



Consensus Statement | Pediatrics

Prioritization of Randomized Clinical Trial Questions for Children Hospitalized With Common Conditions

A Consensus Statement

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Abstract

IMPORTANCE There is a lack of randomized clinical trial (RCT) data to guide many routine decisions in the care of children hospitalized for common conditions. A first step in addressing the shortage of RCTs for this population is to identify the most pressing RCT questions for children hospitalized with common conditions.

OBJECTIVE To identify the most important and feasible RCT questions for children hospitalized with common conditions.

DESIGN, SETTING, AND PARTICIPANTS For this consensus statement, a 3-stage modified Delphi process was used in a virtual conference series spanning January 1 to September 29, 2022. Forty-six individuals from 30 different institutions participated in the process. Stage 1 involved construction of RCT questions for the 10 most common pediatric conditions leading to hospitalization. Participants used condition-specific guidelines and reviews from a structured literature search to inform their development of RCT questions. During stage 2, RCT questions were refined and scored according to importance. Stage 3 incorporated public comment and feasibility with the prioritization of RCT questions.

MAIN OUTCOMES AND MEASURES The main outcome was RCT questions framed in a PICO (population, intervention, control, and outcome) format and ranked according to importance and feasibility; score choices ranged from 1 to 9, with higher scores indicating greater importance and feasibility.

RESULTS Forty-six individuals (38 who shared demographic data; 24 women [63%]) from 30 different institutions participated in our modified Delphi process. Participants included children's hospital (n = 14) and community hospital (n = 13) pediatricians, parents of hospitalized children (n = 4), other clinicians (n = 2), biostatisticians (n = 2), and other researchers (n = 11). The process yielded 62 unique RCT questions, most of which are pragmatic, comparing interventions in widespread use for which definitive effectiveness data are lacking. Overall scores for importance and feasibility of the RCT questions ranged from 1 to 9, with a median of 5 (IQR, 4-7). Six of the top 10 selected questions focused on determining optimal antibiotic regimens for 3 common infections (pneumonia, urinary tract infection, and cellulitis).

CONCLUSIONS AND RELEVANCE This consensus statement has identified the most important and feasible RCT questions for children hospitalized with common conditions. This list of RCT questions

(continued)

Key Points

Question What are the most important and feasible randomized clinical trial (RCT) questions for children hospitalized with common conditions?

Findings In this consensus statement, a 3-stage modified Delphi process involving multidisciplinary input from 46 individuals across 30 institutions produced 62 unique RCT questions, ranked according to importance and feasibility.

Meaning These RCT questions can guide investigators and funders in conducting impactful trials to improve care and outcomes for children hospitalized with common conditions.

+ Supplemental content

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Abstract (continued)

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Introduction

Randomized clinical trials (RCTs) are the criterion standard design to determine the efficacy or effectiveness of a given intervention. Although the number of RCTs involving adult participants has increased over time, the number of RCTs involving children has stalled in the last 2 decades.¹ The relative lack of RCTs including children results in pediatric clinicians more often having to make medical decisions based on observational studies, adult studies, or expert opinion.

Children are vulnerable to morbidity and mortality while hospitalized, making hospitalized children a priority population for RCTs. The pediatric RCTs that have led to the greatest recent improvements in outcomes for hospitalized children have focused on novel therapeutics for severe but relatively uncommon conditions, such as cystic fibrosis² and neuromuscular disease.³ Randomized clinical trials for the most common pediatric conditions that lead to hospitalization are comparatively scarce.⁴ For example, based on prevalence of disease, there are several hundred fewer RCTs than would be expected for childhood respiratory infections.⁴

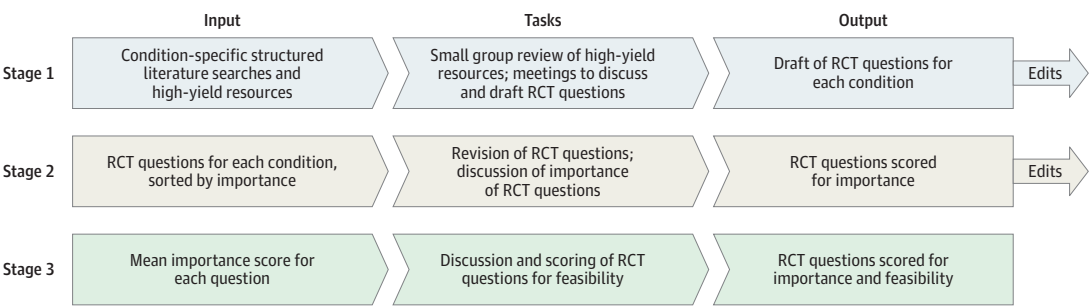
A first step toward conducting more RCTs involving common pediatric conditions for hospitalized children is to prioritize research questions for researchers and funders. The objective of this consensus statement was to identify the most important and feasible RCT questions for children hospitalized with common conditions.

Methods

Overview

In this consensus statement, we report on a 3-stage modified Delphi process conducted from January 1 to September 29, 2022 (Figure), and modeled after previous prioritization efforts incorporating clinician, researcher, and patient-parent perspectives.⁵⁻⁷ Construction of RCT questions occurred during stage 1, followed by evaluation of trial question importance in stage 2 and feasibility in stage 3. This study was reviewed by the University of Utah institutional review board and received an exemption determination because the research included only interactions involving educational tests, survey procedures, interview procedures, or observation of public behavior. Participants provided written consent and were offered a \$250 gift card for participating in the conference series.

Figure. Overview of Modified Delphi Process



RCT indicates randomized clinical trial.

Study Participants

We used purposive sampling to recruit study participants. The study team developed an initial expertise-based list of clinicians and researchers who were invited to participate. Patient-parent partners with affiliations to the study team and their institutions were also invited to participate. We then used a snowball sampling procedure to recruit participants with additional perspectives and expertise as needed. Participant race and ethnicity were reported by the participants themselves. The US Department of Health and Human Services Office of Minority Health categories for race and ethnicity were used. These variables were collected as a measure of the diversity of conference participants. Ensuring a diversity of backgrounds and perspectives was prioritized in recruitment. For example, in addition to diversity of gender, race, and ethnicity, we sought diversity by clinical background (eg, nurses, pharmacists, and physicians) and practice environment (eg, children's hospital and community hospital). Inclusion of community hospital participants was a priority because most children, particularly those hospitalized for common conditions, receive their care in settings other than freestanding children's hospitals.⁸

Stage 1: Construction of Trial Questions

We began stage 1 of our modified Delphi process in January 2022 by identifying common pediatric conditions to serve as the basis for generating RCT questions. We used national hospitalization utilization data to identify the 10 most common pediatric conditions leading to hospitalization.^{9,10} We excluded conditions for which surgical or other specialist clinicians may lead management (eg, appendicitis, diabetic ketoacidosis, and epilepsy). After applying this exclusion, we found that the 10 most common pediatric conditions (in decreasing order of prevalence) were birth hospitalization, bronchiolitis, pneumonia, asthma, mood disorders, cellulitis, neonatal hyperbilirubinemia, urinary tract infection, gastroenteritis, and septicemia. Together, these conditions accounted for more than 75% of all pediatric hospitalizations annually in the US.^{9,10}

A medical librarian (E.F.) performed structured literature searches for each condition. The medical librarian hand-searched the reference lists provided with each condition's diagnosis and treatment summaries in Dynamed and UpToDate, 2 evidence-based clinical resources. Next, the librarian created structured literature searches in PubMed to capture relevant guidelines or evidence syntheses for each condition. The core strategy is available in the eFigure in [Supplement 1](#). Four authors (E.R.C., C.E.M., N.P., and S.V.K.) with pediatric hospital medicine expertise reviewed the search results and selected 3 to 5 high-yield resources for each condition that were most pertinent to understanding the evidence gaps related to diagnosis or management of each condition. For example, clinical practice guidelines with a section devoted to evidence gaps or research needs existed for most conditions and were included in the high-yield resources.

We divided participants into small groups (n = 10) for each condition, making sure that community and children's hospital clinicians were represented in each small group. Each small group had at least 1 researcher with peer-reviewed publication expertise for that condition. Small groups had 2 months to review their high-yield resources, share additional resources with one another, and meet virtually to generate a list of at least 3 RCT questions for their assigned condition.

Stage 2: Evaluation of Trial Questions for Importance

We conducted a virtual conference in June 2022 for stage 2 of our modified Delphi process. The purpose of stage 2 was to refine the RCT questions generated in stage 1 and evaluate them in terms of importance. Stage 2 was grounded within a framework of 6 guiding questions (**Box 1**). This framework mirrored existing quality domains developed by the National Academy of Medicine.¹¹ Small groups took turns presenting their RCT questions to conference participants, sharing their impression of the importance of each question, receiving input from conference participants, and refining the questions. For each condition, patient-parent partners were asked to comment on patient centeredness of the presented RCT questions. We prioritized parent input within the discussion of each condition to ensure RCT questions were relevant and important to families. At the

conclusion of the first conference, individual participants anonymously scored all the RCT questions for importance on a scale of 1 to 9, with 9 indicating the highest level of importance. To establish external validity of the generated questions, the RCT questions were then distributed for public comment to the American Academy of Pediatrics Society of Hospital Medicine listserv (approximately 4000 members). We invited listserv members to provide input and feedback on the generated questions through 3 mechanisms: (1) scoring each question on the same importance scale, (2) providing commentary on the questions, and (3) offering suggestions of additional important questions for consideration.

Stage 3: Additional Evaluation of Trial Questions for Feasibility

We conducted a second virtual conference in September of 2022 for stage 3 of our modified Delphi process. The purpose of stage 3 was to incorporate feasibility into the prioritization of the RCT questions. The public comment and ratings of RCT questions generated in stage 2 were reviewed for incorporation and consideration. Small groups were given time to discuss the feasibility of their RCT questions guided by 3 core questions (Box 2). Small groups group-scored each of their RCT questions on a feasibility scale of 1 to 9, where scores higher than 6 indicated RCT questions that were feasible for all 3 core feasibility questions, scores of 4 to 6 indicated RCT questions with a feasibility concern in 1 core feasibility question, and scores lower than 4 indicated RCT questions with a feasibility concern in more than 1 core feasibility question. Small groups then reported to the full group of conference participants, sharing their impressions and scores for the feasibility of each RCT question, with further input from conference participants.

At the conclusion of this conference, participants were provided the summary scores and comments related to the importance and feasibility of each question and asked to submit a final overall score for each question. This scoring was individual and anonymous, using a 1 to 9 scale, with higher scores indicating the most important and feasible RCT questions.

Results

Study Participants

A total of 46 individuals from 30 different institutions participated in our modified Delphi process. Participants included children's hospital (n = 14) and community hospital (n = 13) pediatricians, parents of hospitalized children (n = 4), other clinicians (ie, nurse and pharmacist; n = 2),

Box 1. Framework for Evaluating the Importance of the RCT Question

- To what extent will this RCT...
1. Answer a question that patients and their families care about (patient centeredness)?

2. Improve the patient experience?

3. Improve important clinical outcomes?

4. Increase efficiency or reduce variation in care delivery?

5. Improve safety?

6. Promote diversity, equity, and inclusion?

Abbreviation: RCT, randomized clinical trial.

Box 2. Framework for Evaluating the Feasibility of the RCT Question

1. How straightforward, or not, would it be to administer the proposed intervention and control group requirements at your institution? Are the intervention and controls doable at your institution?

2. In your usual practice, how commonly do you care for patients who would be eligible for this trial (eg, weekly, monthly, and yearly)?

3. What challenges, if any, do you anticipate for collection of outcomes data in this trial?

Abbreviation: RCT, randomized clinical trial.

biostatisticians (n = 2), and other researchers (eg, trialists and research coordinators; n = 11). Pediatric clinical expertise represented by these participants included hospital medicine (n = 27), general pediatrics (n = 3), infectious disease (n = 2), emergency medicine (n = 1), and critical care (n = 1). Participant geographic representation included Canada (n = 4) and all 4 US Census Bureau regions: West (n = 24), Midwest (n = 7), Northeast (n = 7), and South (n = 4). Conference participants who shared their demographic data (n = 38) self-identified as women (24 of 38 [63%]) and men (14 of 38 [37%]) and as having the following races and ethnicities: Asian ([4 of 38] 11%), Black or African American ([3 of 38] 8%), Hispanic ([2 of 38] 5%), Native Hawaiian or Other Pacific Islander ([1 of 38] 3%), and White ([30 of 38] 79%). A total of 115 listserv respondents provided comments and/or ratings of RCT questions generated in stage 2 of the modified Delphi process.

Most Important and Feasible RCT Questions

This process produced 62 unique RCT questions. Participant scores for the importance of each RCT question ranged from 1 to 9, with a median of 5 (IQR, 3-7). Participant overall scores, incorporating both importance and feasibility of the RCT question, ranged from 1 to 9, with a median of 5 (IQR, 4-7). The 10 RCT questions with the highest overall mean scores are summarized in the Table in a PICO (population, intervention, control, and outcome) format. The remaining 52 questions generated by this work and their mean scores are displayed in the eTable in Supplement 1.

A total of 7 of 62 questions (11%) scored higher than 6 for importance. Five of those questions also had overall scores higher than 6, and all 5 of those questions were in the top 10 RCT questions by overall score. Six of the top 10 selected questions focused on determining optimal antibiotic regimens for 3 common infections (pneumonia, urinary tract infection, and cellulitis). Two questions scored higher than 6 for importance but decreased below 6 after considering feasibility. These 2 questions involved antibiotic duration for children with bacteremia or meningitis and ultimately ranked 25th and 29th (eTable in Supplement 1).

Discussion

For this consensus statement, we led a national, 3-stage modified Delphi process involving interdisciplinary, expert stakeholders, including patient-parent partners, to identify the most important and feasible RCT questions for children hospitalized with common conditions. Most of the

Table. Most Important and Feasible RCT Questions for Children Hospitalized With Common Conditions

Rank	RCT question				Mean (SD) score ^a	
	Population: children hospitalized for condition	Intervention	Control	Outcome	Importance	Overall
1	Cellulitis	Short-course antibiotics (≤5 d)	Longer-course antibiotics	Treatment failure	5.9 (2.1)	7.2 (1.1)
2	Pneumonia and medical complexity	Narrow-spectrum antibiotics	Broad-spectrum antibiotics	Clinical deterioration	6.7 (2.1)	7.0 (1.7)
3	Urinary tract infection and aged ≤2 mo	7 d of Antibiotics	>7 d of Antibiotics	Treatment failure	6.6 (1.9)	6.9 (1.3)
4	Urinary tract infection and aged >2 mo	7 d of Antibiotics	>7 d of Antibiotics	Treatment failure	5.7 (2.4)	6.7 (1.6)
5	Pneumonia	Oral antibiotics	IV antibiotics	Time to recovery	6.6 (2.0)	6.6 (1.2)
6	Urinary tract infection, bacteremia, and aged >2 mo	Transition from IV to oral antibiotics based on clinical course	Fixed duration of IV antibiotics	Treatment failure	6.3 (1.9)	6.6 (1.6)
7	Asthma	Prednisone or prednisolone	Dexamethasone	Readmission or ED revisit	5.1 (2.6)	6.4 (1.8)
8	Gastroenteritis	Nasogastric or subcutaneous hydration	IV hydration	Length of stay	6.1 (2.2)	6.3 (1.4)
9	Fever and aged <2 mo	Telemedicine follow-up	In-person follow-up	Caregiver satisfaction	5.8 (2.3)	6.3 (2.0)
10	Mood disorders	Health care team de-escalation training	Usual or standard training	Behavioral health security activation or use of restraints	6.0 (2.3)	6.2 (1.5)

Abbreviations: ED, emergency department; IV, intravenous; RCT, randomized clinical trials.

^a RCT questions were scored on a scale of 1 to 9, with 9 indicating the highest level of importance (Importance column) or importance and feasibility (Overall column).

RCT questions that we identified were pragmatic, comparing interventions in widespread use for which definitive effectiveness data are lacking. Our findings serve as an empirical foundation to guide investigators and funders in conducting impactful trials that improve outcomes for children hospitalized with common conditions.

The present research prioritization effort differs from existing prioritization studies in several fundamental ways. Some prior studies have focused on understanding condition prevalence, care variation, and costs for pediatric hospitalizations as a means to prioritize specific conditions for research.^{9,12,13} Identification of condition-specific research topics or questions was outside the scope of these studies. Other prioritization studies have focused on broader (eg, all of pediatrics⁶) or narrower (eg, chronic conditions¹⁴ and palliative care¹⁵) sets of conditions or settings that overlap with hospitalization (eg, emergency care¹⁶ and patient safety¹⁷). Nearly all existing prioritization studies, including a recent study focused on hospitalized children,⁷ have produced priority topic areas (eg, What methods of communication are most effective between patients and clinicians?), as opposed to specific PICO-framed questions. Questions developed within existing prioritization studies were also not honed for a specific empirical research strategy, such as RCTs. To our knowledge, our research prioritization is unique in its focus on hospitalized children with common conditions and its development of specific PICO-framed questions designed to be readily answered in RCTs.

The questions that were prioritized in this process reflect broad goals of improving the value of care delivered to hospitalized children by avoiding unnecessary treatments. Six of the top 10 selected questions focused on determining optimal antibiotic regimens for 3 common infections (pneumonia, urinary tract infection, and cellulitis). There is wide variation in antibiotic prescribing for these infections, raising concerns for potential antibiotic overtreatment and its detrimental effects for children (antibiotic-associated adverse effects), families (stress and costs), and communities (emergence of resistant organisms).^{18,19} A growing body of RCT literature is demonstrating that less-aggressive antibiotic regimens are safe and effective for serious infections among adults (eg, pneumonia, bacteremia, osteomyelitis, and endocarditis), but trials on this topic remain rare for children, to our knowledge.^{20,21}

To address this ambitious list of RCT questions, investigators will likely need to augment traditional RCT designs with innovative and efficient RCT approaches. Many of the RCT questions developed in this study have natural overlap and could be considered for funding mechanisms that can support addressing multiple trial questions in a single application. For example, platform trials examine multiple research questions for a single condition.²² Given that the present work generated multiple RCT questions for each condition, platform RCTs might be an efficient design to address more than 1 of these RCT questions at once. Similarly, factorial RCT designs could be used to address multiple questions at once when understanding the synergistic effect of 2 or more interventions is key.²³ As an example, 3 of the top 6 RCT questions developed here involve children hospitalized with urinary tract infections and their antibiotic regimens. The single condition entity and similar interventions could lend themselves to a platform or factorial design. Randomized clinical trial questions developed here may also lend themselves to a high-efficiency randomized controlled (HEROIC) trial approach, which uses a dispersed enrollment strategy to efficiently conduct pragmatic RCTs.²⁴

Limitations

The consensus statement has several important limitations. First, these RCT questions will require further refinement as the trial is designed, including additional definitions for each intervention and careful consideration of the right primary outcome. Second, our consideration of feasibility focused on trial infrastructure (the ability to recruit, administer intervention or control, and collect data). This feasibility assessment was within the scope of conference participant skills and resources. During formal trial design or preparation, an additional feasibility assessment would be completed, including human participants protection review, confirmation of adequate numbers of eligible participants at

proposed study sites, formal sample size estimates, power calculations, and budget or cost estimates. These considerations will undoubtedly influence the feasibility of each RCT question. Third, conference participants were diverse in many ways but did not represent all perspectives pertinent to RCT question generation in this population. Fourth, RCT question development was organized around common conditions. Undoubtedly, there are additional important and feasible questions that are not condition based (eg, RCTs comparing processes such as transitions of care) or that are focused on less-common conditions. Fifth, our 3-stage process could have been subject to anchoring bias, in which decisions made early in the process by smaller numbers of participants are difficult to reconsider later in the process. Sixth, investigators who pursue the RCTs described in this study will still contend with pervasive impediments to RCTs for children, such as relatively modest disease prevalence, lower frequency of objective outcome measures (eg, mortality), and fewer sources of funding compared with RCTs for adult populations. For example, the 2 questions that scored higher than 6 for importance but then ultimately decreased below 6 after considering feasibility involved less-common subpopulations of hospitalized children (children with bacteremia or meningitis). For RCT questions with particularly low feasibility scores, observational study designs might be more practical.

Conclusion

In this consensus statement, we have identified the most important and feasible RCT questions for children hospitalized with common conditions. These conditions are responsible for more than three-fourths of pediatric hospitalizations. Answering these pressing questions with RCTs has great potential to improve care and outcomes for hospitalized children.

ARTICLE INFORMATION

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Author Contributions: Dr Coon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Coon, McDaniel, Paciorkowski, Jennings, Wilson, Kaiser.

Acquisition, analysis, or interpretation of data: Coon, McDaniel, Paciorkowski, Grimshaw, Frakes, Ambroggio, Auger, Cohen, Garber, Gill, Joshi, Leyenaar, McCulloh, Pantell, Sauers-Ford, Schroeder, Srivastava, Wang, Wilson, Kaiser.

Drafting of the manuscript: Coon, Frakes, Gill, Pantell.

Critical review of the manuscript for important intellectual content: Coon, McDaniel, Paciorkowski, Grimshaw, Frakes, Ambroggio, Auger, Cohen, Garber, Gill, Jennings, Joshi, Leyenaar, McCulloh, Sauers-Ford, Schroeder, Srivastava, Wang, Wilson, Kaiser.

Statistical analysis: Coon.

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Administrative, technical, or material support: Grimshaw, Ambroggio, Gill, McCulloh, Wilson, Kaiser.

Supervision: Wilson, Kaiser.

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SUPPLEMENT 1.

eFigure. Core Search Strategy for Structured Literature Search

eTable. Additional RCT Questions, Ranked by Overall Score

SUPPLEMENT 2.

Nonauthor Collaborators

SUPPLEMENT 3.

Data Sharing Statement