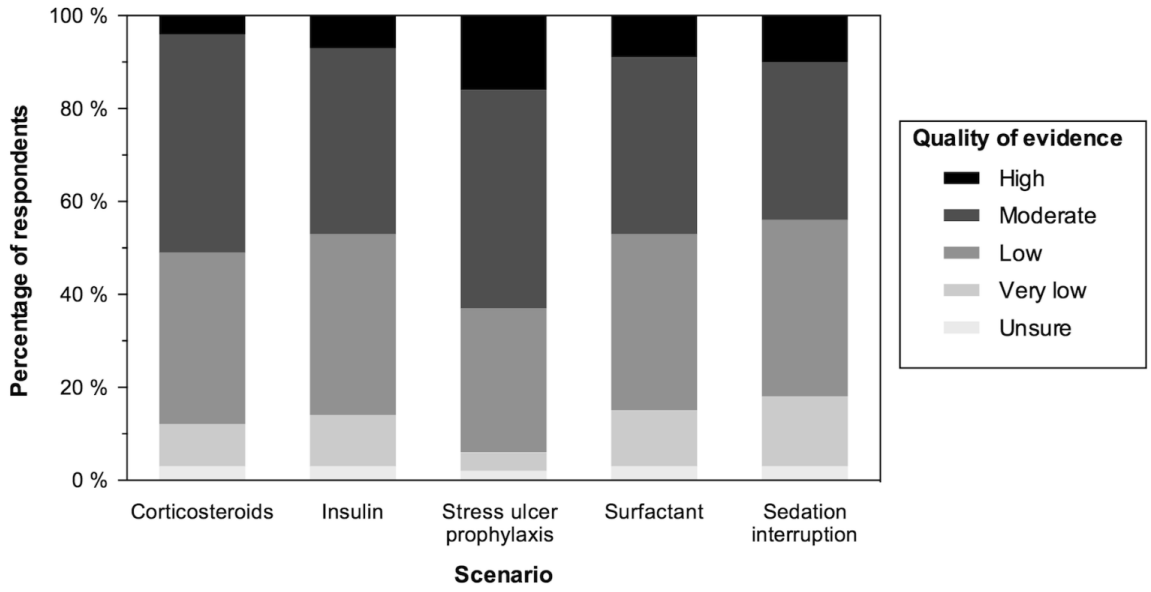

Figure 4.3. Respondents' ratings of the strength of evidence for the intervention in the 5 scenarios .

Importance of Specific Factors: Differences Among the Five Scenarios

In the multivariate analysis, we evaluated the independent effect of the scenario on the respondents' rating of the importance of specific factors, controlling for respondent characteristics and clustering of responses by centre. There were statistically significant differences among the five scenarios in the rated importance of eight of the specific factors (Figure 4.4 and Table C2). The two factors that did not vary in importance among the scenarios were RCTs in critically ill children and other clinical research. When ranked, the most important factors varied among the five scenarios (Table 4.3). There was, however, more consistency in the least important factors: the same four factors (drug costs, written unit policies or protocols, RCTs in non–critically ill children, and RCTs in neonates) were ranked as the four least important in all scenarios.

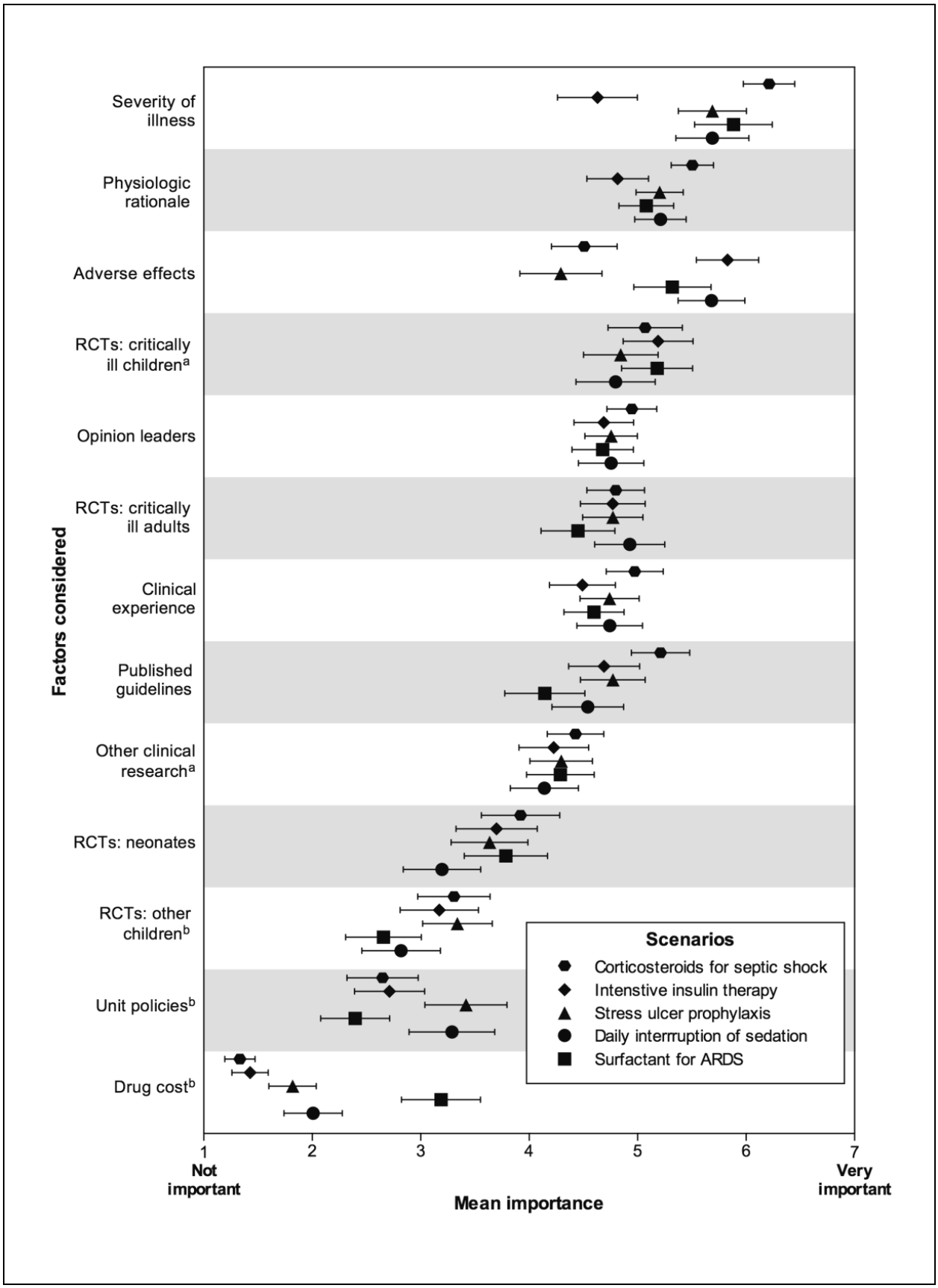
Severity of illness
Physiologic rationale
Adverse effects
RCTs: critically ill children[a]
Opinion leaders
RCTs: critically ill adults
Clinical experience
Published guidelines
Other clinical research[a]
RCTs: neonates
RCTs: other children[b]
Unit policies[b]
Drug cost[b]
Factors considered
Scenarios
Corticosteroids for septic shock
Intenstive insulin therapy
Stress ulcer prophylaxis
Daily interruption of sedation
Surfactant for ARDS
1
2
3
4
5
6
7
Not important
Very important
Mean importance

Figure 4.4. The importance of factors in respondents' decisions to use, or not use, the intervention in each of the five scenarios. The importance of factors in respondents' decisions to use, or not use, the intervention in each of the 5 scenarios. Error bars show the 95% confidence interval for the mean. In multivariate analysis there were statistically significant differences among the scenarios in the importance of 11 of the 13 factors. *Only RCTs in critically ill children and other clinical research were not different across scenarios. ARDS, Acute respiratory distress syndrome.

Table 4.3. Five most important factors for each scenario

Rank[a]	Corticosteroids for fluid refractory septic shock	Intensive insulin therapy	Stress ulcer prophylaxis	Surfactant therapy for ARDS	Daily interruption of sedation
1	Severity of illness	Adverse effects	Severity of illness	Severity of illness	Severity of illness
2	Physiologic rationale	RCTs: critically ill children	Physiologic rationale	Adverse effects	Adverse effects
3	Guidelines	RCTs: critically ill adults	Opinion leaders	RCTs: critically ill children	Physiologic rationale
4	RCTs: critically ill children	Physiologic rationale	Guidelines	Physiologic rationale	Guidelines
5	Clinical experience	Opinion leaders	RCTs: critically ill children	Opinion leaders	RCTs: critically ill children

[a]Factors are ranked by the mean importance rating for each scenario.

Importance of Specific Factors: Differences Associated with Respondent Characteristics

In the same multivariate analysis we also evaluated the independent effect of respondents' reported practice patterns, their assessment of the quality of evidence, and demographics on their rating of the importance of the specific factors while controlling for scenario and the clustering of responses by centre (Table 4.4). To assess the effect of practice patterns on the importance of specific factors, we compared respondents who reported more frequent use of intervention in that scenario (>4 on a scale from "1=no patients" to "7=all patients without contraindications") with those who reported less

frequent use. Respondents reporting more frequent use of intervention in that scenario rated all factors except the three types of RCTs (critically ill children, critically adults, and neonates) as more important. To assess the effect of the respondents' ratings of the quality of the evidence for the intervention in each scenario, we compared respondents who rated the level of evidence as moderate or high with those who rated it as low or very low. Those who rated the evidence as moderate or high rated all three types of RCTs and published guidelines as more important, and potential adverse effects as less important.

With respect to differences between physicians' and pharmacists' opinions, pharmacists rated all three types of RCTs, opinion leaders, and severity of illness as more important

Table 4.4. Effect of respondent characteristics and practice on the importance of specific factors

Participant variables	**Research evidence**			
	RCTs: critically ill children	**RCTs: critically ill adults**	**RCTs: neonates**	**Other clinical research**
Practice patterns: Participants reporting more frequent use of intervention vs. less frequent use.	0.01 (-0.43, 0.45) p=0.96	0.13 (-0.16, 0.42) p=0.36	0.13 (-0.25, 0.51) p=0.50	0.2 (0.02, 0.38) p=0.03
Rating of the evidence: Respondents who rated the level of evidence as moderate or high vs. those who did not.	0.91 (0.42, 1.41) p<0.001	0.28 (0.04, 0.53) p=0.02	0.47 (0.07, 0.87) p=0.02	0.22 (-0.02, 0.46) p=0.08
Profession: Pharmacist vs. physician	0.92 (0.28, 1.56) p=0.01	0.77 (0.29, 1.24) p=0.002	1.06 (0.29, 1.83) p=0.01	0.39 (-0.53, 1.31) p=0.41
Clinical experience: Years practicing pediatric critical care	0.01 (-0.02, 0.04) p=0.40	0 (-0.03, 0.03) p=0.79	-0.01 (-0.07, 0.04) p=0.61	-0.03 (-0.05, -0.01) p=0.01
Research experience: Experience as investigator or research coordinator vs. those without.	-0.25 (-0.84, 0.35) p=0.42	0.31 (-0.17, 0.8) p=0.20	-0.38 (-1.41, 0.65) p=0.47	-0.08 (-0.89, 0.73) p=0.85

This table shows the results of the multivariate analysis, reporting the coefficient (95% confidence interval) for each covariate. Positive coefficients indicate that respondents with that characteristic rated that particular factor as more important. More frequent use of intervention=5, 6 or 7 on a scale from 1="No patients" to 7="All patients without contraindications".

than did physicians. Clinical and research experience had fewer effects. Clinicians with more years of practice in pediatric critical care rated the influence of opinion leaders and other clinical research as less important than clinicians with fewer years of experience. Finally, participants reporting any experience in research rated published guidelines asless important than participants with no research experience.

Table 4.4 (continued). Effect of respondent characteristics and practice on the importance of specific factors

Published guidelines	Opinion leaders	Child's severity of illness	Physiologic rationale	Adverse effects	Clinical experience
0.51 (0.29, 0.72) p<0.001	0.48 (0.15, 0.82) p=0.004	0.54 (0.22, 0.87) p=0.001	0.57 (0.35, 0.79) p<0.001	0.47 (0.08, 0.86) p=0.02	0.62 (0.2, 1.04) p=0.004
0.54 (0.11, 0.98) p=0.01	0.05 (-0.17, 0.27) p=0.65	0.13 (-0.18, 0.45) p=0.40	-0.07 (-0.30, 0.16) p=0.55	-0.28 (-0.49, -0.08) p=0.01	0.01 (-0.29, 0.32) p=0.93
0.17 (-0.64, 0.99) p=0.68	0.44 (0.12, 0.75) p=0.01	0.54 (0.08, 1) p=0.02	0.13 (-0.34, 0.61) p=0.59	0.03 (-0.49, 0.55) p=0.90	-0.10 (-0.46, 0.25) p=0.57
-0.01 (-0.04, 0.02) p=0.63	-0.03 (-0.05, 0) p=0.04	0.01 (0, 0.03) p=0.13	0 (-0.01, 0.01) p=0.54	0 (-0.02, 0.02) p=0.95	-0.02 (-0.04, 0.01) p=0.21
-0.61 (-1.06, -0.16) p=0.01	-0.02 (-0.24, 0.2) p=0.85	0.13 (-0.47, 0.72) p=0.68	0.06 (-0.49, 0.62) p=0.83	-0.15 (-0.70, 0.40) p=0.60	-0.07 (-0.48, 0.34) p=0.74

Shaded cells are statistically significant (p<0.05). The mean score for 3 other factors: drug costs, written unit policies or protocols, and RCTs in non-critically ill children, was less than 3.5 so we did not include them in the multivariate analysis.

Discussion

In this self-administered survey, PICU physicians and pharmacists reported that the three most important factors influencing their decisions on medication use in critically ill children were severity of illness, physiologic rationale, and the potential for adverse effects. There were significant differences associated with the clinical scenario and the respondent characteristics in the importance of many, but not all, factors.

The role of clinical research evidence is particularly noteworthy. In this survey, the most important source of evidence from clinical research was RCTs in critically ill children. When considering evidence from other populations, RCTs in critically ill adults were more important than those in neonates or other children. In spite of very different bodies of RCT evidence, the importance of RCTs in critically ill children was not different across the five scenarios. Despite being ranked as the fourth most important factor, the importance of RCTs did not vary with practice patterns; the association between the importance of RCTs and frequency of intervention use in each scenario was not significant. This may suggest that there is considerable uncertainly and clinicians arrive at different conclusions about the results of the trials and the implications for their practice. We hypothesize that this is due to the nature of many of these trials. Published RCTs in pediatric critical care are often small and of modest quality; the median number of children randomized in PICU RCTs was 49 and only 4% were judged to be at low risk of bias.[43] This is consistent with our finding that few respondents considered the body of evidence for the intervention in the five scenarios to be of high quality and those who did also rated RCTs as more important. The role of clinical research evidence in particular is clearly complex and context-dependent; it may be better understood using qualitative research methods or a mixed-methods design (a combination of qualitative and quantitative approaches).[59]

Published guidelines were rated quite low (8^{th}) as factors influencing clinical decisions. This is particularly relevant as guidelines are often key elements of knowledge translation

and quality improvement initiatives. The stated relatively low importance of guidelines (and unit policies or protocols, which were also rated quite low) may be due to several factors: lack of guidelines, the quality and relevance of any available guidelines, the quality of the underlying evidence base, or clinician attitudes toward these tools in general. Future research should evaluate which of these are important in a particular context, as the potential solutions are quite different. We hypothesize that the quality of the underlying evidence may be an important contributor because, in this survey, those who rated the quality of evidence as moderate or high rated guidelines as more important and those with research experience rated them as less important. Opinion leaders were rated as more important than guidelines and, as in other clinical areas, may be a useful way to influence practice.[60] The variability we observed in the importance of opinion leaders may contribute to the variability in effectiveness observed in other studies.[60] Any intervention to change practice should also consider the targeted clinicians' characteristics. Experience, both clinical and in research, had minor effects on the importance of specific factors. However, profession and frequency of use had more important effects, thus customizing strategies for pharmacists and physicians or different practice patterns may be helpful.

Strengths of this survey include rigorous development and analytic methods, scenarios that are commonly seen in clinical practice and views of two disciplines involved in drug management: pharmacy and medicine. An important challenge in survey research is the extent to which the results are representative of the larger population of interest. Here, we used a multifaceted strategy to identify all potential respondents, and we had representation from all regions in Canada and all but one centre. In addition, the response rate was reasonably high; the median response rate in published surveys of critical care clinicians is 63%.[61] This survey has some limitations. We did not do formal reliability testing of the instrument and, as in all surveys, we report the respondents' stated views and practice, which may be different from their actual views and practice. Finally, we do not know the relevance of these results to clinicians practicing in other countries for two reasons. First, the importance of the specific factors that clinicians

consider may vary with different resources, health systems, and local medical or cultural norms. For example, we hypothesize that drug cost may be more important where ICU care is not publicly funded, unlike in Canada, and unit policies and opinion leaders may be more important in other cultures or countries. Second, the specific factors we included in the questionnaire were selected because of their potential relevance by our team of Canadian clinician researchers and testers; other factors such as legal concerns, other costs, and parental expectations may be more relevant to clinicians working in other healthcare systems.

Conclusions

Critical care physicians and pharmacists consider multiple factors when making decisions about medications in critically ill children. Although we identified several important factors in these scenarios, there was considerable variability. The clinical context and clinician characteristics, particularly established practice patterns, are associated with significant differences in the importance of many of these factors. Because of this, knowledge translation interventions tailored to address identified barriers may be worthwhile in pediatric critical care.

Chapter five:
High-quality randomized controlled trials in pediatric critical care:
A survey of barriers and facilitators

Abstract

Importance: The care of all critically ill children should be informed by evidence from large high-quality RCTs. Unfortunately such evidence is not always available.

Objective: To identify barriers and facilitators of conducting high-quality RCTs in pediatric critical care, from the perspective of trialists in this field. Our secondary objective was to assess the relationship between respondent characteristics and differences in their ratings of individual barriers and facilitators.

Design: Self-administered online survey.

Participants: We surveyed authors from each of the 294 pediatric critical care RCTs published as of June 2015. 116 researchers from 25 countries responded, with at least one author from 143 (47%) of the published RCTs in pediatric critical care.

Interventions: None.

Main outcome and measurements: The primary outcome was respondents' ratings of the barriers and facilitators on 7-point scales with 1 corresponding to "not a barrier at all" or "not an effective facilitator" and 7 corresponding to "a very large barrier" or a "very effective facilitator".

Results: Respondents reported a median (IQR) of 21 (15, 26) years of experience and 41 (36%) had authored more than one RCT. Survey respondents – when compared to non-respondents – had published more trials and their trials were more often cited. Of the barriers listed, the 5 most important were primarily funding-related. The 5 most effective facilitators were: protected time for research, ability to recruit participants 24 hours per day/7 days per week, conducting RCTs in collaboration with a research network, funding from government agencies specifically for RCTs in critically ill children, and academic department support for conducting RCTs. Respondent experience and country income level were associated with differences in importance ratings for 8 of 41 barriers. There were fewer such differences for facilitators.

Conclusions: Lack of funding and time are major barriers to conducting pediatric critical care RCTs worldwide. In addition to increased funding, respondents identified other strategies within the purview of the pediatric critical care research community, in particular research networks, to facilitate the conduct of the rigorous RCTs needed in this highly vulnerable population.

Introduction

The care of all critically ill children should be informed by evidence from high-quality randomized controlled trials (RCTs). Unfortunately, such evidence is not always available. Only 294 RCTs have been published in this field. RCTs in pediatric critical care are typically small, with a median sample size of 50 children, and are difficult to complete; one third of RCTs that report their planned sample size are stopped early, most commonly because of futility or recruitment problems.[43]

Completing RCTs is challenging in any field – in two recent observational studies 21% of registered surgical RCTs[62] and 28% of RCTs from all fields approved by 6 Research Ethics Boards were stopped early.[63] Others have suggested that important barriers include insufficient funding, burdensome regulations, excessive monitoring, complex trial procedures, restrictive interpretation of privacy laws, and lack of training and education about trial methodology.[64] Some solutions to overcome these barriers have been proposed.[64,65] Experts typically recommend changes to peer-review funding models and priorities and reducing administrative barriers[66] or recommend specific methodologic approaches such as simpler trials and alternative approaches to consent.[65] While these are undoubtedly important, there may be other important facilitators, especially facilitators under the control of individual researchers and group, in the context of pediatric critical care. Although these are important in any area of research, there are likely context-specific. We do not know how these, and other barriers and facilitators, apply to pediatric critical care. With a clearer understanding of the barriers that pediatric critical care researchers face and the strategies they use to overcome these, our overall goal was to

identify effective initiatives to improve the conduct of rigorous RCTs in pediatric critical care. The primary objective of this survey was to identify the self-reported barriers to, and facilitators of, high-quality RCTs in pediatric critical care. The secondary objective was to assess the relationship between respondent characteristics and differences in their ratings of individual barriers and facilitators.

Methods

Questionnaire development

We were interested in the barriers that respondents faced in their personal experience as a researcher conducting RCTs. For facilitators — to avoid missing those that may be very effective, acceptable and feasible but were not encountered by many researchers — we focused on their opinions on the potential effectiveness of specific facilitators, whether or not these facilitators applied to their RCTs. Because the results of this survey might inform initiatives to improve the conduct of RCTs, we classified the barriers and facilitators into 3 categories: those that are largely within the purview of the research community (e.g. trial design, research networks), those that are largely within the purview of the broader PICU community of researchers and clinicians (e.g. culture of research in the PICU, attitudes towards rescue therapy), and those that are largely external to the PICU (e.g. funding, the number of critically ill children).

We used a systematic approach to survey development and testing.[67] The domains for the questionnaire were: 1) respondents' ratings of the importance of specific barriers to RCTs in pediatric critical care, 2) respondents' ratings of the effectiveness of specific facilitators of RCTs in pediatric critical care, and 3) respondents' demographic characteristics. We generated potential items within these 3 domains with content and methods experts within our research group, from previous publications,[64,66,68,69] and by polling 5 pediatric critical care clinician-researchers. We then categorized items, combined similar items and eliminated redundant items. In the questionnaire we presented the barriers and facilitators in groups: the need for research, the clinical environment, research design and

planning, ethical and regulatory approval, consent, RCT conduct, funding, and researchers. Finally, we revised the questionnaire based on feedback from 8 clinician-researchers with experience in critical care RCTs who tested its clinical sensibility, evaluating its comprehensiveness, ease of use, and face validity.

In the questionnaire (Appendix D) we asked respondents to rate the importance of 41 barriers and the effectiveness of 42 facilitators using 7-point Likert-type scales with 1 corresponding to "not a barrier at all" or "not an effective facilitator" and 7 corresponding to "a very large barrier" or a "very effective facilitator". Finally, we asked respondents to name the 3 most important barriers and the 3 most effective facilitators, including any additional items we did not include in the survey. We extracted each researcher's affiliations, the number of RCTs they have published and specific trial characteristics from the RCT publications. We used the Cochrane Risk of Bias Tool to assess the risk of bias for each RCT.[14] To measure their impact we used the impact factor for the journal of publication from the 2013 Journal Citation Reports® (Thomson Reuters, 2013) and the number of times per year each trial was cited since publication using Science Citation Index Expanded™ (Thomson Reuters, 2014).

Sampling frame

Our population of interest was researchers who have published at least 1 pediatric critical care RCT. First we identified RCTs in pediatric critical care published in any language using PICUtrials.net (searched Jan 8, 2015). This database uses robust search strategies and duplicate study screening and data extraction to identify and describe published RCTs in pediatric critical care.[43] Next, we identified an email address for 2 researchers per RCT: (in order of preference) the corresponding, first, or last listed author. We used the RCT publication, other publications, and university and hospital websites to obtain email addresses. We included 2 researchers per RCT to increase the number of potential respondents and to capture a range of research experience and roles, assuming that the primary author would be the most responsible for that particular study and the last author would be the most experienced.

Survey administration

We sent each potential respondent a personalized email with a link to the electronic questionnaire in March 2015 and sent 3 reminders at approximately 2-week intervals to non-responders. We used SurveyGizmo® to administer the survey, which was approved by the Hamilton Integrated Research Ethics Board.

Statistical analysis

In describing the survey respondents, we reported continuous data as medians (interquartile range) ([IQR]), and binary data as counts (percent). We used chi-square and t-tests to compare the characteristics of respondents to researchers who were not approached or who did not respond. and $p<0.05$ as the criterion for statistical significance. We used means and 95% confidence intervals (CI) to summarize the respondents' ratings of the importance of barriers and effectiveness of facilitators. We used linear regression to examine the relationship between respondent characteristics and their ratings of the importance of specific barriers and effectiveness of specific facilitators. The researcher characteristics we included as potential explanatory variables were the number of RCTs they had published, their number of years of experience, the income level of their country of origin, and if they had conducted a multi-centre RCT. We chose these variables because we hypothesized that they would be associated with differences in the barriers faced by the researchers and the opportunities available to them. To adjust for multiple testing, we used $p<0.01$ as the criterion for statistical significance. Two reviewers examined the responses to the 2 open-ended questions ("What are the top 3 barriers to conducting high quality RCTs in pediatric critical care?" and "What are the top 3 facilitators of conducting high quality RCTs in pediatric critical care?"), grouping similar types of barriers and facilitators. We used these responses to identify any additional types of barriers and facilitators. For all analyses, we used the actual number of respondents for the denominator. We used R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) to conduct the statistical analysis.

Results

Survey Respondents

We found a valid email address for 367 trialists, with at least one from 270 (92%) of the 294 published pediatric critical care RCTs. Of these, 116 (32%) responded. Respondents were co-coauthors of 143 (49%) of the published RCTs. Most RCTs (66%) were represented by a single respondent, 28% by 2 respondents, and 6% by 3 respondents. The mean percentage of questions not answered by respondents was 7% overall, 1% for rating barriers, and 13% for rating facilitators. Respondents were from 25 countries (Figure 5.1) and 78% were from high-income countries. Respondents reported a median (IQR) of 21 (15, 26) years of pediatric critical care experience and coauthored between 1 and 12 RCTs. When compared to other researchers (i.e. who were not approached or who did not

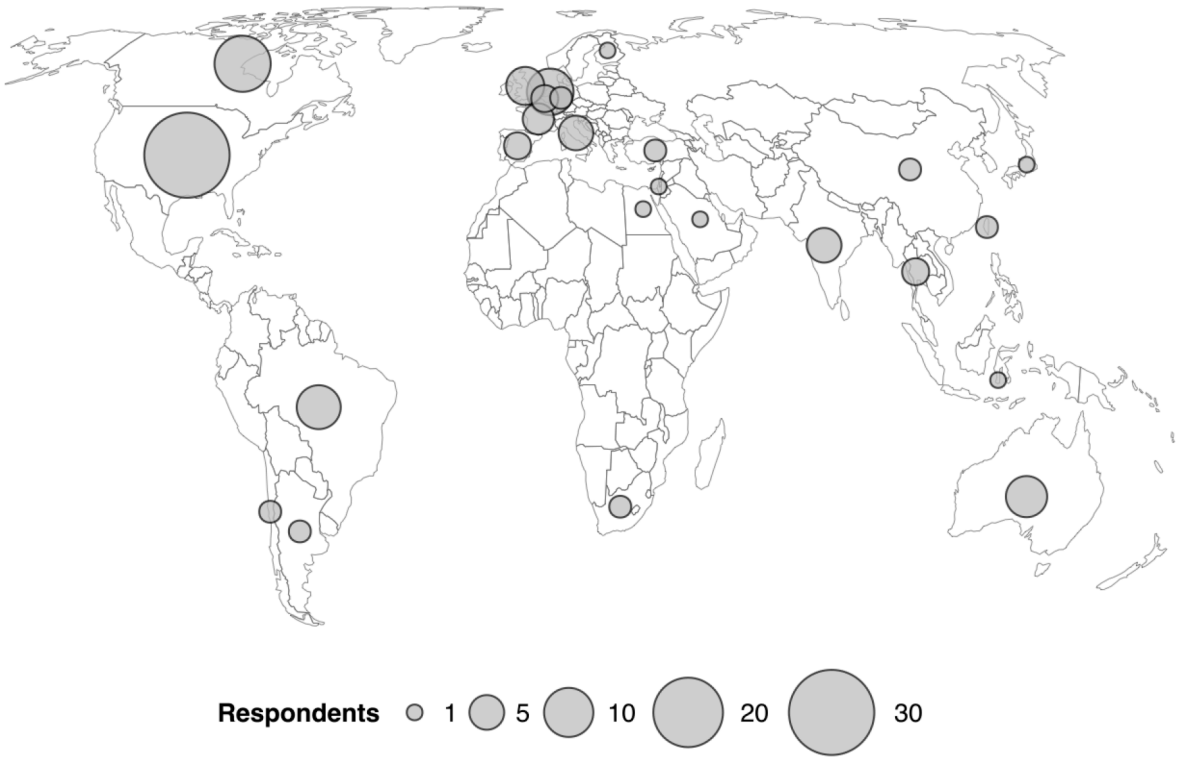

Figure 5.1. Survey respondents per country. The area of each circle is proportional to the number of respondents from that country. We used the affiliations listed in the most recent RCT publication to determine the country of origin for each respondent.

respond), respondents had more often published more than one RCT and their RCTs were more often conducted in collaboration with a research network and were more frequently cited. Other key features were not different (Table 5.1).

Table 5.1. Characteristics of survey respondents, other researchers, and RCTs

Characteristic	Respondents (n=116, representing 143 RCTs)	Other researchers[a] (n=1448, representing 151 RCTs)	p value
Researcher characteristics			
From a high-income country	90 (78%)	1103 (78%)	0.81
Published more than one RCT	41 (35%)	192 (13%)	<0.001
RCT characteristics			
Region			
North America	57 (40%)	57 (38%)	0.65
Europe	35 (25%)	37 (25%)	
Asia	26 (18%)	35 (23%)	
South America	16 (11%)	12 (8%)	
Australia/New Zealand	7 (5%)	5 (3%)	
Africa	2 (1%)	5 (3%)	
Multinational	14 (10%)	8 (5%)	0.18
Multicentred	35 (25%)	21 (14%)	0.03
Conducted by a research network	12 (9%)	1 (1%)	0.001
Children randomized	50 (36, 127)	50 (29, 81)	0.07
At high risk of bias	58 (42%)	66 (44%)	0.72
Citations per year, median	2.4 (1.1, 4)	1.5 (0.5, 2.7)	<0.001
Journal impact factor	3.1 (2.2, 6.1)	3.7 (2.3, 5.5)	0.85

[a]Other researchers includes both non-respondents, those we could not contact and those we did not invite to participate because they were not a first or last author of a published pediatric critical care RCT.

Importance of specific barriers

Figure 5.2 shows respondents' ratings of the barriers in their personal experience as a researcher conducting RCTs. Four of the 5 most highly-rated barriers were funding-related and the other was *the coordination required for multinational RCTs*. Table 5.2 shows the 5 most highly-rated barriers within each of 3 categories: those largely within

the research community, those largely within the control of the broader PICU community of researchers and clinicians, and barriers and facilitators that are external to the PICU. When we grouped the free-text responses to the question about the top 3 barriers, the 5 most commonly reported types of barriers were funding (22%), researcher time (12%), regulatory (9%), population characteristics (7%), and ethical (7 %). Few respondents identified additional barriers that we had not included in the questionnaire: expertise of research staff (5%), a culture of research (2%), and equipoise (2%).

Effectiveness of specific facilitators

Figure 5.3 shows the respondents' ratings of the perceived effectiveness of the individual facilitators. The 5 most highly-rated facilitators overall were *protected time for research*, *ability to recruit 24h per day/7 days per week*, *conducting RCTs in collaboration with a research network, government funding for RCTs in critically ill children*, and *support from academic department*. Table 5.2 shows the 5 most highly-rated facilitators within each of 3 categories: those largely within the research community, those largely within the broader PICU community of researchers and clinicians, and those that are external to the PICU. When we grouped the free-text responses to the question about the top 3 facilitators, the 5 most commonly reported types of facilitators were funding (23%), researcher time (19%), staff and infrastructure (11%), collaboration (10%), and a culture of research (8%). Respondents identified 2 additional types of facilitators that we had not included in the questionnaire: a culture of research (8%) and characteristics of the study (7%).

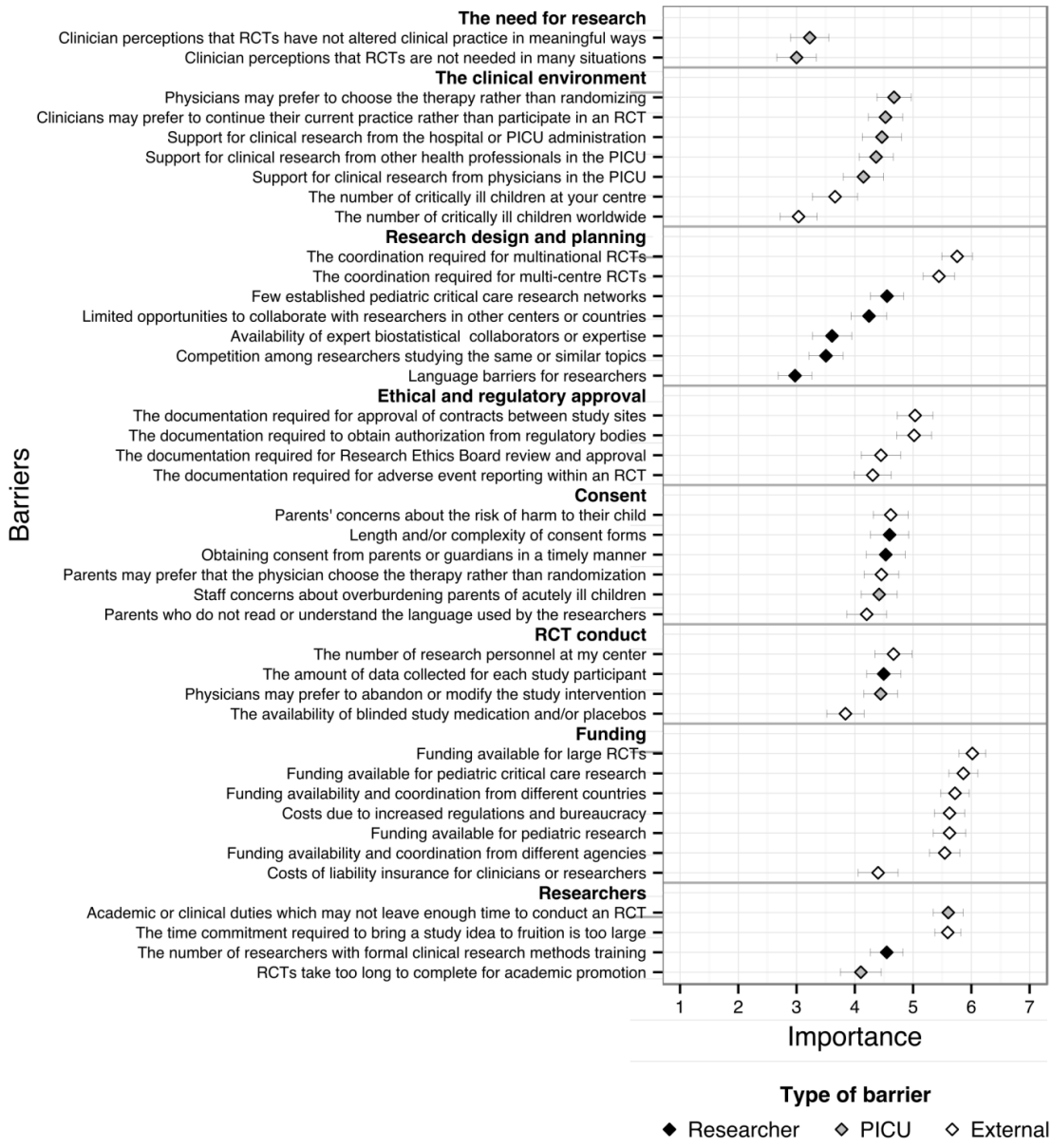

Figure 5.2. Respondents' ratings of the importance of barriers to RCTs in pediatric critical care . Error bars show the 95% confidence interval for the mean.

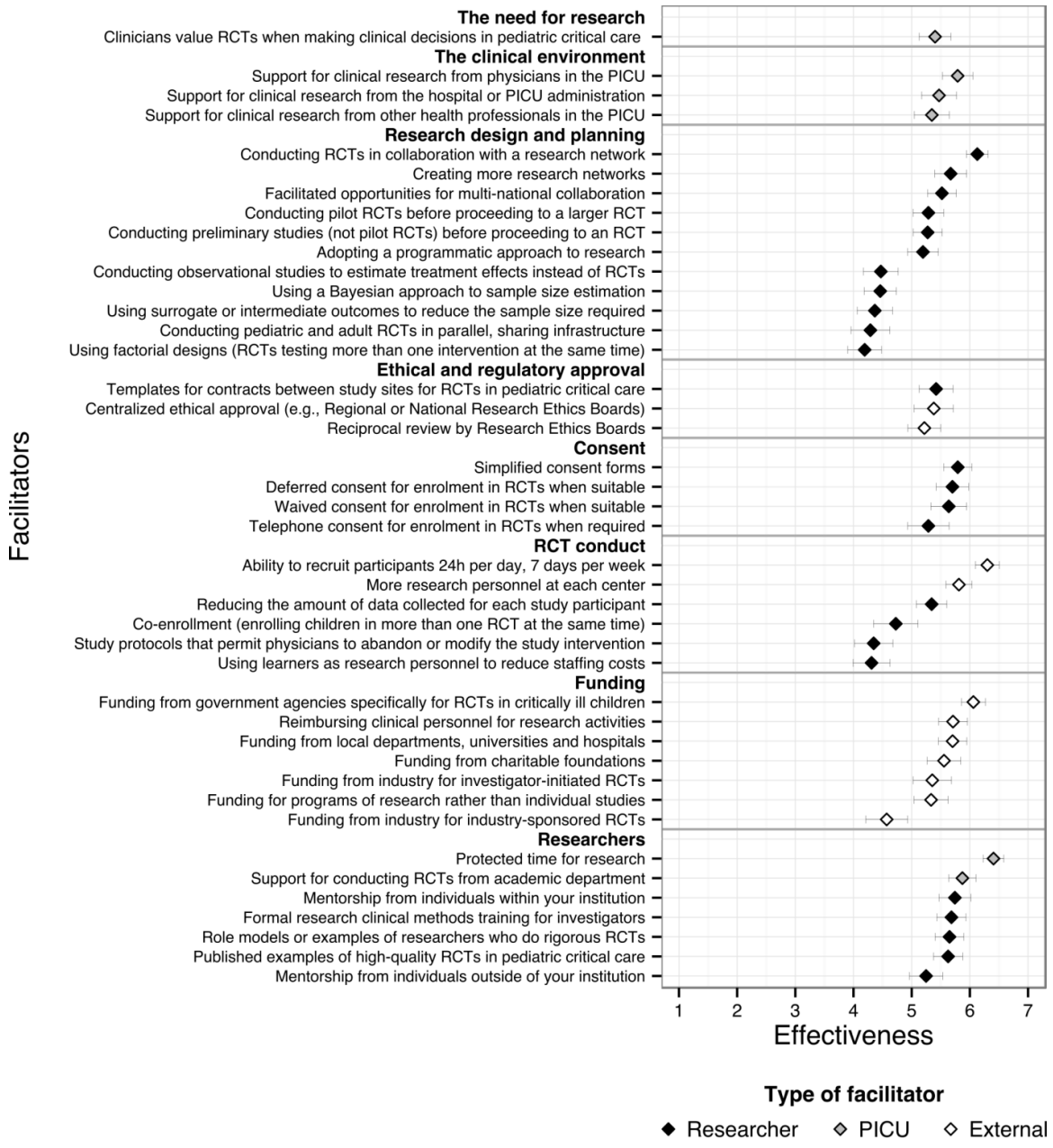

Figure 5.3. Respondents' ratings of effectiveness of facilitators of RCTs in pediatric critical care . Error bars show the 95% confidence interval for the mean.

Table 5.2. Five most highly-rated barriers and facilitators for each category: researchers, PICU, and external.

Category	Barriers		Facilitators	
	Ranking	Rating[a]	Ranking	Rating[a]
Researchers	1. Length and/or complexity of consent forms	4.6 (1.8)	1. Conducting RCTs in collaboration with a research network	6.1 (0.9)
	2. Few established pediatric critical care research networks	4.6 (1.5)	2. Simplified consent forms	5.8 (1.2)
	3. The number of researchers with formal clinical research methods training	4.5 (1.5)	3. Mentorship from individuals within your institution	5.7 (1.4)
	4. Obtaining consent from parents or guardians in a timely manner	4.5 (1.8)	4. Deferred consent for enrolment in RCTs when suitable	5.7 (1.4)
	5. The amount of data collected for each study participant	4.5 (1.9)	5. Formal clinical research methods training for investigators	5.7 (1.3)
PICU	1. Academic or clinical duties which may not leave enough time to conduct an RCT	5.6 (1.3)	1. Protected time for research	6.4 (0.9)
	2. Physicians may prefer to choose the therapy rather than randomizing	4.7 (1.6)	2. Support for conducting RCTs from academic department	5.9 (1.2)
	3. Clinicians may prefer to continue current practice rather than enroll in an RCT	4.5 (1.6)	3. Support for clinical research from physicians in the PICU	5.8 (1.3)
	4. Support for clinical research from the hospital or PICU administration	4.5 (1.8)	4. Support for clinical research from the hospital or PICU administration	5.5 (1.5)
	5. Physicians may prefer to abandon or modify the study intervention	4.4 (1.6)	5. Clinicians value RCTs when making clinical decisions in pediatric critical care	5.4 (1.4)
External	1. Funding available for large RCTs	6.0 (1.3)	1. Ability to recruit participants 24h per day, 7 days per week	6.3 (1.0)
	2. Funding available for pediatric critical care research	5.9 (1.4)	2. Funding from government agencies specifically for RCTs in critically ill children	6.1 (1.0)
	3. The coordination required for multinational RCTs	5.8 (1.4)	3. More research personnel at each centre	5.8 (1.2)
	4. Funding availability and coordination from different countries	5.7 (1.3)	4. Reimbursing clinical personnel for research activities	5.7 (1.2)
	5. Costs due to increased regulations and bureaucracy	5.6 (1.4)	5. Funding from local departments, universities and hospitals	5.7 (1.2)

[a]Mean(SD)

Association between ratings of barriers and facilitators and respondent characteristics

We used linear regression to examine the relationship between respondent characteristics and their ratings of the importance of each barrier or effectiveness of each facilitator. Table 5.3 shows the barriers and facilitators for which there was a statistically significant association with at least one respondent characteristic and Table D1 shows the results for all the barriers and facilitators. There were statistically significant differences among the respondents for 8 of 41 (20%) of the barriers but only 1 of 42 (2%) of the facilitators. More years of pediatric critical care experience was associated with lower importance in 4 of the 8 barriers. There were also geographical differences. Compared to researchers from low- or middle-income countries, those from high-income countries rated *limited opportunities to collaborate with researchers in other centres or countries* and *few established pediatric critical care research networks* as less important barriers and *the documentation required for Research Ethics Board review and approval* and *costs due to increased regulations and bureaucracy* as more important barriers.

Discussion

In this self-administered survey, researchers who have published a pediatric critical care RCT rated funding, time, and coordination for multicentre and multinational RCTs as the most important types of barriers they have faced in conducting their RCTs. In addition to protected time for research and funding, respondents rated research networks, mentorship, and support from academic departments and PICU physicians as the most effective facilitators of high-quality RCTs. When considering only those facilitators that are largely within the control the pediatric critical care research community, respondents rated research networks, simplified consent forms and mentorship as the most effective facilitators.

Table 5.3. Association between respondent characteristics and differences in the ratings of individual barriers and facilitators using linear regression

Barriers and facilitators	Participant variables			
	Years of experience	Number of RCT publications	Country income level[a]	Multicentred RCT completed[b]
Barriers				
Support for clinical research from physicians in the PICU	-0.06 (-0.10, -0.02) p=0.008	0.07 (-0.17, 0.31) p=0.56	-0.07 (-0.92, 0.79) p=0.88	0.73 (-0.07, 1.53) p=0.08
Support for clinical research from other health professionals in the PICU	-0.06 (-0.09, -0.02) p=0.002	0.02 (-0.17, 0.22) p=0.82	-0.23 (-0.93, 0.47) p=0.53	0.36 (-0.28, 1.00) p=0.27
Support for clinical research from the hospital or PICU administration	-0.06 (-0.10, -0.02) p=0.008	0.13 (-0.1, 0.37) p=0.28	0.32 (-0.52, 1.16) p=0.46	0.33 (-0.45, 1.10) p=0.41
The coordination required for multi-centre RCTs	-0.06 (-0.09, -0.02) p=0.002	-0.07 (-0.25, 0.12) p=0.50	0.28 (-0.4, 0.96) p=0.42	0 (-0.63, 0.62) p=0.99
Limited opportunities to collaborate with other centres or countries	-0.03 (-0.07, 0) p=0.06	-0.14 (-0.32, 0.05) p=0.16	-1.33 (-2.01, -0.66) p<0.001	-0.5 (-1.13, 0.12) p=0.12
Few established pediatric critical care research networks	-0.01 (-0.05, 0.03) p=0.58	0.03 (-0.16, 0.21) p=0.79	-1.05 (-1.73, -0.37) p=0.003	-0.67 (-1.3, -0.04) p=0.04
The documentation required for REB review and approval	0 (-0.05, 0.04) p=0.85	0.05 (-0.18, 0.28) p=0.68	1.17 (0.33, 2.00) p=0.007	-0.23 (-0.99, 0.54) p=0.57
Costs due to increased regulations and bureaucracy	0 (-0.03, 0.03) p=0.95	0.03 (-0.16, 0.21) p=0.78	0.92 (0.27, 1.58) p=0.007	0.02 (-0.58, 0.63) p=0.94
Facilitators				
Using learners as research personnel to reduce staffing costs	-0.06 (-0.09, -0.02) p=0.005	0.06 (-0.14, 0.26) p=0.56	0.25 (-0.49, 0.99) p=0.51	-0.41 (-1.09, 0.27) p=0.24

The table shows the results of the multivariate analysis, reporting the coefficient (95% CI) and p-value for each covariate. Shaded values are statistically significant (p<0.01). This table includes only barriers and facilitators for which there was at least one statistically significant association with a respondent characteristic. Table D1 shows the results for all the barriers and facilitators. [a]Respondents from a high-income country vs. middle-income country. [b]Respondents who have published a multicentred RCT vs. those who have not.

External barriers were generally rated as more important than PICU or Researcher barriers; however, this was not the same for facilitators, where there were no major differences among the categories. This is encouraging as many external barriers may be more difficult to address (e.g. the availability of funding, or the number of critically ill children) without multi-pronged approaches. The results of this survey suggest 3 foci for initiatives to improve the number and rigour of RCTs in pediatric critical care: increasing collaboration and mentorship, building a culture of research among clinicians and academic departments, and increased funding dedicated to pediatric critical care research. These 3 foci sometimes are interdependent and synergistic, while also addressing researcher, PICU, and external barriers and facilitators. A single intervention or initiative is not likely to be successful overall for all investigators and all RCTs, as the importance of many barriers varied with researcher experience and among countries. Indeed, the results of this survey suggest that some facilitators such as research networks may serve to address different barriers in different countries or for researchers with different levels of experience. For example, there were no significant differences in the respondents' ratings of the effectiveness of research networks as a facilitator, but those from low- or middle-income countries and those who had completed a single centre study rated the lack of research networks as a more important barrier.

Developing and expanding research networks to increase collaboration and mentorship is a particularly attractive strategy. Lack of research networks was rated as the second most important barrier and the most effective facilitator within the control of pediatric critical care researchers. Such networks may also help to overcome other barriers identified by respondents and implement other effective enablers such as alternate approaches to consent and simplified consent documents. Opportunities for mentorship and collaboration would be important, particularly for more junior researchers, as experience was associated with differences in the importance of many barriers. Networks may be particularly important for researchers in middle-income countries, who identified collaboration and research networks as more effective facilitators and the lack of these as

more important barriers. Pediatric critical care research networks include the Canadian Critical Care Trials Group,[70] the Pediatric Acute Lung Injury & Sepsis Investigators, and the National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network, but these have an inconsistent and limited geographic reach on a global scale.

Successful research networks, increased research activity and increased evidence from trials can also be important parts of initiatives to foster a culture of research among PICU clinicians, administrators, and academic departments. Such an organizational culture that appreciates clinical research may result in increased value that clinicians place on RCTs when making decisions in clinical care and building support from academic departments and hospital and PICU administration. With increased support, researchers are more likely to obtain designated time for research and colleagues' agreement to randomize patients, both of which were identified as important barriers and effective facilitators by our survey respondents.

Finally, while funding was rated as the most important barrier and stated to be one of the most effective facilitators, this may be one of the most difficult barriers to address. Researchers can collaborate to influence the priorities of research funding agencies to increase the absolute amount of funding for RCTs in pediatric critical care. Perhaps the convergence of increased researcher productivity, fruitful collaboration, effective mentorship and an established culture of research will all be advantages as researchers seek funding.

While the importance of many barriers varied with researcher experience and country of origin, there were fewer differences in respondents' ratings of the effectiveness of individual facilitators. We hypothesize that this is because many facilitators may be effective in different contexts – but in different ways. For example, collaboration within a research network may provide less experienced researchers access to the expertise they need, which is still helpful but perhaps less crucial for more experienced investigators; a research network may also facilitate collaboration with many centres caring for many

patients potentially eligible for larger trials conducted by more experienced researchers, while this feature of networks may be relatively unimportant for less experienced researchers initiating smaller pilot trials very early in their career. The questions we posed in our survey may also be a factor. We asked about the actual barriers that respondents faced. In contrast, we asked opinions on the effectiveness of specific facilitators, whether or not these facilitators applied to their RCTs. While not all respondents have encountered some of the facilitators, we posited that they would be able to judge their effectiveness. By design, survey respondents were more experienced than other pediatric critical care researchers whom we did not invite or who did not respond. Respondents' RCTs were also different – more often multicentred, conducted in collaboration with a research network, and cited more frequently.

Strengths of this survey include a rigorous approach to identifying published trials and broad inclusion criteria. We believe that the results of this survey reflect the views of the broad pediatric critical care research community as the respondents have conducted almost half of the published RCTs in this field. We received responses from researchers in 25 of 33 countries who have published an RCT and the geographic distribution of respondents reflects the distribution of the published RCTs. We also confident that we included the most important barriers and effective facilitators in the questionnaire. Few respondents named barriers or facilitators in the free-text questions. This survey also had some weaknesses. All of the respondents finished and published at least one trial — and indeed were more experienced than non-respondents. Thus their perspectives may be different from researchers who have not started a trial or who did not complete a trial. Finally, we conducted this survey in English although 6% of the RCTs are published in languages other than English.

Conclusions

Lack of funding and time are major barriers to conducting rigorous pediatric critical care RCTs worldwide. In addition to increased funding, respondents identified other strategies within the purview of the pediatric critical care research community, in particular research networks, to facilitate the conduct of the rigorous RCTs needed in this highly vulnerable population.

Chapter six:

Improving the randomized controlled trial evidence in pediatric critical care:

The perspectives of trialists

Abstract

Importance: Clinical research is a complex scientific and social enterprise. Strategies for improving the evidence from RCTs in pediatric critical care must consider this complexity. Furthermore, successful strategies are likely to be very context-dependent.

Objective: To identify strategies that pediatric critical care trialists consider to be acceptable, feasible and effective to improve the evidence available from RCTs in pediatric critical care.

Design: Qualitative descriptive study based on semi-structured interviews.

Participants: 26 pediatric critical care researchers from 7 countries who have published an RCT (2005-2015). We used purposive sampling to achieve diversity with respect to the characteristics of the researchers (country of origin, experience, and profession) and the characteristics of their RCTs (size, number of centres, and stopped early or not).

Interventions: None

Main outcome and measures: We used an inductive approach to data analysis, collecting and analyzing the data concurrently in an iterative process. We used qualitative descriptive techniques to analyze interview transcripts to understand participants' multiple perspectives and experiences.

Results: Most participants (24 [92%]) were from high-income countries, 8 (31%) had published more than 1 RCT, 17 (65%) had published a multicentre RCT, and 8 (31%) had published a multinational RCT. An important theme that emerged was *building communities* — groups of individuals with similar interests, shared experiences, and common values, who are bound together by professional and personal relationships. Participants described a sense of community as a source of motivation and as a means to enable larger, more rigorous trials by enhancing collaboration, increasing researcher and clinician engagement, and creating and maintaining enthusiasm. Strategies to build communities focused on the importance of in-person interactions (both professional and

social), capable leadership, and trust. Another important theme was *getting started as an investigator*. Participants stressed the importance of specific research training (in addition to clinical training) and high-quality experiential education collaborating on other people's projects, guided by effective mentorship. Also important was *working within the system* — ensuring fair recognition and academic credit for all research contributions, not just for being the principal investigator. Participants also made specific suggestions for improving the design and conduct of trials.

Conclusions: Experienced trialists shared practical strategies to increase the rigour, efficiency, and impact of individual trials. They also identified several methods to improve the pediatric critical care research enterprise including building a sense of community, and ensuring key training and relevant practical experiences for new investigators.

Introduction

The care of all critically ill children should be informed by evidence from high-quality randomized controlled trials (RCTs). Unfortunately, such evidence is not always available. Only 320 RCTs have been published in this field, and they are typically small, with a median sample size of 50 children. RCTs in pediatric critical care are also clearly difficult to complete; 30% of the RCTs that reported their planned sample size were stopped early, most commonly because of futility or recruitment problems.[43]

Completing RCTs is challenging in any field. 21% of registered surgical RCTs[62] and 28% of RCTs approved by 6 Research Ethics Boards in Switzerland, Germany, and Canada were stopped early.[63] Others have suggested that important barriers include insufficient funding, burdensome regulations, excessive monitoring, complex trial procedures, restrictive interpretation of privacy laws, and lack of training and education about trial methodology.[64] Some solutions to overcome these barriers have been proposed.[64,65] Experts typically recommend changes to peer-review funding models and priorities and reducing administrative barriers[66] or recommend specific methodologic approaches such

as simpler trials and alternative approaches to consent.[65] While these are undoubtedly important, there may be other important facilitators, especially facilitators under the control of individual researchers and group, in the context of pediatric critical care.

This study builds on a survey done to identify the self-reported barriers and facilitators of conducting high-quality RCTs in pediatric critical care. 116 authors of published pediatric critical care RCTs (31.6%) from 25 countries responded. The 5 facilitators that respondents rated as most effective were: protected time for research, ability to recruit participants 24 hours per day, 7 days per week, conducting RCTs in collaboration with a research network, funding from government agencies specifically for RCTs in critically ill children, and academic department support for conducting RCTs. Of those facilitators that are largely under the control of the PICU research community, the 5 most effective were: collaboration with a research network, simplified consent forms, mentorship, deferred consent for enrolment when suitable, and formal research clinical methods training for investigators. Respondent experience and country income level were associated with differences in the importance of many barriers, but there were fewer differences for facilitators. To expand on the results of the survey we used a qualitative approach as it acknowledges that context is important for many facilitators, that any strategy for improvement is likely to include more than one facilitator, and that balancing acceptability, feasibility and effectiveness is a challenging endeavor that requires a more nuanced approach.

The need to improve the quality of the RCT evidence may be served by conducting more RCTs overall — or indeed fewer, focusing efforts on high priority questions, conducting more large multi-centred trials and improving the conduct and reporting of trials. The objective of this study is to identify strategies that pediatric critical care trialists consider to be acceptable, feasible and effective ways to improve the evidence available from RCTs in pediatric critical care.

Methods

This is a qualitative study using individual semi-structured interviews with pediatric critical care trialists to explore and understand their multiple perspectives and experiences.

Study population

The population of interest is clinical researchers in pediatric critical care who have successfully completed and published an RCT. We anticipated that these individuals would have the best insight into the acceptable, feasible and effective strategies to improve the evidence available from RCTs in pediatric critical care.

Sampling strategy

The goal of this sampling strategy was to identify individuals who are the best sources of information to allow us to address the study question. We used a regularly updated scoping review of published pediatric critical care RCTs to identify researchers.[43] We then used a multi-step purposive sampling process to select individuals to approach for participation:[71]

1. **Criterion sampling:** We selected the first and last authors of pediatric critical care RCTs published since 2005. We chose the first and last authors to capture a range of research experience and roles, assuming that the primary author would be the most responsible for that particular study and the last author would be the most experienced. We selected researchers who published in the past 10 years to ensure that the participants' experiences reflect contemporary pediatric critical care research.
2. **Maximum variation sampling:** We used purposive sampling to achieve diversity with respect to the characteristics of the trialists (country of origin, experience [number of published RCTs], and profession [physician vs. non-physician] and the characteristics of the RCTs they have published (size, number of centres, and stopped early or not). We selected these characteristics based on our own hypotheses and the results from the survey of trialists. To achieve this diversity, we

used the matrix shown in Table 6.1 rather than attempt to recruit a representative sample. Each participant may be represented in more than one cell; for example, a non-physician who has conducted more than 1 RCT would appear in at least 2 cells. We attempted to recruit participants until we achieved at least 5 participants in each of the cells.

Table 6.1. Participant sampling matrix

Characteristics Rationale	**Levels to sample from**	
Researchers		
Country We hypothesize that effective strategies may vary among countries.	Countries in the top 10 most productive (RCTs per country)[a]	Other countries
Country income level We hypothesize that effective strategies may vary among country income levels.	High-income countries	Middle-income countries
Experience The expertise and experience gained by the who have completed more than one trial may indicate expertise or resources that may be relevant to our objectives of identifying strategies to improve RCTs.	1 published RCT	>1 published RCT
Profession We anticipate that non-physicians may face different barriers.	Non-physician	Physician
RCTs		
Size The 90th percentile for the number of children randomized=220	<220 children	>220 children
Number of countries The expertise and experience gained in successfully completing one of the few multi-national trials may indicate expertise or resources that may be relevant to our objectives of identifying strategies to improve RCTs.	Single country	Multinational
Number of centres The expertise and experience gained in successfully completing one of the few multi-centred trials may indicate expertise or resources that may be relevant to our objectives of identifying strategies to improve RCTs.	Single centre	Multicentred
Early stopping Successfully completing a trial may indicate expertise or resources that may be relevant to our objectives of identifying strategies to improve RCTs.	Stopped early	Not stopped early

[a]United States, Brazil, India, China, The Netherlands, Canada, Australia, Germany, Italy, UK.

Participant recruitment

To choose researchers to approach for participation, we sorted the eligible researchers in descending order of the number of their publications and contacted each researcher in turn. We skipped any who we are unable to contact or who declined to participate, and oversampled particular groups if needed to achieve participant diversity. We sent personalized emails with a single reminder to potential participants, inviting them to participate. We continued recruitment until we reached data saturation (no new information or themes were identified in the analysis of the interviews).[72] We determined when data saturation occurred by consensus among 2 investigators who interpreted the findings.

Data collection

One investigator (MD) interviewed the study participants in person, by telephone or videoconferencing, depending on the preferences of the study participant. The preamble to the interview reminded the participants that the purpose of the study was to help future trialists benefit fully from the experience of experienced trialists, and that the focus of the interviews would be on RCTs, on facilitators rather than barriers, and on those strategies that individual researchers and groups of researchers can do rather than on external factors (e.g., the number of critically ill children).

The interviewer used an interview guide (Appendix E) including questions, prompts and suggestions for administering the interviews. We developed the guide in discussions with our research group composed of pediatric and adult critical care clinicians and researchers with a range of content and methods expertise and experience. We pilot-tested the content and format of the interview guide by interviewing 3 critical care researchers who were not eligible to participate in the study. The interviewer used a flexible approach, deviating from the guide and following other relevant lines of inquiry if introduced by the study participant, thereby adapting the interview guide if needed. The interviewer made field notes during and immediately after each interview recording.

We digitally recorded audio portion of the interviews then they were professionally transcribed verbatim. The interviewer reviewed all transcripts for accuracy, comparing them to the recording if necessary. This study was approved by the Hamilton Integrated Research Ethics Board. Each participant gave tacit consent for participation by booking a time and date for the interview, then explicitly confirmed their consent for participation and audio recording verbally at the start of each interview.

Analysis and reporting

We used an inductive approach to data analysis, collecting and analyzing the data concurrently in an iterative process. We used a qualitative descriptive approach to analyze the interview transcripts.[20] The first step in analysis was coding the interview transcripts. Two investigators (MD and MS) independently coded 4 transcripts using content analysis with open coding, without the use of a predetermined list of codes.[73,74] From this, we developed a preliminary list of codes and used this to code the remaining transcripts. Two investigators coded the transcripts. One investigator (MD) reviewed all coded transcripts. All changes and uncertainty were discussed at regular coding consensus meeting to ensure that as the coding evolved that there was still consistency. We incorporated any new codes that emerged from the data into the list of codes. All changes to the coding were documented in an audit trail and we applied any new codes to previously coded transcripts.[75]

After coding we organized the codes into meaningful categories. We reviewed and discussed with the aim of achieving consensus on the categories among the investigators. To improve our understanding of the data we used 3 types of triangulation.[76] We used methods triangulation: comparing the results with the results of a previous self-administered quantitative survey we have conducted on this topic. We used source triangulation: comparing the data from participants from different countries and with different levels of experience. We also used investigator triangulation: 2 investigators from different backgrounds (one with experience in pediatric critical care clinical research and one with extensive qualitative and quantitative — including RCTs —

research experience) coded transcripts, and all investigators reviewed and discussed the results).

When presenting the results of this study, we used anonymous quotations from the participants to highlight important findings. In addition to the data from the interviews, we also report participant characteristics including country of origin, years of experience, and the characteristics of the trials they have published. When reporting participant characteristics, we report continuous data as medians (interquartile range [IQR]), and binary data as counts (percent). We used NVivo 10.0 (QSR International, Melbourne, Australia) to manage the qualitative data.

Results

Description of participants

Of the 115 pediatric critical care researchers we invited, 26 participated and 3 declined. The remainder did not reply. 25 trialists participated in the interviews (14 by telephone, 8 by videoconferencing, and 3 in person) and 1 answered our questions via email. Table 6.2 shows the characteristics of the study participants. Most, 24 (92%) were from high-income countries. Excluding the preamble, the interviews were a median of 39 minutes long and varied in length from 22 to 50 minutes. In addition to the interview transcripts, we also included in the analysis an editorial authored by a participant because they referred to it in

Table 6.2. Characteristics of study participants

Characteristics	**Participants** (n=26)
Country	
United States	12 (46%)
Canada	5 (19%)
Netherlands	4 (15%)
Australia	2 (8%)
Brazil	1 (4%)
Indonesia	1 (4%)
Spain	1 (4%)
Profession	
Physician	20 (77%)
Experience	
Years of clinical experience	23 (20, 28)
Published more than 1 RCT	8 (31%) (max=5)
Published a multicentre RCT	17 (65%)
Published a multinational RCT	8 (31%)
Published a trial not stopped early	21 (81%)
Published a large RCT[a]	9 (35%)

Data are n (%), median (IQR), unless otherwise specified. [a]More than the 90th percentile (220) with respect to children randomized

the interview.

Table 6.3 outlines the 4 major themes that emerged from the participant interviews: *building communities, getting started as an investigator, working within the system,* and *building on success*.

Table 6.3. Central themes from participant interviews

Theme	Strategies to improve the research enterprise
Building communities (Creating a sense of community within groups of individuals with similar interests, shared experiences, and common values, that are bound together by professional and personal relationships.)	Creating opportunities for in-person interactions (both professional and social), capable leadership, and trust through: • collaborating on trials and other research studies • establishing and expanding formal research networks • increasing the profile of research at professional society meetings
Getting started as an investigator (How trialists begin their careers in clinical research.)	Creating opportunities for: • specific research training in addition to clinical training • high-quality experiential education • effective mentorship
Working within the system (How trialists navigate the challenges imposed by the clinical and academic systems within which they work.)	Finding a match between the goals for their research career and the centre's institutional priorities and culture Engaging and motivating administrators, clinicians and researchers through enthusiasm and a sense of community showing the secondary benefits of participating in research, and showing productivity to increase: • institutional support (i.e. resources, infrastructure, and time) • fair recognition and academic credit for all research contributions, not just for being the principal investigator
Building on success (Past successes increased the chance of future successes.)	Create opportunities for: • researchers to collaborate with other successful researchers (e.g. through research networks) • new investigators to succeed early in their careers (e.g. collaborating on other researcher's studies before leading their own)

Building communities

One central theme that emerged from the participant interviews was *building communities* — groups of individuals with similar interests, shared experiences, and

common values, that are bound together by professional and personal relationships. This theme was apparent in both the participants' description of their own research successes and in their recommendations for improving the state of research in pediatric critical care.

Participants tended to describe a sense of community as a source of motivation — for them and for others — and as a means to enable larger, better trials by enhancing collaboration (often referring to access to patients), increasing researcher and clinician engagement, and creating and maintaining enthusiasm.

> *"Each one of us wants to improve the life of a child, but by collaborating in a larger group, we can make another kind of difference. I think that's what should drive us, we cannot do it on our own. I think that's important and what's in it for other people to collaborate."*
>
> *"Clinical research is a team sport and you make and you keep friends."*
>
> *"…around the world we've set up people that we've collaborated with forever and I can always count on those folks. But that takes a long time to build that relationship."*
>
> *"It's that sense of community so you can vet your ideas and then vet your protocols and develop relationships within the meeting and then outside of the meeting."*
>
> *"Definitely within the clinical trials networks, the community that's provided is enormous because you go to those meetings and you are commiserating with other people who are trying to get the same things up and running."*
>
> *"Any ICU that continues to participate in trials just keeps you on the edge. You know, you're on the cutting edge, if you will, and you're in the discussion and you're part of the process so I think that the energy and the psyche behind it is just as important as actually participating in the study…just that you are part of that process."*

Participants mentioned other benefits of community, including opportunities to reduce duplication through coordination of efforts, priority setting, and facilitating training new

researchers. Some researchers expressed worries about competition for funding and patients, and the potential for other researchers to steal their ideas while others reported that those worries were largely overstated. Participants in both ends of this spectrum of opinions stated that an increased sense of community, and in particular a culture within the community and leadership that discouraged this, could reduce this risk. Personal relationships, and a history of successful collaboration were also important in reducing the risk of other researchers appropriating ideas. Many researchers stressed the importance of carefully choosing collaborators based on personal relationships, an individual's reputation for productive collaboration and integrity, and a history of successful collaboration.

> *"You have to pick the people you want to work with carefully because your friends will get it done."*

Trust was another important theme in building communities. Participants stressed that they preferred to work with investigators with a track record for successful collaboration, particularly those recommended by investigators with whom they had already worked.

> *"Most mistrust is misguided. And that is, most of the time you can trust people but identifying who you can trust is not always easy and I do think face-to-face time is very, very valuable. That's why I like the [research network] meetings and so forth because you're getting people in the same room. You're getting them to socialize and see each other outside of their professional scope."*

In addition to talking about their experiences with building and working within communities, participants also proposed strategies to build and sustain communities. Some were based on their experience and others on what they believed would be effective and practical. Common themes in these strategies were the importance of face-to-face interactions, personal relationships, effective leadership, and trust. Participants described building many different types of communities at different levels. Important examples were building a community within a trial, the role of research networks in building community, and the role of professional organizations in building community.

Building a community: within a trial

Participants stressed the importance and effectiveness of building a sense of community within a particular trial — among the investigators, research staff, site investigators, and clinicians. In their views, the primary benefits were increased efficiency and enrolment, generating excitement and interest in the trial, and reducing clinicians' concerns. Some noted that enthusiasm and commitment to friends were more effective motivators than financial compensation. Specific strategies that participants recommended (Table 6.3) focused on regular communication, in-person interaction, fair recognition for their efforts, friendly competition, and valuing the intellectual contribution (not just the patients enrolled).

> *"It's the realization that it's a social world. People have many things that they could be doing. For people to put energy into your trial, if it's multi-centred, they need to feel it is of value. You need to reach people through your values."*

> *"The personal contact will always give you a bit more confidence, make you enthusiastic, feel if you're on the same level, if you have the same goal."*

Some participants also stressed the need to sustain and nurture the trial community. This was of particular importance for trials with low recruitment at each centre and for trials that were conducted over a long period of time.

> *"...but like all trials, it takes a lot of... you know, you've got to water the garden...put water on the grass a couple of times a week or it'll stop growing."*

Building communities: the role of research networks

Many participants identified formal, investigator-initiated research networks as very effective strategies for building communities. Most had direct experience with a formal networks such as PALISI or the CCCTG, whereas other participants without network experience thought that these or similar networks would be effective.

Participants cited many advantages of the community created by research networks, including opportunities to collaborate with and learn from more experienced investigators and to recruit study centres from among the membership. They reported that collaborating with a network could improve the design of research studies though input from a wider range of investigators, which could in turn increase their chances of success in procuring funding and then completing the study because of the network's established record of success. Interview participants also considered research networks to be a valuable vehicle to improve the training and experience of novice investigators (both those early in their career and those with more clinical experience, but limited research experience) through more mentorship, the chance to build a network of collaborators, and high-quality experiential education obtained through participating in other research studies.

> *"I'm pretty optimistic about this…there are a lot of unintended, positive consequences of participating in these things. Even if you don't get the answer you expected or the answer that you wanted, it's fun… It's important that you feel you are contributing to sort of a different level. So [research with a network] allows for that to happen. Individual, you know, trials…experiments done in an institution by a single investigator…those are hard."*

> *"And so I had a few people join in because they knew if they joined in they would learn how to do clinical research in a very systematic way and so they saw it as, really, an internship. So that was kind of cool."*

> *"Invite people who are interested in pediatric research or critical care research without obligating them to actually do any research. And they listen to science being debated and they listen to trials being designed but when you actually look down at the core, there are, perhaps, ten or fifteen serious investigators that are designing trials and when they make their presentation, at the end of the presentation they say, 'Who might be interested?' And then, you know, somebody who came to this simply to get intellectual stimulation and perhaps have an opportunity to ski in a nice location realizes that they just listened to something that really prickled their ears. And so, they raise their hand and say, 'You know, we might be*

> *interested in that.' And then they meet with the investigator afterwards and they've made a contact. And I think we don't have too many of those types of opportunities."*

Participants stated that the key elements of a successful network included an open, safe environment to share and improve ideas, in-person meetings, effective leadership, and a membership model that included a core group of members, but also less-experienced investigators who could attend without having to be undertaking a study or presenting their research.

> *"I'll tell you exactly what makes that group effective. It's the attitude that people go to that meeting with. It's open; it's a lot of senior investigators and then a lot of young investigators. The format is such that new ideas are presented in a really non-threatening environment. And it's collaborative. And I just think it's being done, largely, by people that, you know, are not seeking personal gain…but are doing it more in the spirit of, 'let's ask some interesting questions and actually see if we can make a contribution'. So I think it's, more than anything, just attitude…and it's been developed in that way."*

> *"I think, when you're starting, you need a community…you need people who are trying to do the same thing."*

> *"I think networking is huge. I think being open-minded enough and resilient enough to ask questions. We think we're all-knowing but I think it's very honest to just call somebody and go, 'Look, this is what I've seen. What's up?' We need to trust one another. We need to develop strong networks with like-minded people that are pro research, that are multi-disciplinary."*

Participants believed that networks initiated with small groups of researchers who know each other are easier to form and more likely to expand their scope and endure over the years.

> *"Perhaps you should start small. That has something to do with this personal contact, with this collaboration and trust each other and having the confidence that we're doing it together. If you're going for the big networks from the start, that will be very difficult."*

They also stressed the importance of leadership by experienced researchers with an established research career who can focus on developing and mentoring other researchers. One particularly important aspect of effective leadership identified was helping to shape the culture within the community.

> *"I think that whenever you decide whether to join something, it's important to look at who's in charge of it and do they have the track record of including other people and being fair. I think it all depends of the leaders and there is something to be said of picking leaders who are secure enough, that their career is mature enough, that their goal is to advance things, internationally, to the next level. They don't need to go through anymore promotion process and this and that, you know? …You kind of have to pick people who are in charge who are inclusive and collaborative."*

Some participants with research network experience also highlighted some of the problems they encountered as networks become larger. As one participant described, with more members it becomes difficult to maintain the sense of community critical to the success of the research networks:

> *"And some people have left because they don't feel it has the same culture it did at the beginning. It's gotten big, more business-like and people complain it's intimidating."*

Most of the existing pediatric critical care research networks are based in a single country.[77] The majority of participants were generally positive about increasing international collaboration, but reported that it is often challenging, if not infeasible, to coordinate funding and regulatory approvals and to overcome language barriers and practice differences.

Building communities: the role of professional societies.

Participants reported that professional societies (such as the Society of Critical Care Medicine [SCCM], European Society of Intensive Care Medicine [ESICM], European Society of Pediatric and Neonatal Intensive Care [ESPNIC], and World Federation of Pediatric Intensive and Critical Care Societies [WFPICCS]), and in particular their specific

conferences, could be useful avenues to help build communities. Most participants thought that building on existing meetings and conferences would be more useful than holding new meetings at different times and locations. Participants generally found that traditional professional conferences were very clinically focused. They had 4 specific suggestions to increase their relevance for researchers and help to build communities:

1. Increase the profile of clinical trials and other research in the general sessions targeted at clinicians to draw attention to the gaps in the evidence and research methods and stimulate interest among clinicians (and perhaps increase their interest in participating in research).

> *"And you can't maintain enthusiasm going to meetings, in my opinion, if you're not participating in the process. If you just go and observe…and never roll up your sleeves.. sooner or later, you just kind of either lose interest or, you know, you just don't know enough of the people to….to learn."*

2. Hold sessions for researchers (and particularly new investigators) to learn research methods and practical research skills and to share strategies for procuring funding and completing trials. Some participants recommended this approach as they considered that the problems encountered by many trials were similar.

> *"…it's a completely different topic…but the problems encountered were similar. How do you recruit? How do you ask informed consent? How do you manage two or more trials in one centre? How do you start adding centres? How do you do this? What's the right timing for informed consent in the PICU? How do you get centres involved and how do you deal with, 'okay, yes we will include patients and we are completely ready to include them'…but then don't include patients. So how do you deal with these things? I think that's independent from the topic."*

> *"That whole process can be really intimidating to a junior person. At the national and international meetings, workshops and stuff for junior faculty [would be helpful]: 'How do you do research?, How do you get funding?, How do you get started?'."*

3. Hold sessions or meetings focused on research in a specific clinical area. Some participants recommend this approach as it would useful for setting research priorities (and perhaps including clinicians) and planning large trials.

4. Create opportunities to meet other researchers outside of professional settings. Facilitating face-to-face interactions and social interactions were identified as particularly important strategies.

> *"After going to meetings a couple of times and seeing an individual a couple of times a year, you start to realize, 'Well, I can call this person on the phone.' And you're…at some point you can send them email asking them blunt questions and you can get blunt answers back and you develop a level of trust where you're going to be able to accomplish something."*

> *"We did build up trust with each other in our network. We worked on that. If you know each other and, for example, you go to the golf course every now and again or you drink a beer together or whatever, that helps; that really helps. That…that's the way to build on trust."*

Most of the participants' discussion about community and collaboration was focused within pediatric critical care researchers. Some participants did highlight the importance of working with different disciplines and professions. A few participants did say that one potentially effective, and rarely used approach, was sharing infrastructure with researchers in other fields such as adult critical care or other pediatric specialties.

Getting started as an investigator

Another important theme that emerged from the interviews was *getting started as an investigator* — how participants began their careers in clinical research and their ideas on what would be effective for novice investigators. When participants talked about how they became a clinical researcher, *learning by doing* was a common theme: most reported that they learned much from their first trial and would do many things differently in a future trial.

> *"[I learned] by doing. And making mistakes. And trusting my supervisor. He's done it before; he's published before, so he probably knows what it takes but…whoa, there's a lot of stuff we did not do so well, previously. And so it's learning by doing and I think you could think about better training programs for this."*

Those that had started in clinical research by collaborating as a site investigator, co-principal investigator, or other collaborator reported that this approach was particularly valuable and allowed them to learn important skills, particularly the practical aspects of protocol implementation.

> *"…that concept of how you move from a research idea to a full blown, multi-centre randomized trial, I think that whole trajectory is something that a lot of people don't see and they kind of go, 'Okay, I have an idea,' and, they write a proposal for a big, multi-centre randomized control trial and then they're surprised it fails? I think that's important. And it kind of comes with the job but it's not that you can go somewhere to learn this."*

There were important differences among the participants when asked about their training. Most referred exclusively to their clinical training and few had formal research training.

> *"We don't do a great job with our medical trainees of integrating things like study design and statistics into medical training. We just tell them, 'You have to come out with a project,' but we don't [train them]. It'd be crazy if they said, you have to come out of a cardiology Fellowship knowing how to do an echocardiogram but they never taught you how to do it. That's nuts…so why is this any different?"*

> *"We make an assumption that most of our friends and colleagues who have clinical expertise in some area actually know how to do clinical trials."*

Those who mentioned research training most often referred to laboratory or clinical research conducted during their clinical fellowships. Only a few participants described having had formal research training.

> *"I don't think we have enough physicians and other clinicians who actually have received formal, rigorous training in carrying out and implementing clinical trials. I think the real obstacle is that they don't know that they don't know how to do it."*

> *"I had zero formal [research] training in my fellowship. I was lucky enough to be exposed to basic science, or animal lab, which I have not taken now into my practice. But it did expose me to, you know, asking the question, that kind of thing. And it was during my fellowship that I joined the [research network]. So it was that exposure to the [research network] that got me interested in getting more formal training."*

Most participants received their research training through an apprenticeship model: learning by working with a more experienced researcher. They highlighted the impact and importance of effective mentorship in developing their skills as a clinical researcher, and in particular the need for an independent research program.

> *"I think getting the opportunity as being relatively junior, to be part of a trial…I learned a lot from that part, just being part of these studies even if you're not the PI and you're not the complete junior investigator but the median person…Because then it's worth it to do all that legwork for the study. I think that really helped me get a lot of independence. Doing it, but on the same time, you're not on your own."*

> *"And the mentorship really has to be somebody who has experience. In clinical research you need the 'A' mentor who has had success in doing it because a lot of people can help but they can't really help when you start running into some things that you just don't find in the textbooks. So you can't look up stuff and say, 'How can I improve my consent rate?' or 'How do I deal with somebody who always finds an exclusion criteria even when it's a long shot?'"*

> *"Find a mentor but find a mentor…who's 'been there, done that' and would take pride in watching their mentee be very successful."*

Finally, clinical and research training was important for building connections with other researchers; many participants reported that the relationships and collaborations they established in their training continued to be important after their training was complete.

Working within the system

The third important theme that emerged from the interviews was *working within the system* — as participants described how they navigated the challenges imposed by the clinical and academic systems within which they work. Participants stressed 2 types of challenges: the institutional priorities of the hospital or university where they practiced and appropriate recognition for their research contributions.

Participants talked about the importance of finding a good match between the goals for their research career and the culture and institutional priorities of the hospital and university. Some participants recommended joining a more supportive institution if possible, but most recommended strategies for working within the culture and systems in their centres. There were 2 types of institutions that posed particular challenges, particularly in the extremes. First were institutions in which the load of clinical work did not leave sufficient time for research. One common element of the approaches that participants recommended for this type of institution was showing the secondary benefits of research.

> *"The institutions totally saw it as a loss and essentially told people that they couldn't participate in the trial because it wasn't going to be profitable. We tried hard to talk to people and talk to them about the secondary gains of participating in research."*
>
> *"We've been able to convince the hospital over the years that this is… so valuable that they help us pay for the coordinators….I think if you're just starting it, people just need to be convinced. If you practice Pediatric Intensive Care, you can't be good, you gotta be great. I mean, these are people's kids. People don't want to take their kids to a 'good doctor', you know, any more than you or I want a… 'good pilot', right? You don't want a 'good pilot'. You want a great…great pilot. So, I…my pitch is, you can't be a great critical care unit unless you're part of the dialogue."*
>
> *"If you're going to be a nationally recognized children's hospital, you have to do research… If you want to get, you know, US News or World Report, or whatever ranking you consider important, it's really is about research,*

> *education, Fellowship training…you know – academics. People expect you to provide excellent clinical care, so you don't get much credit for that. So my pitch is, if you want to do all that and you want excellence and you want to recruit excellent people, they're not going come to an institution that doesn't do research. Because they recognize that, in terms of either their personal career or the kind of medicine they're going to be able to practice, it's going to have a ceiling unless you really try to go to the next level which requires research and academics and funding and that sort of thing."*

> *"If you talk to the people who participated [in the study], they can definitely say that the patient care improved along with nursing excitement about conducting a study that had direct applications for their practice. And so, that was definitely a secondary gain that you can talk to people about."*

Other participants stressed the importance of showing productivity as part of advocating for change.

> *"I think that there are people that are in leadership positions that can exert some influence on Deans and Vice Presidents about this [importance of clinician-researchers] and I think there is progress that's actually being made."*

> *"I think credibility is probably the biggest thing [for getting institutional support]. You just keep plugging away and working and…grants and manuscripts…the house of cards could collapse at any minute…but you do your best and just keep it up. Credibility and longevity."*

Also important was engaging and motivating administrators, clinicians and researchers – including those without extensive research experience – through enthusiasm and a sense of community. Some participants also highlighted the effectiveness of journal clubs and evidence-based practice initiatives to increase the profile of research, believing that these could lead to more interest in participating in research if there was sufficient expertise and institutional support.

> *"And that made them excited because they weren't going to be PIs and they weren't going to be able to do that but they cared enough to contribute to what was being developed in the field."*

> *"Hospital leaders are trying to [increase their academic profile]. Usually it starts with somebody's idea…We have Fellows who go there and it's interesting and stimulating and they discuss the latest literature and many of them have come from academic centres and would like to get started but don't know how. So, obviously, we try to make the…extend the invitation but there needs to be willingness of them to go along with it because it's all new and it's time consuming and it is a big thing to set up so. They've taken some initiative to say, 'We'd like to do this but we don't know how'."*

The second type of challenging intuitions was large, research-intensive centres that expected researchers to lead large multicentred trials. Some participants said that this impaired collaboration because of the intense competition in such an environment. For example, researchers at those centres may be less willing collaborate (including as site investigator or enrolling participants) in a study for which they were not the principal investigator.

> *"…our job here is to lead to and, if you're going to get promoted, to lead and be publishing and guiding and being in the forefront. We can't just use all the patients just to enroll in other trials and make it not available for things that are led by our own people. For those people's careers will definitely be harmed, 'cause it's pretty cutthroat here as far as the way they set it up for what it takes to get ahead and just helping enroll patients in trials isn't enough."*

> *"If you make [the network] up of these highly intensely, competitive hospitals that are competing with each other you're going to end up having some of those issues because those people live or die based on their publications and why are they helping the competition?"*

The participants did not have any solutions for this problem — and some participants at these leading centres did not consider this to be a problem. Others from smaller centres felt that this asymmetric relationship reduced their willingness to collaborate.

In addition to institutional fit, many participants talked about how important fair recognition for their contribution to research was for their career progress and personal satisfaction. Authorship was the form of recognition mentioned by almost all the

participants, but its importance varied among the participants, depending on their career goals and the stage of their career.

> *"...then I try to get everybody listed in as part of a group. And, for a lot of centres, that's enough. A lot of these people are enrollers and they just want to be part of a process and they want to enroll and get questions answered"*

> *"I'm a tenured, full professor. I ain't going anywhere. I'm not going to get a raise in salary. You know, I'm content to be a senior author if somebody wants to take the lead. The only difficulty with that is, you know, you'd have to do the work."*

> *"That's one of the benefits of being a clinical person [doing research], my job doesn't depend on that. You know, if I don't get an NIH grant I still have a job next year so I can still put food on the table which is kind of the way I like it."*

An important aspect was fair recognition for their contribution, but participants described that fair recognition was often challenged by disagreements and expectations by collaborators. Setting expectations for contribution and recognition early was effective, but they still struggled with ways to recognize the contribution of individuals, especially in a large trial.

> *"I really make sure any time I'm involved in any academic project, whether I'm the author or middle author or senior author, that we make clear from the very beginning what the author list is going to be."*

Several participants noted that changes to MEDLINE (allowing the listing of collaborators in addition to authors) have made it easier to recognize the contribution of site investigators and others.

Another important form of recognition – that often relied on authorship – was academic credit for research activities. Participants said that many institutions placed too much emphasis on authorship (particularly first authorship) and on leading trials. Most felt that academic credit systems that also valued the other ways of contributing to research such

as being a site investigator or enrolling children in trials would encourage more collaboration and large multicentre trials

Similar to their approach to institutions without sufficient time or resources for research, participants emphasized the need to build communities, advocate for change, to show the secondary benefits of participating in research, and demonstrating productivity.

> *"If you want your peers to recognize you and they're involved with the studies, they know. They know you're a part of it. If you're more involved in the leadership role than others and that sort of thing it's a different kind of recognition. It's a sort of a culture that most critical care people understand. That it's not about individual recognition, it's more about collective recognition....You know, you do enough of these and people get to know you enough then you actually get more recognition than you really anticipated or maybe even wanted."*

> *"There needs to be real expectation from that clinical investigator. For example, if you enroll two patients a year in a clinical trial that's not adequate to become an Associate Professor. On the other hand, if you build a program in your ICU that now has ten or fifteen research coordinators that are well trained and you involved yourself in ten or fifteen trials that are in multiple areas or you built a program that provides a clinical trial infrastructure and you're doing this on a really rigorous basis, then that should qualify for promotion to Associate Professor...and onward."*

Building on success

Another important theme that emerged from the interviews was *building on success* — the concept that past successes increased the chance of future successes. Participants mostly considered success to mean obtaining funding or institutional support for their research and completing an RCT as planned. This concept emerged at multiple levels: for the individual, institution, trial, research network, and for the field as a whole. Building a reputation for success was important in each of the major themes we identified: building communities, becoming an investigator, and working within the system.

Participants stressed that creating opportunities for researchers to collaborate with other successful researchers (e.g. through research networks) would be a successful strategy. Within the theme of building communities investigators considered a reputation for success as an important factor when choosing collaborators, preferring to work with investigators with a reputation for successful collaboration and high research productivity.

> *"So, it really is investigator to investigator demonstrating that they deliver and, you know, people get reputations in the field for delivering and not delivering."*
>
> *"You know, you kind of want to bet on the right horse."*
>
> *"They've come to know that if we do a study, it gets published…that's really helpful."*
>
> *"Well, the kind of obvious answer is…showing results; showing that networks work. That's the best thing to do because that's what we see now with our network. People are saying, 'Hey, they have a network. Hey, they have output. Hey, they have trust. That's working'."*

Creating opportunities for new investigators to succeed early in their careers may also be effective. When talking about training, participants credited early success as an important factor in the success of their subsequent career.

> *"We did this first study…I just was happy to be, you know, be part of the fun. And I kind of maintained that sort of disposition my whole career."*
>
> *"And there's nothing that sustains a process like a few wins. You know? And I think we've had a few good wins. And so it's kind of made it fun."*

Demonstrating research productivity was also important for working with the constraints of the system, particularly institutional support and funding. An important aspect was the design of the trial.

> *"That's a superb study that will give an answer. I think they did all of their homework, they were five years in designing that study. If these guys come*

> *up with the next study…I think they'll get funded. Because of what they've done previously."*

Participants identified research successes as an important aspect of maintaining enthusiasm and momentum within a particular trial and on an even larger scale – attracting funding and increasing the profile of research in pediatric critical care was perceived to become easier as the field produces more high-quality research.

Specific strategies for individual trials

In addition to the more general strategies (i.e. *building communities* and *working within the system*), participants also suggested specific strategies to improve the conduct of individual trials, summarized in Table 6.4.

Table 6.4. Strategies to improve conduct and rigour of individual RCTs

Strategy	Quotation
Trial design	
Ask an interesting and relevant question	*"If you pick a topic that people are very interested in and they want to be able to contribute into more clinical research, they volunteer."* *"Make sure that the question is an important question; that is not a question that is going to disappear next year; and that the question, when you get it answered, can lead to another question."*
Plan so any outcome is informative	*"There's only three results that can occur when you have a comparison. Either 'A' is better or worse or equal to 'B'. What are the ramifications for each of those three scenarios?"* *"Address an important question…designing a study, the result of which, whether positive or negative is going to be meaningful."*
Simplify the data collected	*"Collecting the data that pertains only to the research questions. Often we collect too much data and data's expensive. So spend a lot of time designing your case report form and item reducing. Really think these things through, especially the feasibility."*

Consider ancillary studies carefully	*"Even when clinical trials have null results for efficacy of the tested intervention, researchers can learn more about the patient population from banked specimens and clinical data."* *"You end up in a situation [with ancillary studies] where you could get an awful lot of things. The relatively simple task of getting urine on these kids may be an incremental task that reduces the certainty that the research coordinator will correctly collect [most important] samples at the right time."*
Preparation for the trial	
Consider pilot trials	*"It is important that researchers learn from mistakes related to these studies. [Pilot] trials are an opportunity to test many crucial aspects of clinical trial design, including feasibility of enrollment and patient selection."*
Test study procedures	*"Test your inclusion and exclusion criteria in those potential patients."* *"One thing I've learned is every time you make an inclusion or exclusion criteria, be very sure that you need to exclude those patients."*
Trial implementation	
Choose study centres carefully	*"If they have an existing coordinator that's definitely important. And secondly, if they have a point person or two who really have the time to do it; and three, if they have some track record of having done some trials before; and fourth is some pretty realistic evidence that they have a reasonable number of the patients for the trial."* *"We needed those individuals to really be there and to champion the intervention and to be screening and to be really invested in people doing the intervention correctly."*
Communication encourages enthusiasm	*"I did calls with each of the sites so that we could see what they were, you know, what they were doing, what they were contributing, the quality of their data, and ongoing support, as well."* *"We had routine conference calls throughout the duration of the trial, just to maintain people's enthusiasm over time so*

	that everybody bought into the critical nature of what they were doing to contribute to the success of the trial." *"Inform [the nurses] about why we do the study. Keep doing that. Doing a trial is so much about good communication. Don't forget people. Be sure, in between, to explain things. That's actually much more important that anything."*
Make the trial as simple as possible for the centres	*"If they're doing eighty percent clinical, they don't have the time to even think about it so you really have to make it so easy for them so that they don't have to think about the details of the study. You have to make it easy for them to participate."* *"By sharing our experience from the start but also by more support in how to deal with the administrative things and the trial management part."*
Effective research staff are critical	*"Local research coordinator presence is very important. Their style, the knowledge, the availability and cheerfulness and problem solving nature. It's the skills, the knowledge and personality of research coordinators help to illustrate the importance of research, the relevance of research, the responsiveness of the research team to a difficult family or some discomfort about the research. It's responding to questions about the research and the celebration of the research."* *"The attitude and personality are almost as important as the skills. They are largely responsible, dependable, reliable, interested, good interpersonally, communicate verbally, can talk with the bedside staff. That's the research interface, the public face, of research. I think the aura and image that they give off is actually quite important."*
Monitor study progress and provide feedback and support	*What you have to do, of course, is keep reminding people, you know, that, you know, this patient, you know, it's the ones that got missed, you say…you find out why they got missed and you keep reminding people, you know, when you put up…when you're putting people on fluid, put…you know, make sure they're in the trial.*

	And more follow-up, like, okay, so…and I think more close follow-up by a coordinator, not specifically one…one of the physicians but by a national coordinator who would go there, like, every month and say, "Okay, how is it going? Why is it not…how many patients have you recruited? How many patients were eligible? How many did you miss? Is there a reason you missed them," etc., etc. I think that may have helped.
Consent	
Use deferred consent where appropriate	*"We're now doing a trial and we ask for the deferred consent…I think that's a very, very good improvement."*
Train staff and researchers for approaching parents for consent.	*"I also tried to do it by not [having] too many people asking to get informed consent…so that you would get a sort of training. "* *"Certainly, we can all learn of how better to approach parents although I often think of it as being a bit of a sales job and I don't think that's what we should be doing; we should be offering them the opportunity and making it clear to them what the pluses and minuses are."* *"We organized a meeting in which we do role play and train new students how to ask for informed consent and also how to do it in the correct way…all the things you have to explain, how to explain it at the level which is understandable, things like that, I think we underestimate that. We should have done it, perhaps, ages ago but that's something which is very important."*
Advocate for pediatric research and engage the public and parents.	*"The public perception, if we could change that…I love it when I see a research study mentioned on the news because I think it heightens people's awareness that the only way we learn is through the scientific method and experimentation. Sometimes I think parents think we know everything when they come in and they're disappointed to think that there's a lot we don't know."* *"Getting it in the press, getting more attention to pediatric research is the only way because you've got to change*

	people's minds."
Use alternative approaches to providing information to parents	*"You could consider using video and more images instead of wording. I learned from a friend of mine…she asked the parents, 'How do you want to have the information?'"* *"I think, yeah, I think we should ask other experts…for example, I have a graphic designer who I ask for certain things to make [patient material]which look good but is also more reader friendly…we should, perhaps, put more energy in things like that."*
Building community	
Acknowledge contributions	*"They need to believe that they are appreciated for what they do. They need to understand they are crucial; it's not just 'nice to have'."*
Create opportunities for face-to-face interaction and personal connection	*"It's a social world. People have many things that they could be doing. For people to put energy into your trial they need to feel it is of value. You need to reach people through your values."*
Plan authorship	*"I've put a grid together of all the contributions and all the investigators and they have an opportunity to review it and so that it's agreed upon."*
Mentorship	
Include experienced mentors in the study team	*"In clinical research you need the 'A' mentor who has had success in doing it because a lot of people can help but they can't really help when you start running into some things that you just don't find in the textbooks. So you can't look up stuff and say, 'How can I improve my consent rate?' or 'How do I deal with somebody who always finds an exclusion criteria even when it's a long shot?'"* *"Find a mentor but find a mentor…who's 'been there, done that' and would take pride in watching their mentee be very successful."*
Include opportunities to mentor others	*"Other people would join in because they wanted to do clinical trials work. And so they saw it as an opportunity to hook on to an experienced investigator's research to learn*

	how to do it themselves, and get that level of mentorship that they really didn't have locally." *"I had a few people join in because they knew they would learn how to do clinical research in a very systematic way and so they saw it as, really, an internship."*
Knowledge translation	
Share the results so others can learn from your experiences	*"We've published at least two 'lessons learned' papers….we realized that [the trial] just wasn't working. This is another thing about networks that you have long-term memory and it's the aggregate of wonderful experience."* *"Its good to tell them that they'll have been a part of something that can change practice for the kids that we take care of. Letting them know when it gets published. Their name may not be on the paper but they really contributed to the outcome and the findings of the study."*

Discussion

Four major themes that emerged in this qualitative study of pediatric critical care trialists were *building communities, getting started as an investigator, working within the system,* and *building on success*. Within each of these themes the trialists suggested specific strategies to improve the pediatric critical care research enterprise. The participants also made specific suggestions for improving the design and conduct of trials.

The results of this study are consistent with our findings in a survey of pediatric critical care trialists. In the survey the 5 most effective facilitators of high-quality RCTs that are largely within the purview of the research community were: *conducting RCTs in collaboration with a research network*, *simplified consent forms*, *mentorship*, *deferred consent*, and *formal clinical research methods training for investigators*. In this qualitative study we did not ask participants to rank facilitators, but the experienced investigators suggested similar approaches. They also made specific suggestions to implement these, including organizing small research networks and steps to increase the research focus of

professional conferences. Particularly within the theme of *working within the system*, participants recommended strategies that encompassed the 5 most effective facilitators that are largely within the broader PICU community of researchers and clinicians: p*rotected time for research*, *support for conducting RCTs from academic department, physicians in the PICU, and the hospital or PICU administration*, and c*linicians value RCTs when making clinical decisions*. Participants also reported that demonstrating a history of successful research through research networks and effective training opportunities would increase researchers' ability to procure funding. Similarly, in the survey, respondents rated funding-related facilitators as the most important external factors.

Previous qualitative and mixed-methods research has examined the barriers to the conduct of RCTs.[68,69] Researchers themselves have also written about the barriers they face.[64] There has been less focus — and little original research — on the facilitators of RCTs. Experts typically recommend changes to peer-review funding models and priorities and reducing administrative barriers[66] or recommend specific methodologic approaches such as simpler trials and alternative approaches to consent.[65] This study adds an important perspective — while the participants in this did mention these approaches, we purposefully focused on strategies that individual researchers or groups of researchers could implement. A qualitative study including 13 pediatric trialists investigated the barriers and facilitators they face in the design and conduct of unbiased trials.[33] As in our study, protected time and research infrastructure were important facilitators. The other themes that emerged from the interviews were consistent with our themes of *building communities* and *building on success*: *ownership* (investigators take responsibility for generating support and ensuring rigour), *acceptance* (researchers' understanding of the clinical setting), *cohesive study team* (of experienced trialists and methodologists), and *verification* (a reliable review processes and guidance from trusted third parties).

Improving the research enterprise in pediatric critical care is not a simple process and there is not a single entity to prioritize and oversee the implementation of these strategies. It relies on the motivation of individuals and their enthusiasm will be

tempered by the difficulties (e.g. the heterogeneous patient population and need for multi-centre, and often multinational, collaboration) and the limited external pressures (e.g. there are no patient advocacy groups and limited commercial interest). Participants in this study emphasized the importance of advocacy by opinion leaders — experienced researchers with a reputation for successful research — and established research networks. The need for action at multiple levels further complicates efforts to improve the research enterprise. If any of these strategies are to be adopted, they will be adopted by a variety of actors: individuals, institutions, groups of researchers, formal research networks, and national and international professional organizations.

Strengths of this study include the relevant study participants with trial experience, data collection methods, and analysis techniques. We approached researchers who had successfully completed and published an RCT to gain insights to address this research question. A single interviewer (MD) conducted all of the interviews and reviewed all of the transcripts and coding. We also used a semi-structured interview guide with open-ended questions to avoid leading the participants. We did not define "improve" when we asked the participants how we can work to improve the state of RCTs research in pediatric critical care. This let participants focus on the aspects that they considered most important. We used a qualitative descriptive method with minimal interpretation of data, presenting and organizing the data in the language used by participants.

This study also has some limitations. Investigators who declined to participate may be less enthusiastic and interested in this topic; their views on what would be helpful to improve pediatric critical care research may be different. We only conducted the interviews in English, which may have been one reason why researchers from middle-income countries and smaller high-income countries (in terms of research productivity) were not well represented. Future studies should seek the views of such investigators, who may have more setting-specific comments. Finally we interviewed trialists who are only one part of the research enterprise. Individuals from granting agencies, industry, and hospital and academic administration will have different perspectives.

Conclusions

Experienced trialists shared practical strategies to increase the rigour, efficiency, and impact of individual trials. They also identified several methods to improve the pediatric critical care research enterprise including building a sense of community, key training and experiences for new investigators, and strategies to ensure fair recognition for their research efforts.

Chapter seven:
Discussion and conclusions

Introduction

The final chapter in this thesis begins with a brief summary of the results and conclusions of the 5 individual studies that comprise my thesis. Then I summarize the implications of this research program and its contribution to the wider body of knowledge. Finally, I discuss the strengths and limitations of the research program and suggest some avenues for future research.

Summary of the findings of the individual studies

How can we improve the evidence base in pediatric critical care? My overarching objectives in this thesis are to describe the RCT research enterprise in pediatric critical care — the process of creating it and the products of this work, along with problems and some solutions. To meet these objectives I undertook a series of 5 related studies, outlined in the previous 5 chapters.

First, I conducted a scoping review (Chapter 2) to describe the output of the research enterprise in pediatric critical care. In this scoping review we found 320 pediatric critical care RCTs, from 37 countries, published in 8 languages over the past 30 years. The majority of these RCTs were single-centred, focused on intermediate or surrogate outcomes and were small in sample size. Important aspects of their methodology and reporting remain less than optimal.

Second, I used social network analysis (Chapter 3) to describe the community of researchers who produce the evidence I identified in the scoping review. The research enterprise is highly fragmented and highly clustered, particularly geographically. The number of researchers, and their mean number of collaborators have increased over time but other important measures of the network structure have not dramatically changed

since the year 2000. The most important individuals and centres — ranked using a variety of measures — were most often from the United States and Canada.

Third, I conducted a scenario-based survey (Chapter 4) to better understand the importance of RCTs — and other factors — in clinicians' decision-making. We found that despite the gaps in the evidence from RCTs, many clinicians rated the overall quality of the evidence as moderate or high. They rated RCTs as the fourth most important factor they consider — after severity of illness, physiological rationale, and adverse effects. Respondents' ratings of the importance did not vary among the scenarios, suggesting that the quality of the available evidence is inadequate in all the scenarios. Respondents who rated the overall quality of evidence as moderate or high rated the importance of RCTs as being more important in their decision-making process. This implies that high-quality RCTs are likely to have an effect on clinical practice.

Fourth, I conducted a survey (Chapter 5) to better understand the barriers that pediatric critical care trialists face in undertaking RCTs. The 5 most important were primarily funding-related. The 5 most effective facilitators were: *protected time for research, ability to recruit participants 24 hours per day/7 days per week, conducting RCTs in collaboration with a research network, funding from government agencies specifically for RCTs in critically ill children*, and *academic department support for conducting RCTs*. There were statistically significant differences among the respondents for 8 of 41 (20%) of the barriers. Experience and geography had the most effects. For barriers, more years of pediatric critical care experience was associated with lower importance of support from 3 groups of colleagues (*physicians*, *other health professionals,* and *hospital or PICU administration*), and *the coordination required for multicentre RCTs*. There were also geographical differences. Compared to researchers from low- or middle-income countries, those from high-income countries rated *limited opportunities to collaborate with researchers in other centres or countries* and *few established pediatric critical care research networks* as less important barriers and the *documentation required for Research Ethics*

Board review and approval and *costs due to increased regulations and bureaucracy* as more important barriers.

Finally, I conducted a qualitative interview study (Chapter 6) to better understand the perspectives of pediatric critical care trialists on strategies to improve the evidence available from RCTs in pediatric critical care. Four major themes emerged in this qualitative study of pediatric critical care trialists: *building communities*, *getting started as an investigator*, *working within the system* and *building on success*. Within each of these themes the trialists suggested specific strategies to improve the pediatric critical care research enterprise. The participants also made specific suggestions for improving the design and conduct of trials.

Contribution to the wider body of knowledge

This program of research makes a new and important contribution to the field of pediatric critical care. First, for clinicians, the scoping review and the website serve to make RCTs more accessible. PICUtrials.net is a freely-available, regularly updated database of the published RCTs we identified in the scoping review. It includes citations, basic information about the trial and links to the PubMed record and journal website for each RCT. Users can search, browse the RCTs (by indication, intervention, population and publication year). Easy access to the trials and the ability to see the number and type of RCTs may increase clinician interest, raise the profile of both individual RCTs and highlight the gaps. The results of the survey of clinicians will also be useful to clinicians who are planning quality improvement and knowledge translation interventions. This will give them insight into the relative importance of many factors that clinicians consider when making decisions and how those vary among clinicians and contexts.

Second, for clinical researchers planning and conducting trials, the scoping review and the website will simplify identifying — and learning from — previous trials, performing systematic reviews, and identifying gaps in the literature. The results of the qualitative interview study have also highlighted strategies and techniques to make their research easier and more rigorous and to advance their research careers. For methodological

investigators, the scoping review, website and social network analysis will support other methodological research by simplifying searching for RCTs and data extraction. The list of RCTs and basic information about each RCT publicly can be downloaded from the website in a format suitable for analysis. We have also extracted additional data from each RCT that are not yet included on the website. When we complete future methodologic studies we will post the data on the website for other researchers to use.

Third, this program of research advances methodologic research, which is not well developed in pediatric critical care. This research program is the first systematic investigation into the research enterprise. All 5 studies are the first of their kind in pediatric critical care and may lead to increased interest in methodological research in this field. Identifying the RCTs for a particular field and maintaining the database of RCTs is feasible with limited resources only because of the small number of RCTs in pediatric critical care and the relative ease of identifying such trials. Similar initiatives of varying scale have been used in a variety of other fields, including: governance, financial and delivery arrangements and strategies to implement change within health systems (healthsystemsevidence.org); RCTs and systematic reviews of pediatric complementary and alternative medicine (pedcam.ca); RCTs, systematic reviews, and clinical practice guidelines in physiotherapy (PEDro.org.au); and RCTs of treatments for eczema (greatdatabase.org.uk).

This research program also takes a different approach from other methodologic reviews of RCTs in critical care, some of which included children. These have focused on RCTs published in a specific time frame or in high-impact, or in critical care journals. These may identify the most influential research, but likely overestimate the quality, making direct comparisons with our findings difficult. Such reviews have focused on citation impact (391 RCTs published between 1999 and 2012 in 6 high-impact journals randomizing more than 100 participants),[12] outcomes and statistical power (146 RCTs published between 2007 and 2013 in 16 high-impact general or critical care journals),[11] reporting (394 RCTs published between 1975 and 2010 in a single journal),[78,79] sample size

estimation (38 RCTs that used mortality as their primary outcome published between 1999 and 2009 in 5 high-impact journals).[80] The single systematic review of pediatric critical care RCTs focused on sample size calculations was published after the publication of this scoping review.[81] The authors identified 70 RCTs published between 2006 and 2011 by searching MEDLINE and found that there were important opportunities to improve the methods and reporting of sample size calculations. Our goal was broader: to describe the research enterprise in pediatric critical care. We included 320 RCTs published in 114 different journals (including both critical care, pediatric, and other types of journals). All of the types of questions posed in these prior reviews (while focusing on an entire field and specifically on pediatric critical care) can be addressed using our scoping review. The data we collected can be used to directly answer these questions, or to identify relevant RCTs for additional data extraction. In addition to describing the RCTs in pediatric critical care, we also examined collaboration among the researchers who produced these RCTs. Previous studies in critical care (not exclusively pediatric) have used bibliographic analysis to examine worldwide research productivity[82] and publication patterns in a single country[83] but have not used a social network analysis approach.

Finally, this research program makes a novel and important contribution to the broader pediatric critical care research community. It provides data to support the calls for more and more rigorous trials focusing on clinically important outcomes[84,85] and will allow researchers to follow the evolution of research methods in the field. Beyond describing the current state of research, the studies in this research program also provides insight into the forces that shaped the status quo, such as the heterogeneous patient population, need for — and barriers to — multi-centre and multinational collaboration, lack of patient advocacy groups, limited commercial interest, and a system whereby academic credit for research is highly dependent on authorship, and especially first-authorship. These forces have converged to create a clinical and research culture in which small, single-centred trials are the norm. The results of this research program will give researchers the data and strategies to challenge these norms, modify the status quo, and gradually improve the state of research in pediatric critical care.

Working to improve this research has parallels to knowledge translation in the clinical setting. This research program uses components of the knowledge-to-action cycle popular in knowledge translation.[86] Instead of the typical approach of improving patient outcomes by changing clinician behaviours, I focus on improving the research (that will in turn, eventually, improve patient outcomes) indirectly, through changing researcher behaviours. I identified problems — gaps in the evidence base — in the scoping review. I assessed barriers to knowledge use by researchers — important barriers to conducting rigorous RCTs and collaboration patterns — in the survey of trialists and in the social network analysis. I selected strategies to improve the state of research — effective facilitators and strategies to implement them — in the survey of trialists and the qualitative study. The other steps in the knowledge-to-action process (implementing interventions, monitoring knowledge use, evaluating outcomes, and sustaining knowledge use) are beyond the scope of this thesis. Like many knowledge translation endeavors, there are challenges. First, there is not a single entity to implement these strategies. If any of these are adopted, they will be adopted by a variety of actors at different levels: individual investigators, centres, collaborators, formal research networks, and national and international professional organizations. Second, measuring the success of any of the interventions I have identified is likely not feasible in the short term. In the complex research environment it may indeed be impossible to measure the effect of any single intervention, especially as any effects are likely to be small, and the pace of change slow. It will also take a long time to see any changes in the RCTs that are published in part due to the substantial time require to plan and secure funding for trials before they are started. Once RCTs start enrolment, the median (IQR) time to publication was 5 (3.5, 6.1) years for the RCTs included in the scoping review.

Strengths and limitations

Strengths of this research program include the integration of the 5 components, the public availability of the data, regular updates, and a broad approach to understanding the research enterprise in pediatric critical care. I conducted 5 unique, but related, individual studies with a range of research methods. The design of each study was

informed by, and expanded, the results of previous studies to present a more comprehensive picture of the research enterprise and strategies to improve it. To ensure that clinicians and other researchers are able to use the results of this research the website makes publicly available the trials we identified in the scoping review, which we regularly update, and the data from the scoping review and the social network analysis. We also used a broad approach to understanding how to improve the research conducted in pediatric critical care. We investigated the continuum from the individual researchers, through the research they produce and how they collaborate to produce it, to the clinicians who ultimately use the research to inform the care of critically ill children. We also included RCTs published over a broad period — 30 years — to give a perspective on how the field has developed. We also included RCTs from 37 countries published in 8 languages to better understand research done outside of North America and Western Europe, which published the majority of the RCTs.

This research program also has some limitations. We relied on the published reports of RCTs and thus we have likely underestimated the number of RCTs. Unpublished RCTs are common. In a review of RCT protocols in all clinical areas, not only pediatric critical care, submitted to 6 research ethics boards in 3 countries, only 56% were published after a median of 12 years of follow-up.[63] This same review found that, compared to completed RCTs, those stopped early were more likely to be unpublished (34% vs. 55%; OR 3.2 [95% CI 2.3 - 4.4]; $p < 0.001$). Because the characteristics of an RCT may be associated with its eventual publication, we have likely underestimated the need to improve reporting and rigour. The problem of unpublished RCTs may also be relevant for our conclusions about the barriers faced by researchers. When compared to those researchers who completed and published an RCT, it is possible that those who did not publish their trial — or indeed never started an RCT — might face different barriers. Unpublished RCTs are less likely to be relevant for our conclusions about effective facilitators. Participants in the survey of trialists and the qualitative study had all successfully completed and published at least one RCT and are thus ideal sources of information on facilitators. Another limitation is that we did not assess the clinical relevance or impact of the RCTs. We used

relatively crude measures such as the type of primary outcome, the use of blinding, and the Cochrane Collaboration's Risk of Bias tool,[14] but the results of a particular trial are always interpreted in the context of other evidence — and indeed many other factors. We also used the number of times each RCT was cited as a proxy measure of impact. It is not feasible to attempt to measure changes in practice due to each RCT. Further, measuring the role of RCTs in clinical practice guidelines was not feasible because of the paucity of guidelines in pediatric critical care.

Future research

Future studies should continue to build on the results of the scoping review and examine specific methodologic and reporting patterns, focusing in particularly on changes in the RCTs over time.

In this research program I focused on RCTs, acknowledging the merit of diverse study designs of value to clinicians, educators, researchers and policy-makers. The need to consider scope in my thesis is not meant to minimize the role of other research designs such as original observational studies or systematic reviews, the analysis of which would give a more complete picture of research in pediatric critical care. I hypothesize that efforts to improve RCTs would also result in improvements in other research designs and lead to an overall improvement in the research enterprise in the field. Future studies should consider qualitative methods, similar to Chapter 6, focusing on researchers from middle-income countries and smaller (in terms of research productivity) high-income countries, and researchers who have not completed an RCT to further address barriers and explore fruitful facilitators of RCT conduct in different settings. Finally, future studies aligned with this theme of research in adult critical care and other pediatric fields would help with understanding which of these findings are common across various fields of clinical research and which are unique to pediatric critical care.

Conclusions

The number of RCTs in pediatric critical care is increasing but there are important opportunities to improve the methods, outcome measures, and quality of reporting: in particular, the preponderance of small, single-centred RCTs focusing on laboratory or physiological outcomes that are often stopped early because of feasibility problems or futility. The research community is highly fragmented and highly clustered; experienced trialists consider better and broader collaboration as an effective approach to improving the state of RCT research. In addition to practical strategies to increase the rigour, efficiency, and impact of individual trials, trialists identified several approaches to improve the pediatric critical care research enterprise — including building a sense of community and ensuring key training and relevant practical experiences for new investigators. Because of the barriers that researchers face and their ethical obligation to undertake trials that are feasible and make a meaningful contribution to advancing the care of critically ill children, individuals and groups must take an active role in building a healthy research community. Based on the results of this program of research, investigator-initiated research networks are an important strategy. The pediatric critical care research community should expand and link existing networks — and actively encourage and assist researchers to create new networks — with a particular focus on international collaboration. By uniting and pooling their expertise, energy, and resources, investigators can undertake the type of trials needed and train the next generation of investigators. Only by changing how we do RCTs as a research community can we produce the rigorous RCTs that are needed to improve the care of critically ill children.

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Appendix A: Scoping review

Search strategies

MEDLINE

1. intensive care units, pediatric/
2. ((critical$ or intensive) adj2 (care or ill$)).mp.
3. (picu or icu or pccu).mp.
4. or/1-3
5. child:.mp.
6. adolescent:.mp.
7. infan:.mp.
8. or/5-7
9. (neonat$ or newborn or NICU or "low birth$" or VLBW or LBW or birthweight or preterm or "pre- term" or prematur$).ti.
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. clinical trials as topic.sh.
15. randomly.ab.
16. trial.ti.
17. or/10-16
18. exp animals/ not humans.sh.
19. (4 and 8 and 17) not (9 or 18)

EMBASE

1. exp intensive care unit/

2. exp intensive care/

3. ((critical$ or intensive) adj2 (care or ill$)).mp.

4. (picu or icu or pccu).mp.

5. or/1-4

6. child:.mp.

7. adolescent:.mp.

8. infan:.mp.

9. or/6-8

10. newborn intensive care/ or (neonat$ or newborn or NICU or "low birth$" or VLBW or LBW or birthweight or preterm or "pre-term" or prematur$).ti.

11. exp animals/ not humans.sh.

12. random:.tw.

13. placebo:.mp.

14. double-blind:.tw.

15. or/12-14

16. (5 and 9 and 15) not (10 or 11)

CENTRAL

#1 picu or icu or pccu

#2 MeSH descriptor Intensive Care Units, Pediatric, this term only

#3 (critical* or intensive) near/2 (care or ill or illness)

#4 child* or infan* or adolescent*

#5 pediatric* or paediatric*

#6 (neonat* or newborn or nicu or preterm or "pre-term" or prematur* or "low birth*" or LBW or VLBW or birthweight):ti

#7 ((#1 OR #2 OR #3) AND (#4 OR #5))

#8 (#7 AND NOT #6)

LILACS

(MH:"Intensive Care Units, Pediatric" OR MH:"Intensive Care " OR MH: "Critical Care" OR "Cuidados Críticos" OR "Cuidados Intensivos" OR "Intensive care" OR "Critical care" OR "critically ill" OR "critical illness" OR PICU OR "UTI pediatrica" OR "Unidade de Terapia Intensiva") AND (MH:"Infant" OR MH:"Child, Preschool" OR MH:"Child" OR Preescolar$ OR Pré-Escolar$ OR Niño$ OR Criança$ OR Infant$ OR Lactante$ OR child$ OR pediatric$ OR paediatric$)

Supplemental figures

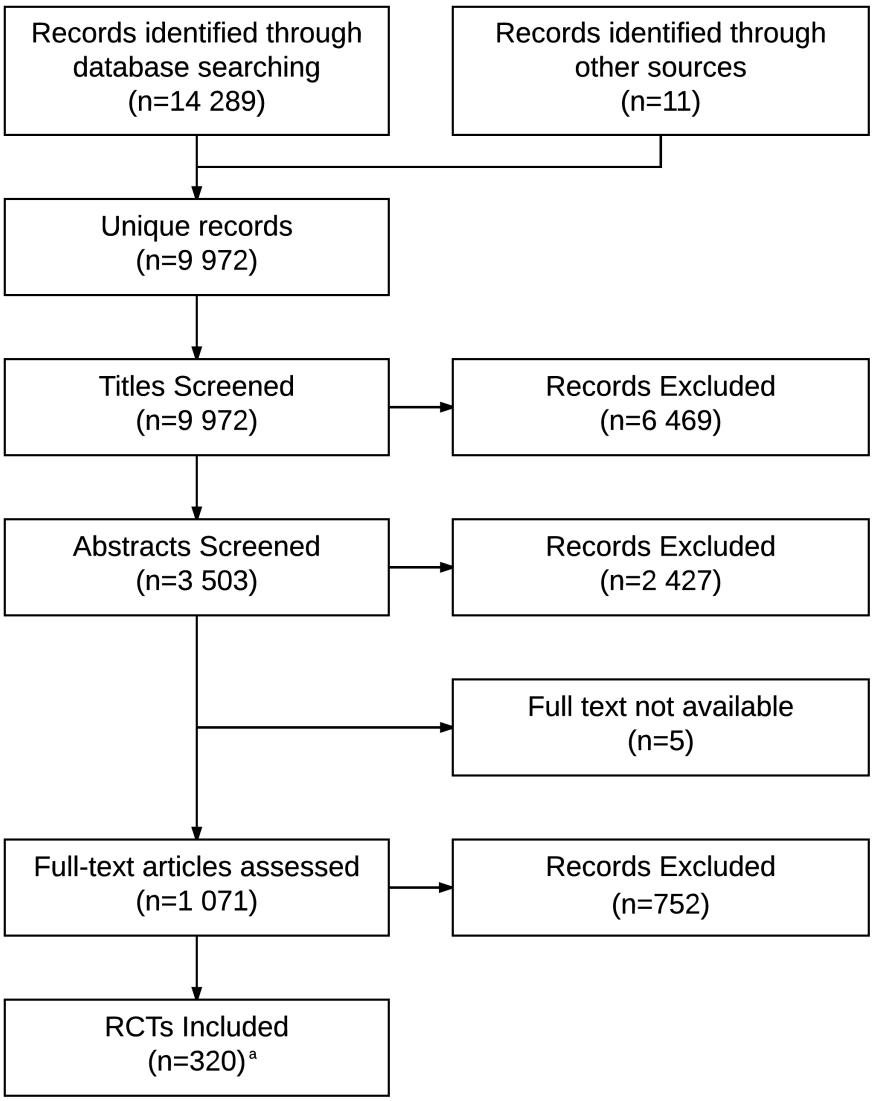

Figure A1. Review flow diagram. [a]One publication included two related RCTs: a single-centre and a multicentre trial with different inclusion and exclusion criteria. RCTs, randomized controlled trials; SR, systematic review; PICU, pediatric intensive care unit; NICU, neonatal intensive care unit.

Appendix B: Included RCTs

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Appendix C: Survey of clinicians

Survey questionnaire

McMaster University Health Sciences

McMaster Children's Hospital

Medication Decision Making in Critically Ill Children: A Survey of Pediatric Critical Care Physicians and Pharmacists

Physicians and pharmacists caring for critically ill children frequently make decisions about medications. Ideally these decisions should be informed by high quality evidence, but there are only a limited number of randomized clinical trials (RCTs) conducted in critically ill children. As you know, these are often small in size and of modest quality. Therefore physicians and pharmacists must often consider other types of evidence and evidence from other populations. The objective of this survey is to understand the importance of the different factors that Pediatric Critical Care physicians and pharmacists consider when making decisions about medications. This survey is part of a broader research program focusing on decision-making for this vulnerable population.

We would appreciate it if you would participate in this questionnaire. It will take approximately 10 minutes to complete. Please return the completed questionnaire in the pre-paid envelope provided. If you are not a physician or pharmacist working in a pediatric ICU, please check the corresponding box on the first page of the survey and return the survey in the prepaid envelope. We value your views.

If you have any questions please contact:
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If you have any questions regarding your rights as a research participant, you may contact:
Hamilton Health Sciences /McMaster University Faculty of Health Sciences Research Ethics Board
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Thank-you for your participation!

Mark Duffett
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Karen Choong
Department of Pediatrics
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Departments of Medicine & Clinical Epidemiology and Biostatistics
McMaster University

Do you work as a physician or pharmacist in a pediatric ICU? ☐ **Yes** ☐ **No**

If you answered **NO**, please do not continue to answer this survey;
Thanks for returning it in the prepaid envelope.

Scenario 1: Corticosteroids for fluid refractory septic shock in children.

1. In your practice, how often do you use corticosteroids for fluid refractory septic shock in children?

☐	☐	☐	☐	☐	☐	☐
NOT used in any patients			**About 50% of patients**			**ALL patients without contraindications**

2. How important are each of the following factors in your personal decisions to use or not to use corticosteroids for fluid refractory septic shock in children?

	Not important 1	2	3	4	5	6	**Very important** 7
Child's severity of illness	☐	☐	☐	☐	☐	☐	☐
Potential for adverse effects	☐	☐	☐	☐	☐	☐	☐
Drug cost for your unit or hospital	☐	☐	☐	☐	☐	☐	☐
Written unit policies/protocols/pre-printed orders	☐	☐	☐	☐	☐	☐	☐
Your personal clinical experience	☐	☐	☐	☐	☐	☐	☐
Opinion leaders	☐	☐	☐	☐	☐	☐	☐
Published guidelines	☐	☐	☐	☐	☐	☐	☐
Published RCTs in critically ill children	☐	☐	☐	☐	☐	☐	☐
Published RCTs in non-critically ill children	☐	☐	☐	☐	☐	☐	☐
Published RCTs in critically ill adults	☐	☐	☐	☐	☐	☐	☐
Published RCTs in neonates	☐	☐	☐	☐	☐	☐	☐
Other clinical research literature	☐	☐	☐	☐	☐	☐	☐
Physiologic rationale	☐	☐	☐	☐	☐	☐	☐

3. How would you rate the overall quality of the body of evidence regarding corticosteroids for fluid refractory septic shock in children?

☐	☐	☐	☐	☐
Very Low	**Low**	**Moderate**	**High**	**Unsure**

Comments:

Scenario 2: Intensive insulin therapy in critically ill children.

1. In your practice, how often do you use intensive insulin therapy in critically ill children?

☐	☐	☐	☐	☐	☐	☐
NOT used in any patients			**About 50% of patients**			**ALL patients without contraindications**

2. How important are each of the following factors in your personal decisions to use or not to use intensive insulin therapy in critically ill children?

	Not important 1	2	3	4	5	6	**Very important** 7
Child's severity of illness	☐	☐	☐	☐	☐	☐	☐
Potential for adverse effects	☐	☐	☐	☐	☐	☐	☐
Drug cost for your unit or hospital	☐	☐	☐	☐	☐	☐	☐
Written unit policies/protocols/pre-printed orders	☐	☐	☐	☐	☐	☐	☐
Your personal clinical experience	☐	☐	☐	☐	☐	☐	☐
Opinion leaders	☐	☐	☐	☐	☐	☐	☐
Published guidelines	☐	☐	☐	☐	☐	☐	☐
Published RCTs in critically ill children	☐	☐	☐	☐	☐	☐	☐
Published RCTs in non-critically ill children	☐	☐	☐	☐	☐	☐	☐
Published RCTs in critically ill adults	☐	☐	☐	☐	☐	☐	☐
Published RCTs in neonates	☐	☐	☐	☐	☐	☐	☐
Other clinical research literature	☐	☐	☐	☐	☐	☐	☐
Physiologic rationale	☐	☐	☐	☐	☐	☐	☐

3. How would you rate the overall quality of the body of evidence regarding intensive insulin therapy in critically ill children?

☐	☐	☐	☐	☐
Very Low	**Low**	**Moderate**	**High**	**Unsure**

Comments:

Scenario 3: Stress ulcer prophylaxis in mechanically ventilated critically ill children.

1. In your practice, how often do you use stress ulcer prophylaxis in mechanically ventilated critically ill children?

☐	☐	☐	☐	☐	☐	☐
NOT used in any patients			**About 50% of patients**			**ALL patients without contraindications**

2. How important are each of the following factors in your personal decisions to use or not to use stress ulcer prophylaxis in mechanically ventilated critically ill children?

	Not important						**Very important**
	1	**2**	**3**	**4**	**5**	**6**	**7**
Child's severity of illness	☐	☐	☐	☐	☐	☐	☐
Potential for adverse effects	☐	☐	☐	☐	☐	☐	☐
Drug cost for your unit or hospital	☐	☐	☐	☐	☐	☐	☐
Written unit policies/protocols/pre-printed orders	☐	☐	☐	☐	☐	☐	☐
Your personal clinical experience	☐	☐	☐	☐	☐	☐	☐
Opinion leaders	☐	☐	☐	☐	☐	☐	☐
Published guidelines	☐	☐	☐	☐	☐	☐	☐
Published RCTs in critically ill children	☐	☐	☐	☐	☐	☐	☐
Published RCTs in non-critically ill children	☐	☐	☐	☐	☐	☐	☐
Published RCTs in critically ill adults	☐	☐	☐	☐	☐	☐	☐
Published RCTs in neonates	☐	☐	☐	☐	☐	☐	☐
Other clinical research literature	☐	☐	☐	☐	☐	☐	☐
Physiologic rationale	☐	☐	☐	☐	☐	☐	☐

3. How would you rate the overall quality of the body of evidence regarding stress ulcer prophylaxis in mechanically ventilated critically ill children?

☐	☐	☐	☐	☐
Very Low	**Low**	**Moderate**	**High**	**Unsure**

Comments:

Scenario 4: Surfactant therapy for ARDS in critically ill children.

1. In your practice, how often do you use surfactant therapy for ARDS in critically ill children?

☐	☐	☐	☐	☐	☐	☐
NOT used in any patients			**About 50% of patients**			**ALL patients without contraindications**

2. How important are each of the following factors in your personal decisions to use or not to use surfactant therapy for ARDS in critically ill children?

	Not important 1	2	3	4	5	6	**Very important** 7
Child's severity of illness	☐	☐	☐	☐	☐	☐	☐
Potential for adverse effects	☐	☐	☐	☐	☐	☐	☐
Drug cost for your unit or hospital	☐	☐	☐	☐	☐	☐	☐
Written unit policies/protocols/pre-printed orders	☐	☐	☐	☐	☐	☐	☐
Your personal clinical experience	☐	☐	☐	☐	☐	☐	☐
Opinion leaders	☐	☐	☐	☐	☐	☐	☐
Published guidelines	☐	☐	☐	☐	☐	☐	☐
Published RCTs in critically ill children	☐	☐	☐	☐	☐	☐	☐
Published RCTs in non-critically ill children	☐	☐	☐	☐	☐	☐	☐
Published RCTs in critically ill adults	☐	☐	☐	☐	☐	☐	☐
Published RCTs in neonates	☐	☐	☐	☐	☐	☐	☐
Other clinical research literature	☐	☐	☐	☐	☐	☐	☐
Physiologic rationale	☐	☐	☐	☐	☐	☐	☐

3. How would you rate the overall quality of the body of evidence regarding surfactant therapy for ARDS in critically ill children?

☐	☐	☐	☐	☐
Very Low	**Low**	**Moderate**	**High**	**Unsure**

Comments:

Scenario 5: Daily interruption of sedation in critically ill children.

1. In your practice, how often do you use daily interruption of sedation in critically ill children?

☐	☐	☐	☐	☐	☐	☐
NOT used in any patients			**About 50% of patients**			**ALL patients without contraindications**

2. How important are each of the following factors in your personal decisions to use or not to use daily interruption of sedation in critically ill children?

	Not important 1	2	3	4	5	6	**Very important** 7
Child's severity of illness	☐	☐	☐	☐	☐	☐	☐
Potential for adverse effects	☐	☐	☐	☐	☐	☐	☐
Drug cost for your unit or hospital	☐	☐	☐	☐	☐	☐	☐
Written unit policies/protocols/pre-printed orders	☐	☐	☐	☐	☐	☐	☐
Your personal clinical experience	☐	☐	☐	☐	☐	☐	☐
Opinion leaders	☐	☐	☐	☐	☐	☐	☐
Published guidelines	☐	☐	☐	☐	☐	☐	☐
Published RCTs in critically ill children	☐	☐	☐	☐	☐	☐	☐
Published RCTs in non-critically ill children	☐	☐	☐	☐	☐	☐	☐
Published RCTs in critically ill adults	☐	☐	☐	☐	☐	☐	☐
Published RCTs in neonates	☐	☐	☐	☐	☐	☐	☐
Other clinical research literature	☐	☐	☐	☐	☐	☐	☐
Physiologic rationale	☐	☐	☐	☐	☐	☐	☐

3. How would you rate the overall quality of the body of evidence regarding daily interruption of sedation in critically ill children?

☐	☐	☐	☐	☐
Very Low	**Low**	**Moderate**	**High**	**Unsure**

Comments:

DEMOGRAPHIC DATA

1. Are you a: ☐ Intensivist
   ☐ Pharmacist
   ☐ Fellow
   ☐ Other (specify:_____)

2. For how many years have you been practicing in pediatric critical care (round to the nearest year)? |__|__|

3. Please indicate all of your current and past role(s) in clinical research:
   ☐ Principal investigator
   ☐ Site investigator
   ☐ Research coordinator or other research staff
   ☐ Caring for patients enrolled in studies
   ☐ Other (specify:_____)
   ☐ None of the above

We are grateful for your support and welcome any other comments or suggestions.

_____

_____

_____

_____

_____

_____

Thank-you for your participation!

Supplemental tables

Table C1. Assessing clustering effects

Factor	Responses	Scenario (5 levels)		Centre (11 levels)	
		ICC	VIF	ICC	VIF
Child's severity of illness	551	0.08	10.33	0.05	3.60
Potential for adverse effects	566	0.11	13.65	0.03	2.65
Drug cost	565	0.01	2.29	0.03	2.75
Written unit policies	560	0.00	1.52	0.03	2.32
Clinical experience	561	0.04	5.48	0.04	3.21
Opinion leaders	565	0.01	1.94	0.05	3.52
Published guidelines	559	0.01	2.07	0.10	6.37
RCTs in critically ill children	563	0.02	2.76	0.03	2.68
RCTs in other children	555	0.00	1.39	0.06	4.13
RCTs in critically ill adults	555	0.03	4.37	0.03	2.39

ICC, intracluster correlation factor; VIF, variance inflation factor.

Table C2. Importance of specific factors: differences among the 5 scenarios

Scenario	Research evidence				Published guidelines	Opinion leaders	Child's severity of illness	Physiologic rationale	Adverse effects	Clinical experience
	RCTs: critically ill children	RCTs: critically ill adults	RCTs: neonates	Other clinical research						
Corticosteroids for septic shock	Reference scenario									
Intensive insulin therapy	0.24 (-0.06, 0.53) p=0.11	0.03 (-0.21, 0.27) p=0.79	-0.07 (-0.45, 0.30) p=0.70	-0.11 (-0.44, 0.22) p=0.51	-0.31 (-0.68, 0.06) p=0.11	-0.11 (-0.42, 0.19) p=0.46	-1.38 (-1.87, -0.9) p<0.001	-0.46 (-0.67, -0.26) p<0.001	1.47 (1.11, 1.84) p<0.001	-0.26 (-0.57, 0.05) p=0.1
Stress ulcer prophylaxis	-0.27 (-0.57, 0.03) p=0.08	-0.11 (-0.49, 0.28) p=0.59	-0.35 (-0.73, 0.02) p=0.07	-0.23 (-0.52, 0.06) p=0.12	-0.66 (-1, -0.31) p<0.001	-0.34 (-0.57, -0.11) p=<0.001	-0.66 (-1.14, -0.18) p=0.01	-0.42 (-0.6, -0.23) p<0.001	-0.31 (-0.68, 0.06) p=0.10	-0.40 (-0.58, -0.22) p=<0.001
Surfactant for ARDS	0.20 (-0.15, 0.54) p=0.26	-0.33 (-0.57, -0.09) p=0.01	-0.06 (-0.49, 0.38) p=0.80	-0.07 (-0.34, 0.21) p=0.62	-0.83 (-1.21, -0.45) p<0.001	-0.07 (-0.32, 0.19) p=0.62	-0.17 (-0.84, 0.5) p=0.63	-0.31 (-0.68, 0.05) p=0.09	0.92 (0.57, 1.28) p=<0.001	-0.18 (-0.52, 0.16) p=0.29
Interruption of sedation	-0.11 (-0.49, 0.28) p=0.59	0.18 (-0.05, 0.41) p=0.12	-0.59 (-1.05, -0.14) p=0.01	-0.26 (-0.56, 0.05) p=0.10	-0.44 (-0.91, 0.03) p=0.07	-0.02 (-0.31, 0.27) p=0.90	-0.20 (-0.49, 0.09) p=0.18	-0.10 (-0.32, 0.13) p=0.40	1.31 (1.12, 1.49) p<0.001	-0.04 (-0.36, 0.28) p=0.81

This table shows the results of the multivariate analysis, reporting the coefficient (95% confidence interval) for each covariate. Positive coefficients indicate that respondents rated that particular factor as more important in that scenario. We used corticosteroids for fluid refractory septic shock as the reference scenario and compared the other scenarios to it. Shaded cells indicate a statistically significant difference in the importance of that factor among scenarios (p<0.05). ARDS, Acute respiratory distress syndrome

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Appendix D: Survey of trialists

Survey questionnaire

McMaster University

Thank you for agreeing to participate in this survey Dr [contact("last name")]. We invited you to participate because of your expertise as an accomplished researcher who has published an RCT in pediatric critical care.

The objective of this survey is to identify the barriers to, and facilitators of, high-quality RCTs in pediatric critical care. With your help we hope to understand the challenges researchers like you face, and how to best overcome them. Based on our testing it will take approximately 10 minutes to complete. [more information]

Thank you, we value your experience and expertise,

Mark Duffett Deborah Cook Kusum Menon
Karen Choong Jennifer Foster Melissa Parker
On behalf of the Canadian Critical Care Trials Group

From the:
Departments of Pediatrics, Medicine and Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada (MD, KC, DC, MP)
Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada (JF)
Departments of Pediatrics and Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada (KM)

If you have any questions please contact Mark Duffett at duffetmc@mcmaster.ca.
This survey was approved by the Hamilton Integrated Research Ethics Board.

I have collaborated on at least 1 pediatric critical care RCT *

○ Yes ○ No, I have received this email in error ○ I have already replied to this survey

Barriers to Conducting High-quality RCTs in Pediatric Critical Care

For the following questions we are interested in your **personal experience as a researcher conducting RCTs** in pediatric critical care.
Please rate the importance of these **barriers** (from 1=not a barrier at all to 7=a very important barrier).
A **barrier** is something that makes conducting high quality RCTs more difficult.

The need for research

	Not a barrier at all 1	2	3	4	5	6	A very important barrier 7
Clinician perceptions that RCTs are not needed in many situations in pediatric critical care	○	○	○	○	○	○	○
Clinician perceptions that RCTs have not altered clinical practice in meaningful ways in pediatric critical care	○	○	○	○	○	○	○

The clinical environment

	Not a barrier at all 1	2	3	4	5	6	A very important barrier 7
The number of critically ill children at your centre	○	○	○	○	○	○	○
The number of critically ill children worldwide	○	○	○	○	○	○	○
Clinicians may prefer to continue their current practice rather than participate in an RCT	○	○	○	○	○	○	○
Physicians may prefer to choose the therapy for a child themselves rather than randomizing them in an RCT	○	○	○	○	○	○	○
Support for clinical research from physicians in the PICU	○	○	○	○	○	○	○
Support for clinical research from other health professionals in the PICU	○	○	○	○	○	○	○
Support for clinical research from the hospital or PICU administration	○	○	○	○	○	○	○

Research design and planning

	Not a barrier at all 1	2	3	4	5	6	A very important barrier 7
The coordination required for multi-centre RCTs	○	○	○	○	○	○	○
The coordination required for multinational RCTs	○	○	○	○	○	○	○
Competition among researchers studying the same or similar topics	○	○	○	○	○	○	○
Limited opportunities to collaborate with researchers in other centers or countries	○	○	○	○	○	○	○
Language barriers for researchers	○	○	○	○	○	○	○
Few established pediatric critical care research networks	○	○	○	○	○	○	○
Availability of expert biostatistical collaborators or expertise	○	○	○	○	○	○	○

Ethical and regulatory approval

	Not a barrier at all 1	2	3	4	5	6	A very important barrier 7
The documentation required for Research Ethics Board review and approval	○	○	○	○	○	○	○
The documentation required to obtain authorization from regulatory bodies to use a drug or device within an RCT	○	○	○	○	○	○	○
The documentation required for adverse event reporting within an RCT	○	○	○	○	○	○	○
The documentation required for approval of contracts between study sites	○	○	○	○	○	○	○

Consent

	Not a barrier at all 1	2	3	4	5	6	A very important barrier 7
Obtaining consent from parents or guardians in a timely manner	○	○	○	○	○	○	○
Length and/or complexity of consent forms	○	○	○	○	○	○	○
Parents or guardians who do not speak, read or understand the language used by the researchers to explain the RCT	○	○	○	○	○	○	○
Parents' or guardians' concerns about the risk of harm to their child	○	○	○	○	○	○	○
Parents or guardians may prefer that the physician make the decision about which therapy to use rather than randomizing their child in an RCT	○	○	○	○	○	○	○
Staff concerns about overburdening parents of acutely ill children	○	○	○	○	○	○	○

RCT conduct

	Not a barrier at all 1	2	3	4	5	6	A very important barrier 7
The availability of blinded study medication and/or placebos	○	○	○	○	○	○	○
Physicians may prefer to abandon or modify the study intervention themselves rather than following the study protocol (e.g., rescue therapy or open label use of the study intervention)	○	○	○	○	○	○	○
The number of research personnel at my center	○	○	○	○	○	○	○
The amount of data collected for each study participant	○	○	○	○	○	○	○

Funding

	Not a barrier at all 1	2	3	4	5	6	A very important barrier 7
Funding available for pediatric research	○	○	○	○	○	○	○
Funding available for pediatric critical care research	○	○	○	○	○	○	○
Funding available for large RCTs	○	○	○	○	○	○	○
Costs due to increased regulations and bureaucracy	○	○	○	○	○	○	○
Funding availability and coordination from different agencies	○	○	○	○	○	○	○
Funding availability and coordination from different countries	○	○	○	○	○	○	○
Costs of liability insurance for clinicians or researchers	○	○	○	○	○	○	○

Researchers

	Not a barrier at all 1	2	3	4	5	6	A very important barrier 7
The number of researchers with formal clinical research methods training	○	○	○	○	○	○	○
The time commitment required to bring a study idea to fruition (funding, approval, implementation) is too large	○	○	○	○	○	○	○
Academic or clinical duties which may not leave enough time to conduct an RCT	○	○	○	○	○	○	○
RCTs take too long to complete for academic promotion	○	○	○	○	○	○	○

In your opinion, what are the top 3 barriers to conducting high quality RCTs in pediatric critical care? Please consider any barriers you can think of, not only the ones listed in this survey.

1.
2.
3.

Facilitators of Conducting High-quality RCTs in Pediatric Critical Care

Next, we will ask some questions about **facilitators** of high-quality RCTs in pediatric critical care.

For the following questions we are interested in your opinions on the effectiveness of these facilitators **in general, whether or not they applied to your RCTs**.
Please rate these effectiveness of these **facilitators (**from 1=not an effective facilitator to 7=a very effective facilitator).
A **facilitator** is something that makes conducting high quality RCTs in pediatric critical care easier.

Need for research

	Not an effective facilitator 1	2	3	4	5	6	A very effective facilitator 7
Clinicians value RCTs when making clinical decisions in pediatric critical care	○	○	○	○	○	○	○

Clinical environment

	Not an effective facilitator 1	2	3	4	5	6	A very effective facilitator 7
Support for clinical research from physicians in the PICU	○	○	○	○	○	○	○
Support for clinical research from other health professionals in the PICU	○	○	○	○	○	○	○
Support for clinical research from the hospital or PICU administration	○	○	○	○	○	○	○

Research design and planning

	Not an effective facilitator 1	2	3	4	5	6	A very effective facilitator 7
Conducting preliminary studies (not pilot RCTs) before proceeding to an RCT	○	○	○	○	○	○	○
Conducting pilot RCTs before proceeding to a larger RCT	○	○	○	○	○	○	○
Adopting a programmatic approach to research (a group of related studies of varying designs on a particular topic)	○	○	○	○	○	○	○
Conducting observational studies to estimate treatment effects instead of RCTs	○	○	○	○	○	○	○
Using a Bayesian approach to sample size estimation	○	○	○	○	○	○	○
Using factorial designs (RCTs testing more than one intervention at the same time)	○	○	○	○	○	○	○
Conducting pediatric and adult RCTs in parallel, sharing infrastructure	○	○	○	○	○	○	○
Using surrogate or intermediate outcomes to reduce the sample size required	○	○	○	○	○	○	○
Facilitated opportunities for multi-national collaboration	○	○	○	○	○	○	○
Conducting RCTs in collaboration with a research network	○	○	○	○	○	○	○
Creating more research networks	○	○	○	○	○	○	○

Ethical and regulatory approval

	Not an effective facilitator 1	2	3	4	5	6	A very effective facilitator 7
Reciprocal review by Research Ethics Boards	○	○	○	○	○	○	○
Centralized ethical approval (e.g., Regional or National Research Ethics Boards)	○	○	○	○	○	○	○
Templates for contracts between study sites for RCTs in pediatric critical care	○	○	○	○	○	○	○

Consent

	Not an effective facilitator 1	2	3	4	5	6	A very effective facilitator 7
Simplified consent forms	○	○	○	○	○	○	○
Deferred consent for enrolment in RCTs when suitable	○	○	○	○	○	○	○
Waived consent for enrolment in RCTs when suitable	○	○	○	○	○	○	○
Telephone consent for enrolment in RCTs when required	○	○	○	○	○	○	○

RCT conduct

	Not an effective facilitator 1	2	3	4	5	6	A very effective facilitator 7
Study protocols that permit physicians to abandon or modify the study intervention (e.g., rescue therapy or open label use of the study intervention)	○	○	○	○	○	○	○
Using learners as research personnel to reduce staffing costs	○	○	○	○	○	○	○
More research personnel at each center	○	○	○	○	○	○	○
Ability to recruit participants 24h per day, 7 days per week	○	○	○	○	○	○	○
Reducing the amount of data collected for each study participant	○	○	○	○	○	○	○
Co-enrollment (enrolling children in more than one RCT at the same time)	○	○	○	○	○	○	○

Funding

	Not an effective facilitator 1	2	3	4	5	6	A very effective facilitator 7
Reimbursing clinical personnel for research activities	○	○	○	○	○	○	○
Funding for programs of research rather than individual studies	○	○	○	○	○	○	○
Funding from peer-review/government agencies specifically for RCTs in critically ill children	○	○	○	○	○	○	○
Funding from local departments, universities and hospitals	○	○	○	○	○	○	○
Funding from charitable foundations	○	○	○	○	○	○	○
Funding from industry for **investigator-initiated** RCTs	○	○	○	○	○	○	○
Funding from industry for **industry-sponsored** RCTs	○	○	○	○	○	○	○

Researchers

	Not an effective facilitator 1	2	3	4	5	6	A very effective facilitator 7
Formal research clinical methods training for investigators	○	○	○	○	○	○	○
Mentorship from individuals within your institution	○	○	○	○	○	○	○
Mentorship from individuals outside of your institution	○	○	○	○	○	○	○
Role models or examples of researchers who do rigorous RCTs	○	○	○	○	○	○	○
Published examples of high-quality RCTs in pediatric critical care	○	○	○	○	○	○	○
Support for conducting RCTs from academic department	○	○	○	○	○	○	○
Protected time for research	○	○	○	○	○	○	○

In your opinion, what are the top 3 facilitators of conducting high quality RCTs in pediatric critical care?
Please consider any facilitators you can think of, not only the ones listed in this survey.

1.
2.
3.

Demographic information

For how many years have you practiced in pediatric critical care?
(Or in your primary area of practice if it is not pediatric critical care)

We welcome any additional comments you may have:

Would you like to receive a brief summary of the results of the survey when it is completed?

○ Yes ○ No

Thank You

Thank you for completing our survey. We value your experience and expertise.

For more information on our research program visit epicc.mcmaster.ca.
For more information on our database of pediatric critical care RCTs visit PICUtrials.net.
Follow @PICUtrials

Supplemental tables

Table D1. Association between respondent characteristics and differences in the ratings of individual barriers and facilitators using linear regression

Barriers and facilitators	Participant variables			
	Years of experience in pediatric critical care	**Number of RCT publications**	**Country income level:** Respondents from a high-income country vs. middle-income country	**Multicentred RCTs:** Respondents who have published a multicentred RCT vs. those who have not
Barriers				
Clinician perceptions that RCTs are not needed in many situations	-0.02 (-0.06-0.03) p=0.41	-0.01 (-0.25-0.24) p=0.94	-0.3 (-1.18-0.57) p=0.50	-0.07 (-0.87-0.74) p=0.87
Clinician perceptions that RCTs have not altered clinical practice in meaningful ways	-0.03 (-0.07-0.01) p=0.19	0.03 (-0.2-0.26) p=0.80	-0.45 (-1.27-0.36) p=0.28	-0.02 (-0.77-0.74) p=0.97
The number of critically ill children at your centre	-0.04 (-0.09-0.02) p=0.17	-0.01 (-0.29-0.26) p=0.93	0.8 (-0.18-1.79) p=0.11	0.73 (-0.18-1.65) p=0.12
The number of critically ill children worldwide	-0.03 (-0.07-0.01) p=0.20	-0.01 (-0.24-0.22) p=0.92	0.53 (-0.3-1.36) p=0.21	0.44 (-0.33-1.2) p=0.26
Clinicians may prefer to continue their current practice rather than participate in an RCT	-0.04 (-0.08-0) p=0.07	0 (-0.22-0.21) p=0.98	0.57 (-0.2-1.34) p=0.15	-0.25 (-0.95-0.46) p=0.49
Physicians may prefer to choose the therapy rather than randomizing	-0.03 (-0.07-0.01) p=0.15	0.04 (-0.18-0.25) p=0.74	0.55 (-0.21-1.31) p=0.16	-0.13 (-0.83-0.57) p=0.71
Support for clinical research from physicians in the PICU	-0.06 (-0.1- -0.02) p=0.008	0.07 (-0.17-0.31) p=0.56	-0.07 (-0.92-0.79) p=0.88	0.73 (-0.07-1.53) p=0.08
Support for clinical research from other health professionals in the PICU	-0.06 (-0.09- -0.02) p=0.002	0.02 (-0.17-0.22) p=0.82	-0.23 (-0.93-0.47) p=0.53	0.36 (-0.28-1) p=0.27
Support for clinical research from the hospital or PICU administration	-0.06 (-0.1- -0.02) p=0.008	0.13 (-0.1-0.37) p=0.28	0.32 (-0.52-1.16) p=0.46	0.33 (-0.45-1.1) p=0.41
The coordination required for multi-centre RCTs	-0.06 (-0.09- -0.02) p=0.002	-0.07 (-0.25-0.12) p=0.50	0.28 (-0.4-0.96) p=0.42	0 (-0.63-0.62) p=0.99
The coordination required for multinational RCTs	-0.04 (-0.08- -0.01) p=0.02	-0.03 (-0.22-0.16) p=0.74	0.16 (-0.51-0.84) p=0.64	-0.28 (-0.9-0.34) p=0.38
Competition among researchers studying the same or similar topics	-0.02 (-0.06-0.02) p=0.26	-0.05 (-0.26-0.17) p=0.67	0.34 (-0.42-1.11) p=0.38	-0.26 (-0.96-0.44) p=0.47

Barriers and facilitators	Participant variables			
	Years of experience in pediatric critical care	**Number of RCT publications**	**Country income level:** Respondents from a high-income country vs. middle-income country	**Multicentred RCTs:** Respondents who have published a multicentred RCT vs. those who have not
Limited opportunities to collaborate with researchers in other centers or countries	-0.03 (-0.07-0) p=0.06	-0.14 (-0.32-0.05) p=0.16	-1.33 (-2.01- -0.66) p<0.001	-0.5 (-1.13-0.12) p=0.12
Language barriers for researchers	-0.01 (-0.05-0.03) p=0.54	-0.06 (-0.27-0.15) p=0.57	-0.66 (-1.4-0.09) p=0.09	0.37 (-0.32-1.06) p=0.30
Few established pediatric critical care research networks	-0.01 (-0.05-0.03) p=0.58	0.03 (-0.16-0.21) p=0.79	-1.05 (-1.73- -0.37) p=0.003	-0.67 (-1.3- -0.04) p=0.04
Availability of expert biostatistical collaborators or expertise	0.01 (-0.04-0.05) p=0.76	-0.12 (-0.36-0.11) p=0.32	-0.71 (-1.56-0.13) p=0.10	-0.17 (-0.95-0.6) p=0.66
The documentation required for Research Ethics Board review and approval	0 (-0.05-0.04) p=0.85	0.05 (-0.18-0.28) p=0.68	1.17 (0.33-2) p=0.007	-0.23 (-0.99-0.54) p=0.57
The documentation required to obtain authorization from regulatory bodies	-0.02 (-0.06-0.02) p=0.34	0.12 (-0.09-0.34) p=0.27	0.1 (-0.67-0.86) p=0.80	-0.07 (-0.78-0.63) p=0.84
The documentation required for adverse event reporting within an RCT	-0.04 (-0.08-0) p=0.07	0.06 (-0.16-0.27) p=0.61	0.71 (-0.07-1.49) p=0.08	-0.09 (-0.8-0.62) p=0.81
The documentation required for approval of contracts between study sites	-0.02 (-0.06-0.02) p=0.36	-0.01 (-0.24-0.21) p=0.90	0.53 (-0.26-1.32) p=0.19	0.18 (-0.56-0.91) p=0.64
Obtaining consent from parents or guardians in a timely manner	-0.02 (-0.06-0.02) p=0.36	0.11 (-0.12-0.34) p=0.35	0.7 (-0.14-1.55) p=0.11	0.21 (-0.55-0.98) p=0.59
Length and/or complexity of consent forms	0.01 (-0.03-0.05) p=0.61	0.09 (-0.13-0.31) p=0.44	0.93 (0.12-1.74) p=0.03	0.43 (-0.31-1.16) p=0.26
Parents who do not read or understand the language used by the researchers	-0.03 (-0.07-0.02) p=0.21	0.12 (-0.13-0.36) p=0.35	0.83 (-0.05-1.7) p=0.07	0.33 (-0.46-1.13) p=0.41
Parents' concerns about the risk of harm to their child	-0.04 (-0.08-0) p=0.04	0.03 (-0.17-0.24) p=0.75	0.46 (-0.32-1.23) p=0.25	0.19 (-0.5-0.88) p=0.59
Parents may prefer that the physician choose the therapy rather than randomization	-0.03 (-0.07-0.01) p=0.10	0.06 (-0.15-0.27) p=0.57	0.02 (-0.73-0.77) p=0.96	0.32 (-0.36-1.01) p=0.36
Staff concerns about overburdening parents of acutely ill children	-0.04 (-0.08-0) p=0.04	0.07 (-0.15-0.29) p=0.55	0.52 (-0.28-1.32) p=0.21	0.26 (-0.47-0.99) p=0.49
The availability of blinded study medication and/or placebos	-0.03 (-0.07-0.01) p=0.19	0.2 (-0.02-0.42) p=0.07	-0.4 (-1.19-0.39) p=0.32	-0.7 (-1.42-0.02) p=0.06
Physicians may prefer to abandon or modify the study intervention	-0.05 (-0.08- -0.01) p=0.02	0.13 (-0.07-0.33) p=0.21	0.32 (-0.41-1.05) p=0.39	-0.45 (-1.12-0.21) p=0.19
The number of research personnel at my center	-0.02 (-0.06-0.02) p=0.39	-0.08 (-0.3-0.14) p=0.46	0.12 (-0.68-0.91) p=0.77	-0.51 (-1.24-0.21) p=0.17

Barriers and facilitators	Participant variables			
	Years of experience in pediatric critical care	**Number of RCT publications**	**Country income level:** Respondents from a high-income country vs. middle-income country	**Multicentred RCTs:** Respondents who have published a multicentred RCT vs. those who have not
The amount of data collected for each participant	-0.02 (-0.05-0.02) p=0.40	0.04 (-0.17-0.24) p=0.74	0.26 (-0.49-1.01) p=0.50	0.23 (-0.45-0.91) p=0.51
Funding available for pediatric research	-0.01 (-0.05-0.02) p=0.49	0.03 (-0.18-0.23) p=0.79	0.51 (-0.22-1.24) p=0.18	0.16 (-0.51-0.84) p=0.64
Funding available for pediatric critical care research	-0.01 (-0.05-0.02) p=0.46	-0.02 (-0.2-0.16) p=0.83	0.53 (-0.12-1.18) p=0.11	0.12 (-0.49-0.72) p=0.71
Funding available for large RCTs	-0.01 (-0.04-0.02) p=0.45	0.06 (-0.11-0.23) p=0.48	0.47 (-0.13-1.07) p=0.13	0.06 (-0.49-0.62) p=0.82
Costs due to increased regulations/bureaucracy	0 (-0.03-0.03) p=0.95	0.03 (-0.16-0.21) p=0.78	0.92 (0.27-1.58) p=0.007	0.02 (-0.58-0.63) p=0.94
Funding availability and coordination from different agencies	-0.02 (-0.06-0.01) p=0.15	0.02 (-0.16-0.2) p=0.85	0.44 (-0.21-1.08) p=0.19	0.29 (-0.31-0.89) p=0.34
Funding availability and coordination from different countries	-0.01 (-0.04-0.03) p=0.70	0.03 (-0.14-0.2) p=0.74	-0.19 (-0.82-0.44) p=0.56	0.13 (-0.44-0.71) p=0.65
Costs of liability insurance	-0.05 (-0.09-0) p=0.03	0.21 (-0.03-0.45) p=0.08	-0.28 (-1.12-0.56) p=0.52	-0.3 (-1.08-0.48) p=0.45
The number of researchers with formal clinical research methods training	-0.01 (-0.04-0.03) p=0.70	-0.01 (-0.2-0.19) p=0.96	-0.58 (-1.28-0.13) p=0.11	-0.23 (-0.88-0.42) p=0.49
The time commitment required to bring a study idea to fruition is too large	-0.01 (-0.04-0.02) p=0.36	0.06 (-0.1-0.22) p=0.49	0.06 (-0.52-0.64) p=0.84	-0.12 (-0.65-0.41) p=0.67
Academic or clinical duties which may not leave enough time to conduct an RCT	-0.02 (-0.05-0.01) p=0.22	0.01 (-0.17-0.18) p=0.95	-0.16 (-0.8-0.47) p=0.62	-0.18 (-0.76-0.41) p=0.56
RCTs take too long to complete for academic promotion	-0.04 (-0.08-0) p=0.07	0.06 (-0.18-0.3) p=0.65	0.03 (-0.83-0.89) p=0.94	-0.06 (-0.85-0.73) p=0.88
Facilitators				
Clinicians value RCTs when making clinical decisions in pediatric critical care	0.03 (0-0.07) p=0.07	-0.01 (-0.19-0.18) p=0.94	-0.37 (-1.04-0.3) p=0.28	-0.21 (-0.81-0.4) p=0.50
Support for clinical research from physicians in the PICU	0.02 (-0.01-0.05) p=0.16	0.05 (-0.11-0.22) p=0.54	-0.29 (-0.9-0.32) p=0.36	0.29 (-0.26-0.83) p=0.31
Support for clinical research from other health professionals in the PICU	0.02 (-0.02-0.06) p=0.24	0.01 (-0.18-0.21) p=0.89	-0.18 (-0.91-0.55) p=0.63	-0.1 (-0.76-0.55) p=0.76
Support for clinical research from the hospital or PICU administration	0.03 (-0.01-0.07) p=0.10	-0.05 (-0.25-0.15) p=0.62	-0.5 (-1.22-0.22) p=0.17	-0.11 (-0.76-0.53) p=0.74

Barriers and facilitators	Participant variables			
	Years of experience in pediatric critical care	**Number of RCT publications**	**Country income level:** Respondents from a high-income country vs. middle-income country	**Multicentred RCTs:** Respondents who have published a multicentred RCT vs. those who have not
Conducting preliminary studies (not pilot RCTs) before proceeding to an RCT	0.01 (-0.02-0.04) p=0.58	0.12 (-0.04-0.29) p=0.16	0.34 (-0.26-0.95) p=0.27	0.04 (-0.51-0.58) p=0.89
Conducting pilot RCTs before proceeding to a larger RCT	0 (-0.03-0.03) p>0.99	0.09 (-0.09-0.27) p=0.33	0.1 (-0.55-0.75) p=0.77	-0.11 (-0.71-0.48) p=0.71
Adopting a programmatic approach to research	0 (-0.03-0.03) p=0.98	0.08 (-0.1-0.25) p=0.38	0.43 (-0.2-1.06) p=0.18	0.17 (-0.41-0.74) p=0.57
Conducting observational studies to estimate treatment effects instead of RCTs	-0.01 (-0.05-0.02) p=0.47	0.21 (0.01-0.41) p=0.04	0.17 (-0.55-0.89) p=0.64	-0.16 (-0.82-0.49) p=0.63
Using a Bayesian approach to sample size estimation	-0.02 (-0.05-0.02) p=0.35	0.14 (-0.04-0.32) p=0.13	-0.01 (-0.67-0.66) p=0.98	-0.59 (-1.19-0) p=0.05
Using factorial designs (RCTs testing more than one intervention at the same time)	-0.02 (-0.05-0.02) p=0.33	0.18 (-0.01-0.37) p=0.07	0.06 (-0.64-0.76) p=0.87	-0.1 (-0.73-0.54) p=0.76
Conducting pediatric and adult RCTs in parallel, sharing infrastructure	0.01 (-0.04-0.05) p=0.81	0.08 (-0.14-0.3) p=0.48	0.36 (-0.44-1.17) p=0.38	0.18 (-0.55-0.91) p=0.63
Using surrogate or intermediate outcomes to reduce the sample size required	-0.01 (-0.05-0.02) p=0.46	0.05 (-0.16-0.25) p=0.64	-0.02 (-0.75-0.71) p=0.96	-0.02 (-0.69-0.64) p=0.95
Facilitated opportunities for multi-national collaboration	0 (-0.03-0.03) p=0.89	0.06 (-0.11-0.22) p=0.50	-0.21 (-0.82-0.39) p=0.50	0.21 (-0.34-0.76) p=0.46
Conducting RCTs in collaboration with a research network	0.01 (-0.02-0.03) p=0.53	0.04 (-0.09-0.16) p=0.56	-0.15 (-0.6-0.3) p=0.50	0.16 (-0.24-0.57) p=0.43
Creating more research networks	-0.01 (-0.05-0.02) p=0.52	-0.01 (-0.19-0.17) p=0.95	-0.53 (-1.18-0.13) p=0.12	-0.16 (-0.76-0.44) p=0.60
Reciprocal review by Research Ethics Boards	0 (-0.03-0.04) p=0.81	0.03 (-0.16-0.22) p=0.79	0.18 (-0.52-0.87) p=0.62	-0.07 (-0.71-0.56) p=0.82
Centralized ethical approval (e.g., Regional or National Research Ethics Boards)	0 (-0.04-0.04) p=0.86	0 (-0.22-0.21) p=0.98	0.74 (-0.05-1.53) p=0.07	0.08 (-0.64-0.8) p=0.82
Templates for contracts between study sites for RCTs in pediatric critical care	0 (-0.04-0.04) p=0.93	0.15 (-0.05-0.34) p=0.14	0.25 (-0.46-0.97) p=0.48	-0.2 (-0.85-0.45) p=0.55
Simplified consent forms	0 (-0.03-0.03) p=0.99	0.04 (-0.12-0.2) p=0.65	-0.06 (-0.64-0.53) p=0.85	-0.13 (-0.67-0.4) p=0.62
Deferred consent for enrolment in RCTs when suitable	0 (-0.04-0.03) p=0.78	0.17 (-0.01-0.35) p=0.07	0.56 (-0.1-1.22) p=0.10	-0.14 (-0.73-0.46) p=0.65
Waived consent for enrolment in RCTs when suitable	-0.01 (-0.04-0.03) p=0.75	0.18 (-0.02-0.38) p=0.08	0.65 (-0.09-1.38) p=0.09	-0.18 (-0.84-0.49) p=0.60

Barriers and facilitators	Participant variables			
	Years of experience in pediatric critical care	**Number of RCT publications**	**Country income level:** Respondents from a high-income country vs. middle-income country	**Multicentred RCTs:** Respondents who have published a multicentred RCT vs. those who have not
Telephone consent for enrolment in RCTs when required	0.01 (-0.04-0.05) p=0.74	0.19 (-0.05-0.42) p=0.12	0.74 (-0.11-1.59) p=0.09	-0.28 (-1.05-0.49) p=0.48
Study protocols that permit physicians to abandon or modify the study intervention	-0.01 (-0.05-0.03) p=0.76	0.12 (-0.1-0.34) p=0.29	-0.64 (-1.44-0.16) p=0.12	-0.17 (-0.9-0.56) p=0.64
Using learners as research personnel to reduce staffing costs	-0.06 (-0.09--0.02) p=0.005	0.06 (-0.14-0.26) p=0.56	0.25 (-0.49-0.99) p=0.51	-0.41 (-1.09-0.27) p=0.24
More research personnel at each center	-0.01 (-0.04-0.01) p=0.34	0.03 (-0.12-0.19) p=0.68	0.16 (-0.4-0.72) p=0.58	-0.16 (-0.66-0.35) p=0.55
Ability to recruit participants 24h per day, 7 days per week	0.01 (-0.01-0.04) p=0.30	0.05 (-0.09-0.18) p=0.50	0.35 (-0.14-0.85) p=0.16	-0.1 (-0.55-0.36) p=0.68
Reducing the amount of data collected for each study participant	0 (-0.03-0.03) p=0.90	0.08 (-0.1-0.25) p=0.39	0.46 (-0.17-1.1) p=0.16	-0.05 (-0.63-0.52) p=0.86
Co-enrollment (enrolling children in more than one RCT at the same time)	-0.01 (-0.06-0.04) p=0.74	0.18 (-0.08-0.43) p=0.18	0.47 (-0.46-1.4) p=0.32	-0.06 (-0.92-0.79) p=0.89
Reimbursing clinical personnel for research activities	-0.01 (-0.04-0.02) p=0.34	-0.11 (-0.27-0.05) p=0.18	-0.17 (-0.75-0.41) p=0.57	0.32 (-0.22-0.85) p=0.25
Funding for programs of research rather than individual studies	-0.03 (-0.07-0) p=0.08	0.15 (-0.04-0.34) p=0.13	-0.13 (-0.83-0.56) p=0.71	0.13 (-0.52-0.77) p=0.70
Funding from government agencies specifically for RCTs in critically ill children	0 (-0.03-0.03) p=0.97	0.05 (-0.09-0.18) p=0.51	0.03 (-0.47-0.53) p=0.90	0.17 (-0.29-0.62) p=0.48
Funding from local departments, universities and hospitals	0 (-0.03-0.03) p=0.83	0.07 (-0.1-0.23) p=0.41	-0.05 (-0.65-0.55) p=0.86	-0.08 (-0.63-0.47) p=0.77
Funding from charitable foundations	-0.02 (-0.05-0.02) p=0.37	0.12 (-0.07-0.31) p=0.20	0.47 (-0.21-1.16) p=0.18	0.36 (-0.27-0.99) p=0.26
Funding from industry for investigator-initiated RCTs	-0.02 (-0.06-0.02) p=0.34	0.02 (-0.19-0.24) p=0.82	0.68 (-0.11-1.48) p=0.09	-0.1 (-0.83-0.63) p=0.79
Funding from industry for industry-sponsored RCTs	0 (-0.04-0.04) p=0.99	-0.03 (-0.26-0.2) p=0.80	0.71 (-0.14-1.56) p=0.11	-0.12 (-0.9-0.66) p=0.76
Formal research clinical methods training for investigators	-0.01 (-0.04-0.02) p=0.64	-0.03 (-0.19-0.14) p=0.75	-0.41 (-1.01-0.2) p=0.19	-0.11 (-0.66-0.44) p=0.70
Mentorship from individuals within your institution	0.01 (-0.02-0.05) p=0.54	-0.02 (-0.2-0.16) p=0.83	-0.07 (-0.74-0.6) p=0.84	-0.45 (-1.06-0.16) p=0.15
Mentorship from individuals outside of your institution	-0.01 (-0.04-0.03) p=0.71	-0.01 (-0.2-0.18) p=0.93	-0.03 (-0.72-0.67) p=0.94	0.3 (-0.33-0.94) p=0.35

Barriers and facilitators	Participant variables			
	Years of experience in pediatric critical care	**Number of RCT publications**	**Country income level:** Respondents from a high-income country vs. middle-income country	**Multicentred RCTs:** Respondents who have published a multicentred RCT vs. those who have not
Role models or examples of researchers who do rigorous RCTs	0.01 (-0.02-0.04) p=0.69	-0.04 (-0.2-0.13) p=0.67	-0.38 (-0.98-0.22) p=0.22	0.11 (-0.45-0.66) p=0.71
Published examples of high-quality RCTs in pediatric critical care	0 (-0.04-0.03) p=0.80	0.05 (-0.12-0.21) p=0.58	-0.42 (-1.02-0.19) p=0.18	0 (-0.56-0.56) p>0.99
Support for conducting RCTs from academic department	0.02 (-0.01-0.04) p=0.30	0.05 (-0.1-0.21) p=0.52	-0.35 (-0.92-0.22) p=0.23	-0.29 (-0.81-0.23) p=0.27

The table shows the results of the multivariate analysis, reporting the coefficient (95% CI) and p-value for each covariate. Shaded values are statistically significant (p<0.01).

Appendix E: Qualitative interview study

Participant information sheet

Participant information

Study title: The future of randomized controlled trials in pediatric critical care.

Principal Investigator: Mark Duffett (McMaster University, Hamilton, Canada)

Co-investigators: Marilyn Swinton, Karen Choong, Deborah Cook
(McMaster University, Hamilton, Canada)

Funding: The Canadian Institutes of Health Research

We are inviting you to participate in a study focusing on identifying acceptable, feasible and effective strategies to improve the evidence available from RCTs in pediatric critical care. We are inviting you because of your expertise as an accomplished researcher who has published an RCT in pediatric critical care. Your participation is of course voluntary and choosing not to participate will not have any negative consequences for you.

Why is this study being done?

The care of all critically ill children should be informed by evidence from high-quality RCTs. Unfortunately, such evidence is not always available. The objective of this study is to identify strategies that pediatric critical care trialists consider to be acceptable, feasible and effective strategies to improve the evidence available from RCTs in pediatric critical care.

Who is eligible to participate in this study?

We will recruit approximately 30 participants from around the world. We are inviting researchers who have published an RCT in pediatric critical care in the past 10 years to participate in this study. We will select researchers to capture a wide range of perspectives and experiences and achieve diversity with respect to their country of origin, number of published RCTs, profession and the characteristics of the RCTs they have published.

What will participants in this study be required to do?

The only requirement is your participation in a single interview lasting 30-45 minutes, focusing on your experiences a researcher conducting RCTs. If you agree to participate, we will schedule the interview at a time that is convenient for you. You can choose to participate in the interview by video conference (using GoToMeeting®) from your computer or mobile device, or by calling

Interview guide

General principles

1. Don't present data from survey so as to avoid leading participants.
2. Steer conversation back to focus on facilitators that are within the purview of pediatric critical care researchers and clinicians.
3. Keep conversation focused on the study participant and their experiences and views to make them feel important and engaged.

Preamble

1. **Introduction:** Thank you for agreeing to participate in this study. We asked you to participate because you have successfully completed an RCT(s) and we believe that you will have important experience and perspectives to share.
2. **Introduction to interviewer:** So that you have a bit of background about me, I'm a PhD candidate in Health Research Methodology at McMaster University, Canada. I work as pharmacist in the PICU and I've completed a trial too. This study is part of a program of research on RCTs in pediatric critical care
3. **Focus and objectives:** The main purpose of this study is to help future researchers benefit fully from the experience of experienced researchers like yourself. We are hoping to get practical advice for new investigators. The focus of this study is on RCT pediatric critical care and we are focusing on facilitators rather than barriers to research. We are also most interested on what pediatric critical care researchers can do rather than external things like funding.
4. **Reminder of interview length and recording:** The interviews usually take approximately 30-45 minutes and we will keep this conversation confidential. Did you have a chance to review the information sheet I sent you? Do you have any questions about the study? So with your consent I'll audio-record the interview.
5. **Summary:** I've prepared some questions, some may not apply or you might not be able to answer. That's ok, just let me know. Do you have any questions before we

start? Ok, great. Just to remind you, the main goal of this discussion is to get practical advice for researchers.

Questions

First I have some questions about your experiences.

1. I know you have been a co-author on at least __ published trials, [name them].
    a. Can you give me an example of something that you did in the trial that worked out really well?
    b. What was the biggest thing you learned doing your trial(s)?
    c. What did you find most surprising about doing your trials?
    d. How were your experiences different with your different trials [if more than one done]
2. What things did you find most helpful when you were doing your RCTs?
    a. Are there things that really helped with the design/planning/starting/conducting your trials?
    b. potential categories: mentorship, funding, collaborators

    Prompts: Why/how/who…

    Can you think of examples…

    What type of…/What added value was…

3. What type of things at your **centre** support this type of research?
    a. Are there particular things at your **centre** that make it easier to do RCTs than at some other centres?
    b. How/why are some **centres** better than others at supporting this type of research?
    c. potential things: research culture, value placed on research, sense of collaboration, academic credit for clinical research)

    Prompts: Why/how/who…

    Can you think of examples…

What type of…

How are things different being a PI instead of a site investigator?

4. What type of things at your **country** support this type of research?
    a. Are there particular things at your **country** that make it easier to do RCTs than at some other centres?
    b. How/why are some **countries** better than others at supporting this type of research?
    c. potential things: culture, regulatory environment.

    Prompts: Why/how/who…

    Can you think of examples…

    What type of…

5. Knowing what you know now, what would you have liked to do differently if you were to start again?
    a. Are there things you would have added?/done better?/done differently?/eliminated?
    b. Break down into stages: design/planning/starting/conducting/teams

    Prompts: Why/how/who…

    Can you think of examples…

    What type of…/What added value was…

6. Are you planning or conducting another RCT now?
    a. [if yes] What are you doing differently now?
    b. [if no] What would make you do it again (aside from funding)?

[Regroup, summarize a few key points from this section here]. So a few of the things you mentioned were____.

7. Those are all great ideas for individuals. What about as a group? What are the important things that the pediatric critical care research community can do right now?

    Prompts: Why/how/who…
    Can you think of examples…
    What type of…
    If not now, what about in the future?
    How/why do you think these will work?

8. Those are really great ideas, how do you think we can make them happen?
9. What will it take for researchers to adopt/join/participate etc?
10. What are the characteristics of people who could successfully lead/champion this?

    Prompts: What type of leadership would be most important?
    Are there particular people who you think would be able to lead/coordinate this ?

11. Are there particular organizations that could play a role in improving how RCTs are done in pediatric critical care?

    Prompts: meetings/conferences/consortia/research groups
    Why/how/who…
    Can you think of examples…/What type of…
    If not now, what about in the future?
    How/why do you think these will work?

[Regroup, summarize a few key points from this section here]. So a few of the things you mentioned were____.

Thanks for your answering my questions, your answers have been very helpful. We are almost done, but before I go, I do have a few final questions to help us better understand who has participated in this study.

12. For how many years have you been in clinical practice?
13. Have you been doing clinical research in pediatric critical care for all that time?
14. Were there aspects of your training were particularly helpful in preparing you for doing clinical research?

    Prompts: What type of training in research did you receive?
    Are there other things that that would have been helpful in your training?

Those are all the questions I have. You have been most helpful.

15. Is there anything else you want to say that you haven't mentioned yet? Is there anything you'd like to discuss in more detail?

Thanks very much, your thoughts have been very insightful and most helpful. Please email me or call me if you think of anything else that might be useful for this study. If you are interested, we'll also send you a brief summary of the findings when the study is completed this spring.

Strategies to redirect

1. ok, so we've covered funding…
    a. that is a common problem people have mentioned…..I'm also interested in….
2. that is indeed an important barrier/problem…
    a. how did you deal with it?
    b. how could you have overcome this the next time?
    c. how have other people dealt with it?
    d. do you have any ideas on how you could have overcome this?
    e. do you have any ideas on how you would deal with this next time?
3. ok, those are all great points, can we focus on [name one of their points] next?