PROTOCOL TITLE: Comparing Two Durations of Antibiotic Treatment for Children Hospitalized for fewer than 5 days with Common Infections (TRIAD)

CCHMC IRB#: 2025-0661

PRINCIPAL INVESTIGATORS:

Dual PI Names	Sunitha Vemula Kaiser	Katherine Ann Scott Auger
PI Title	Professor of Pediatrics, Epidemiology & Biostatistics Chief of Pediatric Hospital Medicine	Professor of Pediatrics Research Director of the Division of Hospital Medicine
PI Division	Pediatric Hospital Medicine	Hospital Medicine
PI Institution	University of California, San Francisco	Cincinnati Children's Hospital Medical Center
PI Office Phone	415-476-3392	513-803-3234
PI E-mail Address	Sunitha.kaiser@ucsf.edu	Katherine.auger@cchmc.org

VERSION NUMBER/DATE: 5.0 20Feb2026

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	18Nov2025	Responded to comments from IRB chair before committee review	No
2	25Nov2025; 12Dec2025	Responded to feedback from PCORI; added Appendix 1	No
3	17Dec2025	Responded to IRB committee comments	No
4	20Feb2026	Incorporated DSMB recommendations; updated compensation allocation	Yes

Table of Contents

1.0 Study Summary 3
2.0 Objectives* 4
3.0 Background* 4
4.0 Study Endpoints* 6
5.0 Study Intervention/Investigational Agent 10
6.0 Procedures Involved* 111
7.0 Data and Specimen Banking* 143
8.0 Sharing of Results with Subjects* 143
9.0 Study Timelines* 144
10.0 Inclusion and Exclusion Criteria* 14
11.0 Vulnerable Populations* 176
12.0 Local Number of Subjects 176
13.0 Recruitment Methods 16
14.0 Withdrawal of Subjects* 198
15.0 Risks to Subjects* 198
16.0 Potential Benefits to Subjects* 209
17.0 Data Management* and Confidentiality 209
18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects* 243
19.0 Provisions to Protect the Privacy Interests of Subjects 297
20.0 Compensation for Research-Related Injury 297
21.0 Economic Burden to Subjects 297
22.0 Consent Process 297
23.0 Process to Document Consent in Writing 28
24.0 Setting 308
25.0 Resources Available 319
26.0 Multi-Site Research* 29

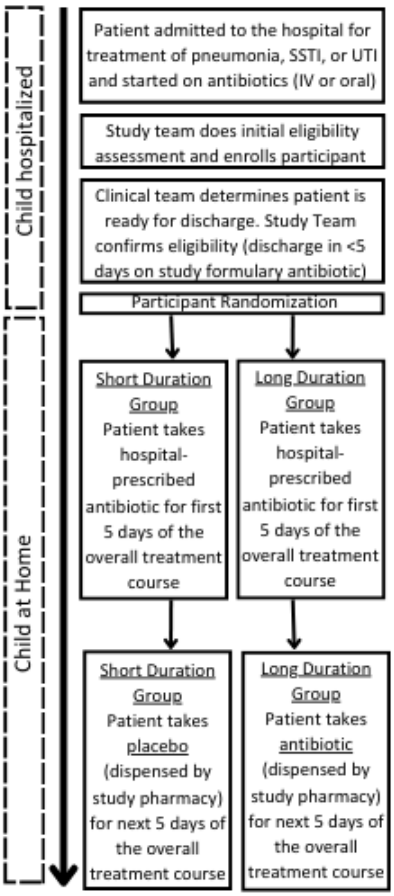
1.0 Study Summary

Protocol Information	Description
Study Title	Trial of Reducing Inpatient Antibiotic Durations in Children (TRIAD)
Study Design	Double-blinded, placebo-controlled randomized controlled trial
Primary Objective	Determine if short duration antibiotic treatment (5 days total) is superior to long duration treatment (10 days total) in children hospitalized with common bacterial infections (pneumonia, skin and soft tissue infection, urinary tract infection)
Secondary Objective(s)	Determine condition-specific and subgroup effects of short versus long duration treatment
Research Intervention(s)/ Investigational Agent(s)	5-days vs. 10-days of antibiotics; Antibiotics include: Amoxicillin, Amoxicillin-clavulanate, Cefdinir, Cefixime, Cephalexin, Ciprofloxacin, Clindamycin, Sulfamethoxazole/ Trimethoprim. Placebo: designed to be look alike/taste alike
IND/IDE #	N/A
Study Population	Children: 1) discharged from pediatric hospital medicine services at 11 enrolling hospitals; 2) treated for pneumonia, skin and soft tissue infection, or urinary tract infection, and 3) prescribed on one of the study formulary antibiotics
Sample Size	1200 randomized, up to 2000 enrolled
Study Duration for individual participants	From hospitalization to up to 40-days after discharge
Study Specific Abbreviations / Definitions	RCT – Randomized controlled trial EHR -- Electronic health record PNA – Pneumonia SSTI – Skin and soft tissue infections UTI – Urinary tract infections HTE – Heterogeneity of treatment effect DOOR-RADAR - Desirability of Outcome Ranking [DOOR] and Response Adjusted for Duration of Antibiotic Risk [RADAR] HM- Hospital medicine SCOUT-CAP - Short vs Standard-Course Outpatient Antibiotic Therapy for Community-Acquired Pneumonia in Children CCHMC – Cincinnati Children's Hospital Medical Center IDS – Investigational drug services IRB – Institutional Review Board CCC – Clinical Coordinating Center DCC – Data Coordinating Center DSMB – Data and Safety Monitoring Board AE – Adverse Event SAE – Serious Adverse Event HRS-Huron Research Systems (CCHMC IRB System) Note: We will also reference the PCORI Methodology Standards (as required by PCORI) in the following fashion **XX-#.** https://www.pcori.org/research/about-our-research/research-methodology/pcori-methodology-standards

2.0 Objectives

Aim 1. *Determine if short duration antibiotic treatment (5 days total) is superior to long duration treatment (10 days total) in children hospitalized with common bacterial infections (pneumonia, SSTI, UTI):* We will conduct a multicenter, double-blinded, placebo-controlled trial to compare short versus long antibiotic duration (1:1 allocation). We hypothesize that 5 days will be adequate to effectively treat children hospitalized with pneumonia, SSTI, and UTI and that children receiving fewer days of antibiotic therapy will have fewer side-effects. We will randomize 1200 children ages 60 days to 17 years hospitalized for <5 days for treatment of these infections (**Figure 1**). We will recruit participants from a total of 11 study sites across the US (combination of children's and community hospitals). Our primary outcome captures the full range of beneficial and harmful treatment effects using input from caregivers: treatment failure, symptom and function recovery, and antibiotic-associated adverse effects. Our analysis is powered for analyzing our total sample and each condition separately (pneumonia, SSTI, UTI). Our expected outcome is definitive, rigorous evidence on antibiotic treatment durations for the most common bacterial infections leading to childhood hospitalization.

Figure 1. Overview of Trial Design



Aim 2: *Determine condition-specific and subgroup effects of short versus long duration treatment:* We will determine treatment effects by condition (pneumonia, SSTI, UTI) using heterogeneity of treatment effect analyses of data collected in Aim 1. We will also examine the heterogeneity of treatment effects across several important clinical features (e.g., age, presence of bacteremia). Our expected outcome is tailored, evidence-based guidance to bolster clinician confidence in application of our trial results, even in higher-risk subgroups. **(RQ-4, (HT-1-3))**

Aim 3*: In the context of this trial, we will utilize qualitative methods to understand participant experiences with the recruitment and trial processes.* Using qualitative interviews, we will develop an understanding of participant experience, perspectives, and decision making related to trial participation. Our goal is to help maximize the feasibility of studies and to support optimal recruitment, retention, and data collection practices.

3.0 Background* (RQ-1, PC-1)

Bacterial infections are a leading cause of childhood hospitalization, and antibiotics are essential for effective treatment; however, using antibiotics for longer than necessary causes preventable harms. Pneumonia (PNA), skin and soft tissue infection (SSTI), and urinary tract infection (UTI) are leading causes of hospitalization in US children (~160,000 hospitalizations annually),[1] and are collectively responsible for millions of days of antibiotic therapy each year.[2] Although antibiotics are highly effective for treating these infections,[3-10] they are often used longer than needed.[11-15] This disrupts the normal human microbial environment

(i.e., the microbiome), reducing diversity and function of microbes and promoting the emergence and spread of antibiotic resistant bacteria. These changes have important consequences, including immediate antibiotic-associated adverse effects (e.g., upset stomach or diarrhea) as well as delayed effects (e.g., increased lifetime risk of severe allergic or autoimmune disease).[16-18] A subset of children experience severe antibiotic-associated adverse effects, including life-threatening drug reactions (e.g., anaphylaxis, Stevens-Johnson syndrome) and secondary infections with *Clostridioides difficile*, which can cause severe colitis, bowel perforation, or sepsis. There are over 70,000 estimated annual ED visits due to antibiotic adverse effects in children.[19] Further, the preferential selection for bacteria that are resistant to commonly used antibiotics also means more infections for which we have limited effective options. Over the past 20 years, there have been alarming increases in cases of children suffering from severe infections caused by resistant strains of *Streptococcus pneumoniae, Staphylococcus aureus*, and *Escherichia coli*.[20-22] Our team and others have demonstrated even small increases in antibiotic treatment duration, **by even a single day**, are associated with significantly greater risks of these preventable, harmful effects.[23-25]

Stakeholders broadly agree that the preventable harms of antibiotic overuse are important and studies that directly compare different antibiotic durations in hospitalized children are needed. Over the past 2 years, our team conducted a grant-funded national conference. It involved a 3-stage, modified Delphi process to prioritize research questions for improving outcomes in hospitalized children.[26] Forty-six stakeholders from 30 institutions participated, including children's and community hospital physicians, nurses, and pharmacists; caregivers of hospitalized children; and child health scientists. We also solicited broad input from professional organization listservs with thousands of members across the US. The conference involved review of guidelines and systematic reviews on the top conditions leading to hospitalization in children (both infectious and non-infectious, e.g., asthma) to identify evidence gaps and high-priority research questions. These research questions were ranked based on both importance and feasibility to answer with a randomized controlled trial. A total of 63 questions were identified. The top 6 highest-ranked questions focused on comparing antibiotic strategies to potentially reduce the preventable harms of antibiotics in children hospitalized with PNA, SSTI, and UTI while maintaining effectiveness—these stakeholder-prioritized studies are the foundation of this research. Additionally, in designing this study, we conducted a preliminary qualitative study of caregivers of hospitalized children. Caregivers raised many concerns about antibiotics, including the cost and difficulty of administering antibiotics to their children, worries about their children experiencing antibiotic-associated adverse effects (e.g., diarrhea, allergic reactions), and concern around developing antibiotic resistance. National and international health organizations also agree it is critical to determine the most effective antibiotic durations that minimize unnecessary harms.[27-29]

High-quality RCTs comparing antibiotic duration in hospitalized children are needed because of critical evidence gaps in this population. Evidence-based guidelines recommend a wide range of antibiotic durations for treating children hospitalized for PNA, SSTI, or UTI (5 to 14 days) **(RQ-3)**. Guideline authors acknowledge the limitations of needing to base these recommendations on expert opinion and low-quality studies.[3-10] Importantly, nationally, the average LOS for these three conditions is <5 days (ranging from 2.8-3.7 days based on condition)[108], which means that the discharging clinician most commonly chooses duration of antibiotics before day 5 of therapy. Clinicians prescribe durations across this recommended range, but most commonly choose longer durations,[11-15] likely due to uncertainty or a desire to minimize the risk of treatment failure.[30] Although there have been RCTs in children in the outpatient setting,[25,31,32] we found in our prior work[26] that clinicians are reluctant to apply these findings to hospitalized children, because they are more severely ill, have higher risk for critical

deterioration and infection complications, commonly have complex medical needs, and have higher diagnostic and therapeutic uncertainty. RCTs in adults have demonstrated that shorter durations are effective for common infections and driven changes in guidelines and practice.[33,34] However, no RCTs have been exclusively focused on and powered to compare treatment duration in hospitalized children. Prior studies of hospitalized children have been limited by observational designs[35,36] which are at risk of confounding bias, as clinicians tend to prescribe shorter durations for children that are less ill. Additionally, some antibiotic trials have focused only on treatment failure and are not designed to minimize antibiotic days. In contrast, our proposed study utilizes a high-quality, double-blinded, placebo-controlled design that: 1) is powered/designed to explicitly compare treatment durations in hospitalized children, and 2) incorporates the full range of outcomes important to caregivers and patients, including treatment failure, symptom and function recovery, and antibiotic-associated adverse effects.

Preliminary Studies:
We analyzed recent antibiotic prescribing patterns for these 3 conditions using a large, national dataset of over 43,000 pediatric hospitalizations from 118 hospitals between 2020-2022.[37] We found that: 1) there is **widespread use of both short and long antibiotic durations indicating a lack of consensus for appropriate treatment**; and 2) most children are prescribed antibiotics for long durations, thus there is a **tremendous amount of potentially avoidable antibiotic use in hospitalized children**. Condition specific guidelines currently recommend 5-10 days of antibiotics for treatment of PNA, 5-10 days for SSTI, and 5-14 days for UTI.[3-10] In this large cohort of 43,195 children, ~1.7% received less than 5 days of antibiotics, 9.6% received 5 days of antibiotic, 36.4% received BETWEEN 5 and 10 days, 43.6% received 10 days, and 8.6% received more than 10 days. In this national cohort, 89% of children (n=38,570) received >5 days of antibiotics, so **over 352,000 days of antibiotic therapy could have been avoided if 5-day antibiotic treatment is superior when considering the full range of patient-centered outcomes**. We also collected data from 8 of the 11 proposed sites included in this study, which showed similar practice patterns, with children receiving both short and long duration treatment, but most receiving >5 days of treatment.

4.0 Study Endpoints* (RQ-6, PC-3, CI-3)

Study definitions:

Date of antibiotic initiation: The date of antibiotic initiation is defined as the first dose of systemic antimicrobial therapy (concordant with infection treatment) given in a healthcare facility within 48 hours of hospital admission or at hospital admission. Most commonly, this antibiotic date will be administered in the ED prior to admission.

Date of hospital discharge: This is the date at which the participant leaves the hospital (during the hospitalization in which a participant is enrolled.

Table 1. Outcomes and Timepoints/Endpoints for Assessment

Aim	Primary or Secondary	Name of Outcome	Specific measure to be used	Timepoint/ Endpoint for Assessment	Estimated power (if applicable)
1	Primary	DOOR-RADAR	See Figure 2	Day 15 after antibiotic initiation	>90% power to detect at least a 56% probability of a more desirable outcome with short duration

					treatment
1	Secondary	Condition-specific DOOR-RADAR	See Figure 2—Each condition analyzed separately (pneumonia, SSTI, UTI)	Day 15 after antibiotic initiation	90% power to detect at least a 60% probability of a more desirable outcome with short duration treatment
1	Secondary	DOOR-RADAR	See Figure 2	10 days after antibiotic **completion** (Day 15 after initiation in those randomized to short duration and Day 20 after initiation in those randomized to long duration)	>90% power to detect at least a 56% probability of a more desirable outcome with short duration treatment
1	Secondary	Treatment failure	Yes/No where failure is defined as any of the following at any point until Day 15 after antibiotic initiation: 1) Change in antibiotic treatment plan due to treatment failure 2) Unplanned rehospitalization[49] 3) Death	Daily from hospital discharge until day 15 after antibiotic initiation	80% power to detect a treatment failure rate of 7% in the short duration arm, assuming a treatment failure rate of 3% in the long duration arm*
1	Secondary	Full symptom and function recovery	Yes/No where full recovery requires all of the following according to caregiver report: 1) fever-free for at least 24 hours 2) either at or better than their usual state of health 3) no condition-specific symptoms	Day 15 after antibiotic initiation	80% power to detect recovery rate of 87% in the short duration arm assuming a recovery rate of 92% in the long duration arm*
1	Secondary	Antibiotic side effects	Yes/No to ever having antibiotic side-effects rated as moderate or severe[25]	Daily from hospital discharge until day 15 after antibiotic initiation	80% power to detect side effects rated as moderate or severe in 24% in the long duration arm assuming side effects of more than mild in 17% in the short duration arm*
2	**Primary**	**Heterogeneity of treatment effect by condition**	**Statistically significant interaction by condition (e.g., pneumonia) and treatment arm**	**Day 15 after antibiotic initiation**	**80% power to detect an interaction between treatment duration and a pair-wise condition comparison (e.g., pneumonia compared to SSTI) with a ratio of odds ratios of 2.9**
1	Exploratory	Time-to-defervescence	Days to the first day without fever >38 °C (based on either the electronic health record from the hospitalization or caregiver surveys after discharge)	Daily from hospital discharge until day 15 after antibiotic initiation	N/A
1	Exploratory	Time-to-return to usual health	Days to the first day caregivers report their child's health as "back to usual health" or "better than usual health."	Daily from hospital discharge until day 15 after antibiotic initiation	N/A
1	Exploratory	Full recovery/resolution of condition-specific symptoms	Yes/No	Day 15 after antibiotic initiation and Day 30 after hospital discharge	N/A
1	Exploratory	Urgent healthcare reutilization	Unplanned rehospitalization or ED visit	Day 15 after antibiotic initiation and Day 30 after hospital discharge	N/A

Primary Outcome:

Our primary outcome will be a composite, ordinal outcome that captures 3 domains: clinical treatment failure, symptom and function recovery, and antibiotic-associated adverse effects. These domains of our primary outcome and all secondary outcomes are measured through

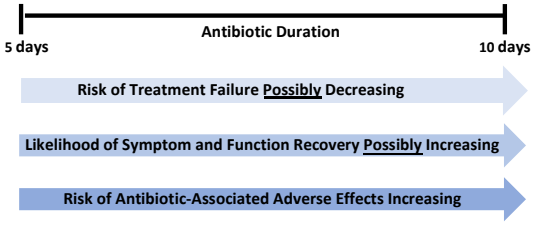
caregiver surveys **(see Figure 2 for overview, survey instruments uploaded in HRS, CI-1)**. The DOOR-RADAR methodology uniquely allows tailoring of our outcome to incorporate this full range of benefits and harms important to children and caregivers.[38]

Importantly, while participants will be randomized to either the short or long duration treatment, the total duration of antibiotic treatment *actually taken* by each participant is incorporated in the DOOR-RADAR outcome. Specifically, first, each child will be assigned a clinical outcome category. For example, if a child has no treatment failure, full symptom and function recovery, and no antibiotic-associated adverse effects, they get assigned the best category, 1. Then, the final DOOR-RADAR rank is determined. When "ties" occur in the clinical outcome, the RADAR methodology assigns a better rank to the child who *actually took* fewer days of antibiotics. This primary outcome will be analyzed for all children enrolled in the trial (all 3 conditions) at Day 15 after antibiotic initiation.

As a secondary outcome, we will assess DOOR-RADAR for each of these conditions separately. For another secondary outcome, will analyze DOOR-RADAR at a different timepoint/endpoint, 10 days after antibiotic treatment completion.

Figure 2. Conceptual Model and Application of DOOR-RADAR Methodology[38]

Conceptual Model:
Longer antibiotic durations may decrease risk of treatment failure, but they increase risk of antibiotic-associated adverse effects and antibiotic resistance. So, antibiotics should be limited to the shortest effective duration.



Step 1. Define Clinical Outcome Categories:
To use DOOR-RADAR methodology, you must define categories that describe the potential clinical outcomes of antibiotic treatment. We began with the categories previously used by our team.[25] We then interviewed caregivers of hospitalized children (n=26), asking about important benefits and harms of antibiotics. We refined our clinical outcome categories using themes from our findings. The main refinement was incorporation of function recovery. Major themes included:

- Return to normal activities (e.g., school)
- Return to baseline energy and mood
- Return to baseline thirst and appetite
- Resolution of systemic symptoms

Step 2. Assign a Clinical Outcome Category to Each Participant:
During the trial, each participant will be assigned to a clinical outcome category based on longitudinal assessment that includes 3 domains: treatment failure (assessed daily thru Day 15 after antibiotic initiation), symptom and function recovery (assessed at Day 15 after antibiotic initiation), and antibiotic-associated adverse effects (assessed daily thru Day 15 after antibiotic initiation).

Step 3. Determine final DOOR-RADAR: (Desirability of Outcome Ranking and Response Adjusted for Antibiotic Duration). Final DOOR-RADAR is determined. RADAR refers to the use of antibiotic duration (total days *actually taken*) to "break ties" in outcomes when comparing participants with the same clinical outcome category.

Clinical Outcome Category	Treatment Failure (can occur anytime in days 0-15)	Symptom and Function Recovery On Day 15	Maximal Antibiotic-Associated Adverse Effects (occurring anytime in days 0-15)
1 (BEST)	No	Full	None
2	No	Full	Mild
3	No	Full	Moderate
4	No	Full	Severe
5	No	Partial	Any
6	Yes, ED/clinic visit with antibiotic change	Any	Any
7	Yes, hospitalization	Any	Any
8 (WORST)	Death	N/A	N/A

Each participant is assigned a clinical outcome category (**Step 2**)

Participant	Treatment Arm	Clinical Outcome Category	Days of Antibiotic Use	Final DOOR-RADAR
A	Short	1	5	1
B	Long	1	10	2
C	Short	2	5	3
D	Long	2	10	4
F	Long	3	10	5
E	Short	4	5	6
G	Short	5	5	7
H	Long	5	10	8
I	Short	6	5	9
J	Long	7	12	10

When determining the final DOOR-RADAR, ties between participants with the same clinical outcome are broken using the number of antibiotic days the participant *actually takes*. (**Step 3**)

Domains of Primary Outcome (also analyzed as Secondary Outcomes):

Treatment failure will be defined as a change in antibiotic treatment plan by a clinician due to concern for infection not being appropriately treated with antibiotic", all-cause unplanned rehospitalization, or death. This definition, including change in antibiotic treatment plan, is a

standard outcome definition that has been used in prior studies, including RCTs.[25,46,47] Unplanned hospital readmission is an important negative outcome for caregivers and, thus, endorsed as an important measure to payers and hospitals and used in quality measurement.[48] This will be defined using a previously validated algorithm to determine if a readmission was planned or unplanned.[49]

Symptom and function recovery will be measured via caregiver survey tools that have all been validated or used in prior research. Caregivers previously have expressed that symptom and function recovery was most important to them, so we selected validated and previously utilized tools that will be used for evaluating this domain of the DOOR-RADAR outcome, including measures of return to baseline, health related quality of life, and condition-specific symptoms.[25,41,50-56] Recovery will be measured **at** day 15 after antibiotic initiation. We will use the return to baseline measure previously developed by our caregiver-centered team and utilized in our prior PCORI-funded RCT[41] with hospitalized children and their caregivers to assess recovery after hospital discharge. We will also utilize an adapted version of the KINDL Health-Related Quality of Life in Children and Adolescents scale.[50] This instrument has been used in multiple studies with healthy children and children with chronic disease.[51-53] For children with PNA, we will assess cough using the Pediatric Cough Questionnaire,[54] a validated instrument that measures cough severity and effect on quality of life. For children with SSTI, we will assess for symptoms using an adapted version of the validated Cellulitis Risk score.[55] For children with UTI, caregivers will report on symptoms including dysuria, frequency, and incontinence (among children who are toilet trained). For a child to be classified as fully recovered, the caregiver must endorse that their child: 1) has not had fever for >24 hours, 2) is at or better than their usual state of health, and 3) is not having condition-specific symptoms.[25] Minor wording changes to the tools were incorporated based on caregiver suggestion to enhance clarity. For example, the Health-Related Quality of Life in Children and Adolescents scale was developed and validated in Europe. Our caregiver Co-Is recommended changing the word “seldom” to “rarely,” to align with common usage in American English. Likewise, the pediatric cough scale asks about night-time cough only. We will ask about cough in the past 24 hours to capture daytime and night-time symptoms.

Antibiotic-associated adverse effects have been defined *a priori* based on the known common adverse effects (irritability, vomiting, diarrhea, diaper rash, generalized rash, yeast infection, mouth sores) and uncommon but serious adverse effects (severe allergic reactions, including anaphylaxis, Stevens Johnson Syndrome, and Toxic Epidermal Necrolysis). We will identify and classify severity of antibiotic adverse effects (i.e. mild, moderate, or severe) using a reporting tool adapted by our team from the SCOUT-CAP trial that aligns with standards of Good Clinical Practice.[25] Caregivers will be surveyed to assess these outcomes. These effects will be classified based on the worst severity experienced within the first 15 days after antibiotic initiation. As the safety profiles of the included antibiotics are well established and this trial is not powered to detect new, unknown safety signals, non-protocol defined events will not be considered in this outcome. The categorization table is included below:

Symptoms	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Irritiability	More irritable or fussy than usual but can be consoled; no interference with smiling/playing	Irritiability or fussiness that is difficult to console and interfeers with smiling/playing	Irritiability or fussiness that lasts more than 4 consecutive hours in a 24 hour period or cannot be consoled
Vomiting	1 episode per day	2-3 episodes per day	>4 episodes per day

Diarrhea	Looser than normal stools occuring ≤6 per day	Looser than normal stools occuring > 6 times per day	Bloody diarrhea, or diarrhea that requires medical intervention, lab testing, or hospitalization
Allergic reaction/Drug reaction	Localized rash OR puritis without rash	Diffuse rash with or without itching (urticarial, maculopapular)	Generalized rash consistent with Stevens-Johnsons, erythema multiforme, toxic epidermal necrolysis, anaphylaxis, or angioedema. OR a diagnosis of serum sickness or serum sickness like reaction (SSLR)
Stomatitis	Oral lesions associated with parental report of mild discomfort	Oral leasions associated with difficulty swallowing/pain with eating; but still drinking well enough to maintain hydration	Oral lesions associated with inability to swallow solids or liquids and requires medical intervention, IV fluids, or hospitalizaton
Candidiasis	Mild mucocutaneous candidaiasis or diaper dermatitis with no treatment or requiring topicla treatment only	Moderate mucocutaneous candidasis requiring oral anti-fungal	Severe mucocutaneous candidasis; requires medical intervention, intravenous treamtn, or hospitalization.

5.0 Study Intervention/Investigational Agent (RQ-5)

The overall timeline of the study intervention is outlined in **Figure 1**. All participants will receive 5 days (defined as 24-hour periods) of clinician-prescribed antibiotics in an unblinded fashion. This 5-day count will begin from the antibiotic initiation dose (defined above in "Study Endpoints: Study Definitions.") This may involve a combination of ED/hospital administered antibiotics and antibiotics taken at home (prescribed by the hospital discharging physician). For example, if a patient was admitted for 3 days and had taken antibiotics each day of the admission, the initial 5 days of antibiotics will include those 3 days and 2 days of the clinician-prescribed antibiotic for the participant to take at home. The participant's hospital discharging physician will identify the appropriate antibiotic for treatment of their infection. They will prescribe antibiotics at the time of hospital discharge to be filled by the clinical pharmacy, as usual in patient care outside of the trial.

Participants will be randomized if/when hospital discharge day is determined by the clinical team. Randomization will determine what study product they receive from Days 6-10 of their total course: 1) an additional 5 days of the same antibiotic prescribed by the hospital discharging physician, or 2) placebo. For children enrolled and randomized in the study, the

investigational pharmacist/investigational drug services (IDS) will provide a date and time to the caregiver for the child to STOP taking the clinically prescribed antibiotic and SWITCH to the study product. This switch will occur on Day 6 after antibiotic initiation. Study products (antibiotics and placebo) will be designed to look and taste similarly. Study product instructions and information will be identical for caregivers in the short and long duration arms.

Study medication will be stored, prepared and distributed by the CCHMC Investigational Drug Service according to standard procedures. CCHMC IDS will act as the central pharmacy for this study, so will be responsible for distributing study product to the site investigational pharmacies at participating locations in addition to dispensing study product for any participants locally enrolled and randomized (i.e., those at CCHMC Base and Liberty locations). Each site's IDS, with IDS pharmacist oversight will distribute the study product to site participants. Patients will not be randomized if the local IDS does not have the correct study product on hand.

The antibiotics included in this study are listed below and will be available in pill or liquid formulation from IDS. These were selected to include those recommended by clinical guidelines around treatment of these conditions and most prescribed at our planned study sites. The inclusion of multiple antibiotic agents in a single trial mirrors other trials which examine treatment strategies for infections[109-112]. Formulary medications for trial inclusion are as follows:

- Amoxicillin (for PNA, SSTI, or UTI)
- Amoxicillin-clavulanate (for PNA, SSTI, or UTI)
- Cefdinir (for PNA or UTI)
- Cefixime (for UTI)
- Cephalexin (for SSTI or UTI)
- Ciprofloxacin (for UTI)
- Clindamycin (for PNA or SSTI)
- Sulfamethoxazole / trimethoprim (for SSTI or UTI)

Intervention Blinding (IR-6)
Clinicians (e.g., nurses, physicians), caregivers, patients, investigators, and research staff will be blinded to allocation and participant randomization assignment throughout the trial. Site investigational pharmacists will be unblinded; they will access the randomization tool within the Eureka study platform to allocate study product. The DCC statistician will be able to unblind records in order to prepare safety reports and the DCC PI will also be able to unblind records in the case of serious adverse events (see below in "Provisions to Monitor the Data to Ensure the Safety of Subjects").

6.0 Procedures Involved

We will conduct a multicenter, patient-level randomized, double-blinded, placebo-controlled, superiority trial comparing short versus long course antibiotic treatment strategies among children hospitalized for PNA, SSTI, or UTI.

Eligible patients and their caregiver(s) will be approached during their hospitalization and will provide informed consent prior to any research procedures. All enrolled patients and their caregivers will complete an enrollment survey during the patient's index hospitalization **(CI-4)**. Children who enroll will be randomized individually around the time of discharge (+/- 48 hours) in Eureka (the study's data platform) using permuted-block randomization stratified by study site and condition (PNA, SSTI, UTI) to receive either short course or long course antibiotic therapy. Children will not be randomized until close to hospital discharge, after it is confirmed that: 1)

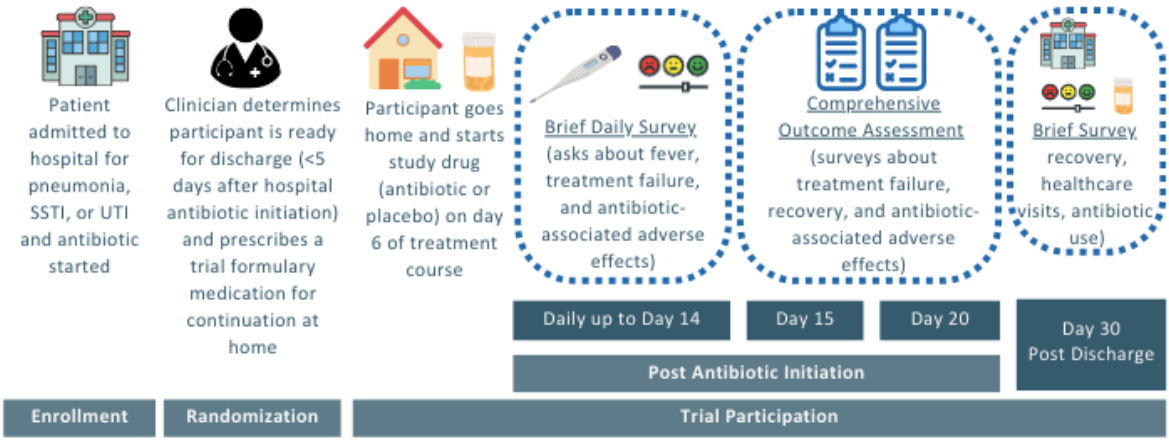
they are being discharged from the hospital so that they receive <5 days of antibiotics inpatient, and 2) a guideline concordant, study formulary antibiotic is selected for the discharge prescription. Specifically, children will only be eligible if they are discharged within 112 hours of their initial dose of antibiotics, ensuring that no child will be randomized to receive a placebo while they are still hospitalized. 112 hours was selected as 4 days and 16 hours, allows for completion of 4 days of TID dosing from initial antibiotic and allows some time for the study product to be prepared and delivered by the first dose on day 5.

Importantly, we will utilize a pragmatic trial approach to antibiotic prescribing and dosing. Clinicians caring for the patient in the hospital will decide which antibiotic the child will receive in the hospital and which will be prescribed for the caregiver to administer to the participant after hospital discharge. The hospital-based clinicians will specify the dose and frequency, usually in collaboration with a hospital pharmacist. Thus, the only differences between real-world practice and our proposed trial are the antibiotic duration and associated study procedures (i.e., data collection). Specifically, the investigational pharmacist at each site will provide either the same antibiotic and dosing for days 6-10 of dosing or a placebo. The antibiotic (for those randomized to receive antibiotics) will be the same dose and drug as the antibiotic prescribed for treatment after hospital discharge, but the formulation will be different to ensure blinding (look alike to the placebo). The Clinical Coordinating Center (CCC) will distribute study products (placebo and antibiotics) to the investigational pharmacies at all recruiting sites. All antibiotics in the study formulary are FDA-approved for use in children and have been in widespread use for many years. To minimize risks, condition eligibility will be verified by a study physician (most often the site PI), study antibiotic will match the dosing specified by the hospital discharging physician. Additionally, all participants must demonstrate clinical improvement, as measured by being well enough for hospital discharge, within 5 days of antibiotic therapy, such that children are not randomized to receive placebo while in the hospital for an infection.

The caregiver will administer the remaining days of the hospital-prescribed antibiotic (5 days total counting both doses given in-hospital by clinical staff and at home doses given by caregiver). They will then switch to giving the blinded study product provided to them by the recruiting site investigational pharmacy (antibiotic or placebo) for days 6-10 of treatment at home. This blinded study product will be tailored to the child (e.g., weight-based dose) matching hospital-prescribed antibiotics. Staff at the Data Coordinating Center (DCC) can access blinding linkages in case of severe antibiotic-associated adverse effects or serious adverse events (see below for definitions). Adherence will be monitored via daily surveys and an electronic medication adherence system for both the liquid and the pill formulation of the study product.

The caregiver will complete daily surveys daily from hospital discharge until 14 days after antibiotic initiation, on Day 15 and 20 after antibiotic initiation, and 30 days after hospital discharge (see **Figure 3** for timeline). Daily surveys will be opened in the afternoon/evening and participants will be notified of the survey availability through an ap push notification. Reminders to complete all surveys may be sent via push notification, text, email, or phone call. There are no plans for longer-term follow-up. Thermometers will be provided to participants with their study product in order to answer the daily temperature question. Additionally, each site will collect data from the patient's electronic medical record on demographics and clinical course (e.g., daily temperatures). A description of these variables is uploaded in Huron Research Systems and provided below (see "Data Management and Confidentiality).

Figure 3. Participant Intervention Timeline



For persistent fevers, worsening of symptoms, severe antibiotic-associated adverse effects, or healthcare reutilization (outpatient or inpatient), a study nurse from the CCC will contact the caregiver via phone to ascertain if the event is a treatment failure and collect a few additional data elements (see Nurse Questions in HRS). The nurse will also use clinical assessment (working through standard Schmidt-Thompson nurse triage protocols), to determine when to refer children to seek care at their primary care office or emergency department (depending on illness severity).

All data collection will occur via the Eureka platform, which can deliver survey instruments to caregivers via mobile app, webpage, email, or text link/mobile interface (based on their preference). This platform was selected to maximize caregiver ease/feasibility. This platform as previously been used for a CCHMC IRB-approved study (IRB: 2017-0683). Caregivers may choose to complete surveys via phone to accommodate other languages, technology limitations (e.g., limited internet access), limited literacy, or stated preference; a CCC team member will be available to make phone calls for participants enrolled at all sites as needed.

We will ask a subset of caregivers and assenting children who are approached at each actively recruiting site (both those that enroll and those that refuse the trial) to participate in a brief (~20 minute) semi-structured interview regarding the enrollment process and the study. We will ask another subset of caregivers of enrolled patients and assenting children to complete a brief semi-structured interview (~20 minute) at the conclusion of data collection focusing on the acceptability of study processes, including outcome measurement, and the applicability of study outcomes. Study staff will collect the contact information of interested participants and then someone from the Qualitative Methods and Analytic Collaborative (QMAC) team will contact them for an interview. Recruiting staff and site PIs will be asked to self identify if they are willing to participate in an interview and study staff will share their contact information with QMAC. These will be conducted either in-person, via phone, or via Teams/Zoom, recorded, and transcribed. If a participant refuses transcription, detailed notes will be maintained during the interview process to record participant perspectives for use during the analytic process.

7.0 Data and Specimen Banking

No data or specimens will be banked for future use.

8.0 Sharing of Results with Subjects

Individual results will not be shared with participants. Within 6 months of publication of study results in a peer-reviewed journal, we look forward to sharing our research findings with our study participants. We will plan to share the lay language "Results Summary" on the PCORI website, with any additions from our parent co-investigators or study team members. We will ask caregivers during the enrollment survey how they would like to receive study results.

9.0 Study Timelines

Participants will be in the study from enrollment (during hospital admission) for up to 40-days after hospital discharge to ensure they have sufficient time to complete the 30-day post-discharge survey (see **Figure 3**). We anticipate enrolling all study subjects by 8/26/2031 and completing primary analyses by 3/1/2032.

Feasibility phase
This trial is funded by PCORI and will be executed in 2 stages: the feasibility phase (18 months) and the full trial. PCORI's Expert Advisory Panel (EAP) will review the progress made within the feasibility phase and decide on continued funding for the full trial. If the trial is not recommended for full funding by the EAP, the trial will stop prior to enrollment goals. The milestones that our study team needs to meet during the feasibility phase are outlined in Appendix 1.

During the feasibility phase, we will execute 2 aims.
Feasibility Phase (18 months):
Aim F1: Pilot test and refine trial procedures: Four study sites will begin active recruitment during the feasibility phase, including 3 free-standing children's hospital and 1 community hospital (since many children with these common conditions are hospitalized at community hospitals). We will randomize a total of 75 participants for this aim, and iteratively refine study procedures using quality improvement methods. Our **expected outcome** is refinement and finalization of trial procedures and related operating procedures to optimize recruitment and retention.

Aim F2: Refine trial materials and procedures to promote diversity and equity in trial participation: As we implement trial procedures (Aim F1), we will use a stratified purposive approach to recruit a diverse sample caregivers and patients (e.g., by race, ethnicity). We will conduct a qualitative study to: 1) understand what factors are important to families in deciding whether to enroll in the trial, and 2) understand how best to fully support families throughout trial procedures so they are feasible and acceptable. Our **expected outcome** is a model for family decisions about trial enrollment and participation to inform refinement of materials and processes (e.g., consent documents, data collection processes) to promote diversity and equity in trial participation.

Of note, feasibility aim 2 is directly related to aim 3 of this protocol.

10.0 Inclusion and Exclusion Criteria (RQ-3)

Site PIs will work closely with research coordinators to identify eligible participants. Screening for eligibility will be performed by reviewing chief complaint, problem list, diagnoses, test results, and medication lists in the electronic health record (EHR). Inclusion and exclusion criteria will be verified by chart review of the hospitalization in the EHR. Research coordinators will notify the clinical team prior to approaching eligible patients and their guardians for consent and direct the clinical team to discuss concerns with the site PI. Participant eligibility and time of the administration of the first dose of antibiotic will be verified by the site PI (site physician) prior to randomization. The clinical team will be informed after the site physician verifies eligibility and the child is enrolled. The discharge antibiotic will be verified by the clinical team.

All Participant Inclusion Criteria*:* We will include children and adolescents ages 60 days to 17 years and 10 months admitted to the hospital medicine service with a primary diagnosis of PNA, SSTI, or UTI receiving an antibiotic agent that is concordant with any microbiologic results and guideline-concordant.[3-10] Children are eligible if they are prescribed a post-discharge antibiotic for home that is within our trial formulary and, thus, has an available look-alike placebo that will taste as similar as possible. The study formulary includes amoxicillin, amoxicillin-clavulanate, sulfamethoxazole/trimethoprim, clindamycin, cefdinir, cefixime, cephalexin, and ciprofloxacin.

Condition Specific Inclusion Criteria
For PNA, children must have radiographic evidence of pneumonia (specifically an infiltrate consistent with pneumonia OR an infiltrate read as atelectasis or pneumonia) as read by a radiologist, and clinical diagnosis of pneumonia, and clinician prescription of guideline-concordant antibiotics for pneumonia. For SSTI, we will include children with cellulitis alone (redness, swelling, and/or induration) or cellulitis with abscess that was either drained (source control) or deemed too small for drainage. For UTI, children must meet guideline-specified diagnostic criteria, as shown in the table below.[3,7,10]

Urinalysis Results	**Urine Culture Results***	
	Clean Voided Sample	Catheter Sample
Positive leukocyte esterase (≥trace) on dipstick analysis, OR ≥5 WBC/hpf with standardized or automated microscopy OR ≥10 WBC/mm3 on a hemocytometer with an enhanced urinalysis	Growth of ≥100,000 colony forming units (CFU)/mL of a single uropathogen**, or ≥100,000 CFU/mL of one uropathogen and <50,000 CFU/mL of a second uropathogen***	Growth of ≥10,000 CFU/mL of a single uropathogen
*bag only culture will be excluded		
**uropathogens (definite): Enterobacterales e.g. E coli, Klebsiella, Proteus, Enterobacter, Citrobacter, Serratia; Pseudomonas & other glucose non-fermenting GNR; Staphylococcus saprophyticus. (possible): Enterococcus, group B streptococcus. Generally not considered uropathogens: Lactobacillus spp, coagulase-negative staphylococci, Corynebacterium spp/GPR		

*** Allow for inclusion of quantities e.g. <50,000 cfu/mL of mixed flora or non-uropathogenic bacteria on clean voided samples in children >4, IF they meet the uropathogen criteria with at least 50,000 CFU/mL

All Participant Exclusion Criteria:
We will exclude any patients who live independently (without a parent or guardian in the home), including those in county or state custody. We will exclude patients who previously enrolled (i.e., consented and randomized) in the study. We will exclude patients who are not discharging home from hospital medicine service.

For all conditions, we will exclude children who require inpatient antibiotics longer than 4 days, as guidelines indicate that a child should be clinically improving to be a candidate for short duration treatment.[3-10] If a child is still hospitalized on day 5 of antibiotics, then we will not have clear signal that the child has improved enough to stop antibiotics after 5 days and thus are not eligible for inclusion. We will also exclude children discharged with >1 systemic antibiotic prescription, as this may indicate greater severity of infection or greater diagnostic uncertainty.

Other exclusion criteria are also all aligned with guidelines, which exclude children that may require longer duration antibiotics or have higher risk of infections with resistant or atypical organisms.[3-10] Specifically:

- We will exclude patients requiring >24 hours in intensive care.
- We will exclude patients with immunodeficiency (e.g., HIV, hypogammaglobulinemia, use of systemic steroids for >2 weeks within the past 2 months, use of other immunosuppressive medications)
- We will exclude patients who have been hospitalized in the preceding 30 days before the index hospitalization, as these children are at higher risk of nosocomial infections (e.g., catheter associated UTI) and antibiotic-resistant organisms.
- We will exclude patients who are admitted after completing more than 48 hours of outpatient antibiotics to treat the current infection, as these children likely represent treatment failure and atypical infections.
- We will exclude known pregnant patients
- We will exclude anyone who has an allergy to any of the components of the placebo
- We will exclude anyone with clear alternate diagnosis than the diagnoses/infections of focus, need for treatment of a concomitant diagnosis requiring antibiotics, or uncertainty regarding the qualifying diagnosis (PNA, SSTI, UTI).

Condition Specific Exclusion Criteria:

- For pneumonia, we will exclude children with a parapneumonic effusion larger than "trace" or "small" (based on radiologist impression), tracheostomy, high intensity neurologic impairment,[60] cystic fibrosis, sickle cell disease (acute chest syndrome), chronic respiratory failure (as indicated by baseline oxygen need or use of CPAP/BiPAP), or received 3 or more doses of azithromycin.
- For SSTI, we will exclude children with surgical site infections, cellulitis around a medical device (e.g., gastrostomy tube), bone or joint infections, infectious myositis or pyomyositis, implanted hardware or other deep infections (e.g., abdominal cavity, pharyngeal space, parotiditis, lymphadenitis), have concomitant HSV, significant chronic dermatologic conditions other than eczema (e.g., epidermolysis bullosa), or pre-septal or orbital cellulitis. Dental abscess without overlying facial cellulitis will also be excluded. We will exclude those discharged from the hospital with a drain in place. However, any

abscess at the skin would qualify even if it is drained by a subspecialist, unless it connects with an internal cavity (like a colonic fistula).

- For UTI, we will exclude children with major genitourinary anomalies (including duplicated renal collecting system, single kidney, horseshoe kidney, neurogenic bladder), high-grade vesicoureteral reflux, history of urologic surgery other than circumcision, indwelling urinary catheters, need for regular intermittent catheterization, or current renal abscess.

11.0 Vulnerable Populations

Children (age 60 days to 17 years 10 months), along with their caregiver, will be enrolled in this study. Staff who enroll participants at each study site may be asked to complete a qualitative interview.

12.0 Number of Subjects

Aims 1 and 2:
We anticipate needing to consent and enroll 2000 patients to randomize 1200 participants across all sites (in order to be powered for our analyses). More patients will be enrolled/consented than randomized, as some participants that are enrolled will become ineligible if complications arise during hospitalization (e.g., prolonged stay, worsening infection).

Sites are free to accrue as many patients as possible. Both the DCC and CCC will be closely monitoring enrollment at each site to ensure they are meeting or exceeding goals for their site.

Aim 3:
We will recruit up to 60 parents of patients (and if present and able to assent to interview, child) to complete a qualitative interview about the recruitment process and study participation. Some of the interview participants may also be trial participants, though we will also interview caregivers of eligible participants (and assenting children) who declined trial participation. We will ask up to 10 study staff to complete confidential interviews conducted by a QMAC staff member to support/substantiate findings from child participants and caregivers.

13.0 Recruitment Methods (PC-2)

Recruitment steps and timelines are illustrated in **Figures 1 and 3**.

Stage1: Initial Eligibility Screening:
CRCs will collect a daily census list of all children admitted to the general pediatric/pediatric hospital medicine service and narrow this list to those with a potential diagnosis of interest via review of chief complaints, problem lists, diagnoses, and medication lists. This initial screening list will contain name, demographics (date of birth, sex, gender, race, ethnicity, insurance status and type, primary language), home address, medical record number, unique admission identifying number, admission date and time, diagnosis, and phone number. This list will be uploaded to the Eureka platform via secure upload system.
If sites are unable to generate an automatic list including the demographics, CRCs will hand enter these data into Eureka.

Stage 2: Full Eligibility Screening:

Next, the more narrowed list of children likely with a condition of interest (PNA, SSTI, UTI) will be randomly sorted to facilitate random sampling for full eligibility screening. Given the anticipated high numbers of children with PNA and SSTI, only a subset of patients will be randomly selected to undergo full eligibility screening and be approached for participation. This will ensure we accrue participants equally per condition over the course of the trial (as PNA and SSTI are more common than UTI). We will determine the appropriate numbers/percentage of eligible patients to approach during the first 18 months of the trial. This percentage may change based on site enrollment rates. The random sorting will effectively allow us to randomly select the number of people we approach/enroll.

CRCs will perform full eligibility screening by verifying inclusion and exclusion criteria through more detailed review of patient notes, laboratory, and radiographic data of the hospitalization in the EHR.

Stage 3: Enrollment and Consent
For patients that have confirmation of eligibility on full screening, the patient and their caregiver will be recruited during a hospital admission at any of the recruiting study sites; this study will be by invitation only. Trained research staff will prioritize approaching patients in person to complete the informed consent process. However, if recruitment is not feasible in person, research staff will follow institutional policies regarding initial contact for research participation including e-mail, text, or phone when appropriate. If consenting takes place virtually, we will utilize the e-consent framework in Eureka.

Step 4: Final Eligibility Confirmation
A final eligibility confirmation will be performed by a study physician to ensure the patient: 1) has been diagnosed with a condition of interest (PNA, SSTI, UTI) and verify the date and time of the first healthcare administered antibiotic dose. The physician review will be either documented in Eureka directly or via study physician sign off or CRC with attestation of having documentation of agreement eligibility.
The study staff will also confirm the patient being discharged within 5 days of antimicrobial therapy, and was prescribed a guideline-concordant, study formulary antibiotic by the hospital discharging team. The participant will then be randomized by the investigational pharmacist.

Participants will be compensated for their time. Payment will be handled by University of California, San Francisco, the Data Coordinating Center for this study.

Participation Compensation Table	
Study Procedures	Compensation Rate
In-hospital survey	$20
Daily check ins after you go home (days 2-14 of antibiotic use, starting the day after you go home)	$5 each (up to $65 total)
Day 15 outcomes assessment survey	$30
Day 20 outcomes assessment survey	$30
Day 30 survey	$10
Bonus if all surveys/check ins completed	$45
Total	**Up to $200**

Additionally, the subset of participants who complete qualitative interviews will receive $40 per interview, up to $80 total.

Qualitative Interviews:

A subset of caregivers will be asked if they are interested in participating in the brief qualitative interview regarding the enrollment process and the study after consent is complete (some interviews will be with families that consent and some will be with families that refuse). The local study staff will collect the contact information of interested participants and then someone from the Qualitative Methods and Analytic Collaborative (QMAC) team will contact them for an interview using their preferred contact method.

A subset of caregivers will be asked if they are interested in participating in the brief qualitative interview regarding the full study process after they complete their 30-day survey. The contact will be from Cincinnati Children's study staff who is leading both the survey processes and the interviews. The contact information of interested participants will be shared with the Qualitative Methods and Analytic Collaborative (QMAC) team and they will contact them for an interview using their preferred contact method.

Recruiting staff and site PIs will be asked to self-identify to Cincinnati Children's study staff via email if they are willing to participate in an interview and study staff will share their contact information with QMAC. The Cincinnati Children's study staff meet with all sites monthly so will remind staff and site PIs during those meetings to reach out if interested in being interviewed.

14.0 Withdrawal of Subjects

If a participant and/or caregiver chooses to withdraw from the study, they can do so with no repercussions and no effect on their current or future medical care.

Medication non-adherence: Non-adherence is not equivalent to withdrawal from the study. If participants choose to stop taking study product on their own (not under the advisement of a medical provider), we will still ask caregivers to complete follow-up surveys.

Withdrawal: If caregivers request to no longer complete the daily follow-up surveys, we will ask them if they would be willing to complete the primary outcome survey (day 15 of antibiotics). If they agree, we will only send the 15-day survey to them and no additional surveys (partial withdrawal). If they decline the 15-day survey, we will not send any additional surveys.

We will analyze all collected data, unless a caregiver asks for a full withdrawal with removal of previously collected data.

We will also withdraw any patients whose caregivers study staff note are unable to consent to ongoing study participation (i.e., if a child is removed from caregiver custody after consent). Again, if partial data collection has occurred prior to study withdrawal, we will include data in analyses, unless required to exclude it by the IRB.

15.0 Risks to Subjects

Both short and long courses of antimicrobial therapy have been well established in the outpatient population for pneumonia and UTI. Both durations are within routinely prescribed durations in the pediatric inpatient setting. Therefore, it is unlikely that being randomized to

either duration increases risk significantly above clinical care.

However, if a child is randomly assigned a longer course of antibiotics then they would have been prescribed outside of the trial, they are at increased risk of antibiotic side effects. In similar prior studies, most antibiotic-associated effects experienced by participants were considered mild. Importantly, because all participants are receiving treatment with antibiotics used routinely in clinical care to treat these infections in accordance with approved indications and/or clinical guidelines, we do not anticipate the occurrence of *new* or *previously unknown* antibiotic-associated adverse effects.

For children assigned a treatment duration that is less than the duration originally prescribed by a treating clinician, it is possible that they will experience a higher risk of treatment failure. However, in similar prior studies comparing 5 or 10 days of antibiotics for common infections, this increased risk was either not detected or was very small.

Importantly, both durations being compared in this study are recommended in professional condition-specific guidelines and consistent with usual clinical practice.

The main additional risk is the potential disclosure of protected health information. This includes loss of privacy and confidentiality resulting from use of electronic databases for eligible subject identification and potential breach of confidentiality through disclosure of Protected Health Information (PHI). We are collecting the minimum amount of PHI necessary to conduct the study. Participation in ongoing assessments is voluntary, and individuals can discontinue participation at any time. All data will be kept in secure, password-protected, encrypted databases which only research staff will have access to (as detailed below).

We do not anticipate any psychological, economic, or social risks to this study.

16.0 Potential Benefits to Subjects

It is possible that children randomly assigned to short course therapy will receive fewer days of antibiotics than they would have in clinical care, outside of the trial. If this approach results in similar clinical outcomes to longer courses of treatment, it would simplify treatment and might also result in fewer antibiotic-associated adverse effects.

This study will also provide objective data to inform the treatment of hospitalized children in the future, and at the population-level, could influence safe reductions in antibiotic duration, and thus minimize antibiotic-associated adverse effects and curb the development of antimicrobial resistance.

17.0 Data Management and Confidentiality (IR-1-5, IR-7, CI-2)

Statistical Analysis Plan

Aim 1: We will perform descriptive statistics for important patient and clinical characteristics to ensure adequacy of randomization, including: age, sex, condition (PNA, SSTI, UTI), intensive care unit admission, presence of bacteremia, receipt of guideline concordant dosing, and hospital type (children's versus community). We will also examine the balance of these key attributes within each condition, separately. For the primary analysis, we use a Mann-Whitney U Test to compare DOOR-RADAR scores and estimate the probability of a more desirable DOOR-

RADAR rank in the short duration group compared to long duration group based on randomization assignment (intention to treat), using outcome data collected 15 days after antibiotic initiation. The Mann-Whitney U tests pair-wise comparisons of the fully ranked data, which is ranked on clinical outcome category and actual days of antibiotic therapy taken. We will do these analyses for the all-condition dataset and for each of the 3 conditions separately.

For secondary analyses, we will conduct the same analyses in the all-condition dataset with a Mann-Whitney U using the time points of 10 days after active antibiotics are complete. For those randomized to short duration (placebo) this will occur at day 15 after antibiotic initiation; for those patients randomized to the long duration arm, this data collection will occur at day 20 after antibiotic initiation. For binary secondary outcomes (treatment failure, full recovery, antibiotic adverse effects), we will use chi-squared testing to compare short and long duration groups at day 15 after antibiotic initiation.

Given the number of secondary analyses proposed, we will plan to use a Bonferroni test correction to account for the multiple comparisons. Specifically, for the condition-specific analyses we will use this correction. However, for the separate analyses for the 3 domains of the DOOR-RADAR primary outcome (treatment failure, symptom and function recovery, and antibiotic-associated adverse effects) we will not conduct multiple comparison corrections because these are potential explanatory analyses with a precise focus on interpretation as opposed to overall effectiveness of the different durations, so we do not believe multiple comparison corrections are appropriate.[86-88] These analyses will allow us to explore and better interpret our results (i.e., why is the DOOR/RADAR significant? Is it because of improved treatment failure or fewer antibiotic-associated adverse effects?).

Aim 2: We will evaluate for heterogeneity of treatment effects (HTE), using outcome data obtained 15 days after antibiotic initiation. We will do these analyses using ordinal logistic regression analyses, in which we determine if the interaction term between the predictor of interest and study arm is statistically significant. First, we will examine an antibiotic duration (ITT) by condition interaction term to determine if the effect of the duration of antibiotic on our primary outcome depends on the condition. As above, we do not anticipate any key attributes to be unbalanced after randomization, but if they are, we will include them in the models. We will then create additional ordinal logistic regression models in which we will test an interaction between antibiotic duration (ITT) and key clinical characteristics. Specifically, we will consider: 1) age, because younger children may experience higher risk of treatment failure, slower recovery, and antibiotic side effects;[91,92] 2) admission to the ICU, as children requiring ICU care may have higher risk of treatment failure;[93] 3) positive blood culture, as children with transient bacteremia may have higher risk of treatment failure; 4) receipt of guideline concordant therapy, as children who receive non-guideline concordant dosing may have higher risk of treatment failure; and 5) hospital type (community versus academic), as resources and outcomes at community hospitals may be systematically different than children's hospitals.[94,95] Specifically, for HTE 4, we will consider weight-based dosing according to pediatric pharmacotherapy references and clinical guidelines. It may also be that some antibiotics prescribed are not appropriately selected as culture-directed therapy (e.g. in the case of UTI where a prescribed antibiotic may not be listed on the susceptibility report, or if it is not reliable (per Clinical Laboratory Standards Institute) to infer susceptibility based on the organism identification and other antibiotics on the susceptibility report) or that the criteria of culture directed treatment of pneumonia is not met. In these cases, they these will be grouped with non-guideline concordant therapy. Finally, we will conduct an exploratory HTE analysis by the 9 different antibiotics to evaluate if the specific antibiotic may be associated with differential recovery. We

will adjust for condition in all of these attribute HTE models.
(HT-1-3)

Exploratory Analyses: We will perform two time-to-event analyses based on daily symptom reporting by caregivers: time-to-defervescence and time-to-return to usual state of health. We will construct two separate Cox Proportional Hazard models using these two outcomes; our primary predictor will be antibiotic duration (based on ITT). We will include any covariates that failed to balance with randomization. We will test a condition by duration interaction. If this interaction is significant, we will also construct condition-specific models to better understand the time to defervescence and time to return to baseline health within the different conditions. Next, we will assess condition specific symptoms at days 15 and 30, namely, cough (pneumonia only), local symptom resolution (SSTI only), and dysuria (UTI only) using a chi-squared analyses (or logistic regression if key attributes are unbalanced). Finally, given the importance of urgent healthcare reutilization as a health quality measure, we will conduct all-condition logistic regression at day 15 and 30-days with duration as the primary predictor and the outcome is urgent healthcare reutilization (ED visit or unplanned rehospitalization[49]), adjusting for condition.

Missing Data: We will make every effort to avoid missing data (e.g., regular review of data quality reports and follow-up to complete data and/or document reason for attrition). We will assess the reasons, patterns, and distribution of missing data, allowing us to assess whether an assumption of missing completely at random is reasonable or whether missingness is conditional on another variable in the dataset (i.e., missing at random). Descriptive statistics will compare characteristics of patients with and without missing data. If missing at random, we will use full information maximum likelihood for estimation. **(MD-1-4)**

Data Storage and Security

EHR data will be extracted through standard procedures at all trial recruiting sites to support participant screening, enrollment, consent, randomization, and initial survey data collection procedures. Sites will transmit these data to the UCSF Data Coordinating Center, where it will be stored and linked with data in the Eureka Research Platform. Caregivers will additionally directly provide survey data on study outcomes via the Eureka Research Platform (via smartphone or web application, or via phone with CRC). The Eureka Research Platform maintains a secure database and file server system on Amazon Web Services (AWS). The Eureka Privacy Policy can be at https://info.eurekaplatform.org/privacy-policy-and-data-security-measures/.

To ensure data security, Eureka maintains extensive internal security procedures, including identity management, restricted access using AWS virtual private cloud and security groups, least privileges, patch management, secure sharing via OAuth2 and APIs, and others; these are detailed in our Operations Manual and can be provided if needed. Eureka passes Security Risk Assessments and weekly vulnerability scans performed by the UCSF IT Security Team. When major changes are made to the platform, additional risk assessments are performed. Penetration tests are performed periodically when deemed necessary by security audits or after major platform changes. Eureka is designed to safeguard PHI data and meets these requirements: 1) only HIPAA-eligible AWS services can be used, 2) PHI must be encrypted in transit, and 3) PHI must be encrypted at rest. The Eureka production AWS account is registered under the Business Associate Agreement (BAA) between AWS and the University of California.

To ensure data quality, Eureka's dedicated Quality Assurance Team, a subunit of the Technical Team, reviews any new feature extensively to ensure that it 1) meets requirements and 2) does not break existing code. Data collection tools will also be built to facilitate collecting data only within permissible ranges. Study reports will be made available to study teams to facilitate data monitoring and quality assurance.

Analytic data sets without identifiers will be created for each specific analysis and distributed to analysts on the DCC research team. These will be stored in UCSF Research Analysis Environment (RAE). RAE is a secure, HIPAA-compliant desktop environment hosted on servers at the UCSF Data Center. The RAE environment is hosted on 6 Dell PowerEdge R710s and one Dell EqualLogic SAN arrays, which are located inside a locked rack at the datacenter. There are two layers of physical redundant Juniper firewalls that protect the servers and SAN. RAE utilizes VM Ware View Virtual Desktop, which must be logged into using UCSF Active Directory credentials. The servers are locked inside a rack locked with a combination lock. The rack is in a data center secured by two sets of locked doors with an air lock and unlocked via a biometric device. To reach the rack, one must progress through the two sets of locked doors and through an Operations Desk area which is staffed 24 hours a day, 7 days a week. The rack itself has a security camera mounted on it and is tied into the central security camera system to ensure that the feed is continuously monitored. Study data will be stored in Dr. Kaiser's group network folder in RAE, where only the research team members at the DCC are able to view the data, and this access is audited. This folder is physically located in a data store on the SAN in the locked rack, and study staff will only access it through the VMWare remote desktop. Network traffic between MyResearch and the UCSF network traverses an SSL VPN tunnel in encrypted format.

UCSF Computing Environment: All UCSF DCC investigators will have access to personal computers connected to the UCSF network and are supported by UCSF Information Technology (IT) personnel. Data center services including storage, backups, and virtual servers are supported by the UCSF IT. Wide area network connectivity to the data center is via 10Gbps links, and UCSF has 40Gbps connectivity to the Internet. File services are highly available and support a fault tolerant technology such as Redundant Array of Inexpensive Disk (RAID), redundant network connections and clustering, which allows the file servers to continue to function during maintenance and upgrades and protects against service disruption as well as data loss in an event of equipment failure. Data stored on file servers are backed-up daily using CommVault Simpana (with a 90-day retention period) and backups are replicated to the UCSF disaster recovery data center located at the San Diego Supercomputer Center at UCSD. Data centers have uninterruptible power supplies and generator backup capabilities that protect the computer and storage equipment during commercial power outages, avoiding service outages and preventing data loss. To protect the servers, desktops, and laptop computers against viruses, spyware, adware, potentially unwanted applications, and hackers, UCSF runs Symantec Endpoint Protection software, requires that all desktops and laptops are encrypted, and regularly patches systems for security vulnerabilities.

Limited Data Set versions will be distributed to external collaborators with a data use agreement. Any collaborator requiring identifying data elements outside the bounds of a Limited Data Set will first be added formally as research personnel. Aligned with the Patient-Centered Outcomes Research Institute's Policy for Data Management and

Sharing, the DCC will preserve research data and documentation for sharing and reuse, for 7 years after the study's final report.

We are requesting informed consent be waived to allow us to collect a few key data elements from the medical records of patients: 1) who are not randomly selected for full eligibility screening and 2) who were confirmed as eligible but were not enrolled. CRCs will collect a daily census list of information on children with a potential diagnosis of interest via review of chief complaints, problem lists, diagnoses, and medication lists. This initial screening list will contain name, demographics (date of birth, sex, gender, race, ethnicity, insurance status and type, primary language), home address, medical record number, unique admission identifying number, admission date and time, diagnosis, and phone number.

For those that undergo eligibility screening, some will ultimately be enrolled and others not enrolled. Unenrolled patients will be defined as those that were confirmed as eligible after initial screening, but we did not approach, we were not able to reach a caregiver, or who refused. Using these data, we will compare demographics between enrolled and unenrolled patients. This analysis will help us outline any limitations in our study population (i.e., populations which we under-recruited) and ensure our findings are generalizable to other populations. We believe that this approach has no more risk than a retrospective chart review would be or than a retrospective look at our unenrolled population.

Aim 3 (*Qualitative Interviews)*: Interviews will be transcribed verbatim, deidentified, and reviewed for clarity prior to analyzing. We will utilize a grounded theory approach to analysis, and analysis will proceed alongside data collection.[70] We will review transcripts in detail and identify categories (open coding), proceed to axial coding to add depth to categories, and finally refine and integrate/connect categories, resulting in in the final model (selective coding). We will use constant comparative methods throughout.[70,83] Written transcripts and notes will be coded by two study-team members with expertise in qualitative analysis who will then meet to discuss coding, to promote ongoing discussions of reflexivity, in support of trustworthiness and credibility, and systematic application of the codebook.[84] As we proceed through data collection and analysis, we will determine the point at which we are seeing informational redundancy during the coding process, often referred to as saturation.[85] The coding team will maintain memos during the process taking note of surprising findings and evolution of concepts and promote reflexivity. Analytic findings will be regularly discussed with stakeholders to provide input on interpretation and ensure balance and neutrality in the analytic process, aligned with PCORI methodology standards. The final model, which we anticipate will explain factors important to caregivers and patients, will be supplemented with selected quotes to provide nuance to categories. Interview recordings, transcripts, and analytic notes will be kept in locked files in a secure folder on a secure server. Interview transcripts will be reviewed in detail by QMAC staff to ensure all identifying information has been removed prior to coding. Participant identity will be retained in a separate, locked file, until transcripts are analyzed and then this linking file will be destroyed to preserve participant confidentiality.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects: Data and Safety Monitoring Plan (DSMP)

Adverse Event Reporting

As the safety profile of Amoxicillin, Amoxicillin-clavulanate, Cefdinir, Cefixime, Cephalexin, Ciprofloxacin, Clindamycin, Sulfamethoxazole / trimethoprim are well established, and this trial is not powered to detect new, unknown safety signals, there will be no unsolicited adverse event

(AE) collection during this study, and only protocol-defined serious adverse events (SAEs) will be collected.

The study team has established the following definitions for Adverse Events and Serious Adverse Events:

- **Adverse Events**: We will collect solicited adverse events as part of a daily survey that will be administered to caregivers starting the day after hospital discharge through day 14 after the initiation of antibiotic therapy. These include: continued fever, continued symptoms, and antibiotic-associated adverse effects. These expected symptoms are included as part of our study outcome and will not be reported separately.

  If on the daily survey or the 15-, 20, or 30-day outcome surveys, the caregiver reports a change from the previous survey, including continued fever, worsening symptoms, severe antibiotic-associated adverse effects, or unplanned primary care, emergency room, or inpatient visit, the DCC will notify the CCC, who will then facilitate a research nurse call. This call will occur the next business day after survey completion. During the call, the nurse will triage the situation using a standardized script/protocol, and then document the patient's symptoms, if antibiotics were changed during the unplanned visit, and any triage recommendations. Any research nurse call will be documented as an unsolicited adverse event, and it will be reported to the DSMB in regular DSMB sessions (see details in "Data Safety Monitoring Board Charter").

- **Serious Adverse Events (SAEs):** An adverse event or suspected adverse reaction is considered "serious" if it results in any of the following outcomes:
  - Death
  - A life-threatening adverse event (including severe antibiotic-associated side effects such as anaphylaxis, Stevens Johnson Syndrome)
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Classification of Serious Adverse Events:

Relationship to Study Intervention

Each serious adverse event will be investigated by the Site PI to assess its relationship, if any, to interventional treatment. Causality or relatedness should be assessed using the following categories: not related, possibly related, or probably related.

Definitely Related: The event follows compatible temporal sequence from the time of beginning the assigned study intervention. There are no other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject which could reasonably explain the symptoms of the adverse event.

Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention and cannot be reasonably explained by other

factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Possibly Related: The event follows compatible temporal sequence from the time of beginning the assigned study intervention but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

SAEs will be evaluated as to whether their occurrence was expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described for the study intervention.

Expectedness

Expected: An event is considered expected if it is known to be associated with the underlying condition or is related to the study intervention and is mentioned in the protocol, informed consent, or other study documents. An event may be expected despite the study subject's clinical state immediately prior to the event. Any symptom related to the primary diagnosis for which the participant was initially hospitalized is expected. For example, symptoms that would be expected for all of the study conditions are fevers, vomiting, and diarrhea.

Expected symptoms for pneumonia are complaints like cough, shortness of breath, and trouble breathing. Expected symptoms for urinary tract infection are complaints like abdominal pain and dysuria. Expected symptoms for skin and soft tissue infections are complaints like pain, swelling, and redness at the site of infection.

Unexpected: An event is considered unexpected if there are no prior data linking this event with either the condition or intervention under study or an event that occurred unexpectedly in the course of treatment.

Reporting:

The time interval during which patients will be monitored for the occurrence of adverse events/serious adverse begins at initial randomization and ends 30 days following hospital discharge. Adverse events occurring outside of this interval will not be collected. The Site PI at each recruiting site will have primary responsibility for overseeing the monitoring, assessment, and reporting of serious adverse events. If the DCC or CCC nurse identify a potential serious adverse event, the Site PI and Dual PIs will be immediately notified. The Site PI will record their assessment the relatedness and expectedness of the potential serious adverse event adverse using an electronic case report form in the Eureka database. With assistance as needed from the Dual PIs, the Site PI will determine whether the event qualifies for recording and reporting.

The following types of adverse events will be reported:

- Serious and Definitely, Probably, or Possibly Related
- Unexpected and Definitely, Probably, or Possibly Related

The DCC PI will notify the DSMB and the IRB in accordance with the following reporting plan:

Characteristics of the Adverse Event	Reporting Period
Fatal or life-threatening (and therefore serious), unexpected, and definitely, probably, or possibility related, or of uncertain relationship.	Report to the DSMB, IRB within 7 days after notification of the event. Report to PCORI within 10 days after notification of the event.
Serious but non-fatal and non-life-threatening, unexpected, and definitely, probably, or possibly related, or of uncertain relationship.	Report to DSMB, IRB, and PCORI within 10 days of notification of the event.
All other adverse events meeting criteria for recording and reporting.	Report to DSMB in regularly scheduled DSMB safety reports.

We will contact these entities and provide the following information: 1) study ID/contract number, 2) details of the event, 3) the date of the event, 4) who reviewed the SAE. After review, we will provide the date of the decision and a brief description of the decision (e.g., no further action required etc.). PCORI reporting will be sent to the PCORI study team and fundedpfa@pcori.org.

Data Safety Monitoring Board Charter:

The progress of the study will be monitored by the Data Safety Monitoring Board (DSMB). The DSMB will be named prior to the start of the study. We will plan to include members with clinical trials experience, a biostatistician, an ethical expert, among others. The purpose of the DSMB is to provide the oversight and monitoring necessary to ensure the safety of the study participants and the validity and integrity of the trial data. The study governance provided by the DSMB is distinct from the review and approval by an Institutional Review Board (IRB) or any independent adjudication committee. The DSMB will advise the Dual-PIs and the study funder (PCORI) regarding the continuing safety of study participants, the ongoing validity and scientific merit of the trial and whether or not the study should continue.

Prior to implementation of the trial, the DSMB will evaluate the study design, review informed consent documents and plans for recruitment, adherence, interventions, data quality and safety monitoring. On an annual basis, the Study Team will prepare a written report for the DSMB on the progress of the study including:

- Data on enrollment to compare target and actual enrollment and enrollment data stratified by race/ethnicity and gender.
- Overall day 15 status of the study patients, specifically, the secondary study outcome “Full symptom and function recovery”. This is defined as fever-free for at least 24 hours, either at or better than their usual state of health, and no condition-specific symptoms.
- Information on study secondary outcomes that represent moderate/severe adverse antibiotic events by day 15.

- Information on treatment failure by day 15. Treatment failure is defined as change in antibiotic treatment plan due to treatment failure, unplanned rehospitalization, or death.
- Information on any serious adverse events.

Each of these reports will include overall occurrence (n, %) for the whole study cohort and stratified by condition. The reports in the open session will not be separated by treatment arm to preserve blinding of investigators.

Reports presented in the closed session will further stratify these data by treatment arm. Treatment groups will be masked as “Group A” and “Group B.” No formal interim statistical analyses or halting/stopping rules are planned.

Annually, during the course of the trial, the responsibilities of the DSMB are to:

- Evaluate the progress of the study, including, adequacy and timeliness of participant recruitment, adherence to the interventions protocol, data quality and timeliness, participant safety, and other factors that can affect study outcome
- Consider factors and information external to the study when relevant information, such as scientific developments, that may have an impact on the safety of the participants or the ethical conduct of the trial
- Ensure data integrity
- Ensure confidentiality of data and the results of monitoring
- Report to the study funder and investigators on the scientific progress of the trial and the safety of participants
- Make recommendations to the study funders and Investigators and Institutional Review Boards on continuation, termination, or other modifications of the trial

Agendas for the DSMB meetings will be developed by the Dual PIs and the DSMB Chair. The first meeting will take place before initiation of the study to discuss protocol, interventions, safety measures and to establish guidelines for monitoring. Following the initial meeting, the DSMB will meet annually. An emergency meeting of the DSMB may be called at any time by the Chair or study funder should questions of participant safety arise.

DSMB meetings will consist of an open and a closed session. The open session will always include the Dual PIs and the study biostatistician and may be attended by Co-Investigators and study funder staff. Issues discussed at the open session will include conduct and progress of the study, recruitment, adherence with the visit and interventions protocols, data quality and timeliness, problems encountered and aggregate outcome data, and safety reporting (described above). The closed session will be attended only by DSMB members, DCC PI, and DCC Biostatistician but others may attend if requested by the DSMB. All discussion at the closed session is completely confidential. Should the DSMB decide to issue a recommendation to terminate or alter the study protocol, a full vote of the DSMB will be required. In the event of a split vote, a simple majority vote will rule and a minority report should be appended.

The DCC staff take meeting minutes of the open and closed sessions which will be finalized by the DSMB Chair. These will include any recommendations for changes in the study protocol that are approved by the Board. The minutes of the open session will be distributed to the Study Funder and Dual PIs within four weeks of each meeting. The minutes of each DSMB closed session will conclude with a recommendation to continue, terminate or alter the study.

19.0 Provisions to Protect the Privacy Interests of Subjects

A loss of confidentiality or privacy is an unlikely but possible risk. All study materials will be maintained on the secure, password-protected Eureka database or RAE, or in a locked location that is only accessible by study staff.

Trained research staff will conduct the consent process and surveys with caregiver who elect to complete the surveys over the phone. Caregiver are free to decline to answer any questions or withdraw from the research at any time.

The research team will access the patient's medical record only to access necessary information for enrollment and study procedures.

20.0 Compensation for Research-Related Injury

Each site will follow their institutional policies related to research-related injury.

21.0 Economic Burden to Subjects

Participants (and/or their insurance) will be responsible for paying for their hospital stay and first 5 days of antibiotics as prescribed by their inpatient team. The cost of these should be equal to or less than what they would pay if they were not in the study, because patients with these conditions typically receive 5-14 days of antibiotics as part of normal clinical care. All study product, tracking devices, and thermometers provided to participants will be paid for by the study and not billed to the patient or their insurance.

22.0 Consent Process

Study staff will go through the informed consent process, according to Standard Operating Procedures and Good Clinical Practice Guidelines and obtain written consent from one authorized parent or caregiver. Written assent from participants aged 11 and older will be obtained when applicable (i.e., patient is cognitively able to do so). Consent will be obtained via either paper copy or electronic consent form via Eureka. A trained research staff member will discuss details of the study with the potential participants and give them adequate time to review the informed consent form. All questions will be answered prior to consenting to participate in the study.

We will not enroll any participant over the age of 17 years and 10 months; therefore, no participants will turn 18 during their active study period.

Participants are not excluded due to language and therefore, will be prospectively enrolled in the same manner as English-speaking participants and caregivers. For patients and caregiver that speak a language other than English, study staff will use an interpreter either in person or

over video and/or audio to complete all study processes. For consent, study staff will use interpreters to review the full English informed consent form and participants will sign a short form in the patients' and caregiver' preferred languages. We may translate study documents into languages other than English, if funding allows, and will submit translations as they are completed.

If consenting persons are unable to read or write, study staff will follow institutional policies and procedures for obtaining consent.

For the qualitative interviews, we are requesting a waiver of written documentation of consent. Participants will provide verbal consent when agreeing to the interview.

23.0 Process to Document Consent in Writing

Each site will document their consent process in Eureka.

24.0 Setting

The enrollment survey will be conducted either in-person in the hospital or via e-mail, phone, or text message with the family if either the family or coordinator is not present in the hospital

The outcome surveys will be conducted via Eureka app, e-mail, phone, or text message with the family.

The qualitative interviews will either be conducted in the hospital during the patient's index admission or once the patient is home for the post-study interviews.

Cincinnati Children's Hospital Medical Center (CCHMC) is the Clinical Coordinating Center (CCC) for this multi-site study. University of California, San Francisco (UCSF) will act as the Data Coordinating Center (DCC).

There will be eleven sites where participant enrollment will occur:

- Cincinnati Children's Hospital Medical Center-Burnet Campus
- Cincinnati Children's Hospital Medical Center-Liberty Campus
- Children's Hospital of Colorado
- University of Pittsburgh
- Children's National Hospital
- Seattle Children's
- University of Alabama at Birmingham
- Intermountain Health Primary Children's Hospital
- Intermountain Health Primary Children's Hospital Larry H. and Gail Miller Family Campus
- Monroe Carrell Jr Children's Hospital at Vanderbilt University Medical Center

Required documentation from each site will be obtained and submitted to CCHMC's sIRB to obtain approval prior to any research activities occurring. Site approval will be obtained by each site having a subcontract and a Data Use Agreement with UCSF. We may recruit an additional site(s) to ensure we have an adequate sample size and will addend the IRB as needed.

We have assembled a diverse group of Stakeholders (**table below, PC-1, PC-4**) that will advise our team throughout the study and will assist us with disseminating our findings to their networks. This group will supplement the existing expertise on our diverse study team. For example, our nurse scientist, Ms. Beckmann, can advise us if we encounter challenges

collaborating with bedside nurses during our recruitment process. We have both an academic-affiliated (Dr. Fogel) and community-based pediatrician (Dr. Madani) to primary care provider perspectives. Dr. Kuppermann was the founder of the Pediatric Emergency Care Applied Research Network, which has successfully run over 75 studies, including multicenter pediatric clinical trials. He can provide our team guidance on multicenter and network-based research. Our community pediatric hospitalist (Dr. Hamline) can provide a different, additional perspective from our site-PI community hospitalists. Dr. McCulloh is a pediatric hospitalist and infectious disease specialist who has extensive experience in pediatric clinical trials and rural health. We have additional stakeholders with expertise in pediatric pharmacology (Dr. Ramsey) and UTI pathophysiology (Dr. Shaikh). Finally, Dr. Yin will provide expertise in stakeholder engagement in research, specifically in the areas of health literacy and health equity. Dr. Yin has an existing PCORI contract from the "Advancing the Science of Engagement" call and is working with Dr. Auger and other members of our study team on this project. **These members may change as the study progresses, however, the areas of expertise will remain the same.**

Stakeholder Advisory Board Members

Area of Expertise	Name	Practice Location
Nurse Scientist	Nicole Beckmann, PhD, APRN-CNP	Children's Minnesota
Academic-Affiliated Primary Care	Benjamin Fogel, MD, MPH	Penn State College of Medicine
Community Pediatric Hospitalist	Michelle Hamline, MD, PhD, MAS	Lodi Memorial Hospital
Pediatric Research Networks	Nathan Kuppermann, MD, MPH	PECARN, UC Davis Children's Hospital
Community Primary Care	Reza Madani, MD	Center City Pediatrics
Pediatric Hospitalist and Infectious Disease	Russell McCulloh, MD	Children's Nebraska
Pediatric Pharmacology	Laura Ramsey, PhD	Children's Mercy Kansas City
Urinary Tract Infection Research	Nader Shaikh, MD, MPH	UPMC Children's Hospital of Pittsburgh
Stakeholder Engagement in Research (Health Literacy and Language Equity)	Shonna Yin, MD, MS	NYU School of Medicine

25.0 Resources Available

We are confident in our ability to enroll the projected sample size across all 11 hospitals during the recruitment period. See table below for details.

Recruitment, Enrollment, and Retention Plans	Number
Estimated number of potentially eligible participants (from data from the Pediatric Health Information System)	22,228
Total number of potentially eligible study participants expected to be screened	19,116
Total number of screened study participants expected to be found eligible	15,292
Target sample size	1200

We have trained study staff with ample time and resources, such as laptop computers and phones, to conduct the research.

26.0 Multi-Site Research*

This multi-site study will be co-led by Cincinnati Children's Hospital Medical Center and the University of California, San Francisco. The CCC, based at Cincinnati Children's Hospital, will lead the oversight of the clinical trial start up and implementation across the 11 recruitment sites. The CCC will be responsible for developing the study protocol, submitting the study to CCHMC's IRB for single IRB (sIRB) approval, and working with all other sites to get sIRB approval. The CCC will maintain regulatory documents and submit IRB amendments as needed. CCC PI and staff will create study materials including patient screener forms and caregiver study handouts. The CCC will maintain a manual of operations that will be refined as necessary. The CCC will onboard and train Co-investigators and study staff at all 11 sites on study procedures, recruitment, and data collection and entry. The CCC will oversee research operations at all 11 sites, including monitoring of recruitment and enrollment rates (using reports generated by Eureka/the DCC); day-to-day trouble shooting; and general oversight of research conduct. The CCC will lead outcome collection/retention efforts for all sites, reaching out to caregiver via their preferred contact method (app, phone, text, email) to complete the outcomes surveys.

The DCC, based at the University of California San Francisco, will: provide regular reports to the CCC, PCORI, and the DSMB (e.g., study flow, data quality), ensure data security, integrity, completeness, and quality, conduct all primary, secondary, and exploratory analyses, and prepare and deposit the final de-identified study dataset into a PCORI-designated repository. As the primary awardee site, the DCC will also oversee communication with PCORI, monitoring of milestones/study progress, management of the study budget, management of all contracts, and study reports.

Each of the remaining study sites will be responsible for screening, approaching, and enrolling patients as described above. Additionally, site PIs and site study staff will attend monthly study team meetings, site-specific recruitment meetings, and ad hoc meetings as necessary to ensure that they are fully informed of all study procedures, any potential changes, and have the ability to ask the DCC and CCC questions as necessary.

Appendix 1: Feasibility Phase Milestones

The timeline and milestones we expect to reach during this 18 month period are as follows:

Milestone	**Description**	**Date**	**Owner**
Final Feasibility Phase Study Protocol and Data Safety and Monitoring Plan (DSMP)	The Feasibility Phase Study Protocol and DSMP should be submitted to PCORI	12/1/2025	DCC
Submission of PLACER Feasibility Phase Engagement Plan	Complete the feasibility phase engagement plan template and submit to PCORI via PCORI Online.	12/1/2025	Engagement team at CCC
Select and register Full-Scale Study at appropriate site for the study design (Clinicaltrials.gov).	Submit Study Identification Number and the Primary Completion Date to PCORI. .	12/31/2025	DCC
Feasibility Phase IRB Approval(s)	Submit IRB approval, as necessary, for the Feasibility Phase protocol and scope of work.	12/31/2025	CCC creates S-IRB

Readiness of study drug and placebo formulations	Study drug and placebo formulations ready to be used at Cincinnati sites	1/31/2026	CCC
Feasibility Phase site-level training completed at Cincinnati Sites	Feasibility Phase site-level training for sites participating in Feasibility Phase recruitment efforts at Cincinnati sites	1/31/2026	CCC
Initiate Pilot Recruitment or other Full-Scale Study Phase feasibility testing	Begin Feasibility Phase recruitment efforts (n = 75) at one site to validate methods for accurately identifying and enrolling participants.	2/1/2026	CCC
Submission of executed partnership agreements with patient and stakeholder partners	Partnership agreements should include descriptions, with pay scale, roles, responsibilities, expectations.	2/28/2026	DCC
Enroll first patient in Feasibility Study Phase		2/28/2026	CCC
Stakeholder Advisory Board Meeting #1	Stakeholder Advisory Board Meeting #1	2/28/2026	CCC
Report Submission	Submit Interim Progress Report to PCORI via PCORI Online	3/1/2026	DCC
Patient and study stakeholder partners complete onboarding		3/31/2026	DCC
Second Feasibility Phase Site Begins	Second Feasibility Phase Site Begins Recruitment (Liberty)	4/1/2026	CCC
Relevant members of study investigative team complete training on patient-centered CER or participatory research		5/1/2026	DCC
Submission of Advisory Committee charters including team and meeting norms, decision-making pathways, information-sharing approaches, shared vision statement/goal statement		5/1/2026	CCC
Site Subcontracts for Feasibility Phase activities or data use in place or pending signatures		5/2/2026	DCC
Feasibility Phase site-level training completed at Third Site		5/25/2026	CCC
Study Drug and Placebo Ready for Distribution at Third Site	Study Drug and Placebo Ready for Distribution at Third Site	5/25/2026	CCC
Third Feasibility Phase Site Begins	Third Feasibility Phase Site Begins Recruitment	6/1/2026	CCC
Stakeholder Advisory Board Meeting #2	Stakeholder Advisory Board Meeting #2	6/1/2026	CCC
25% (N=18) of Feasibility Phase Sample Enrolled	25% of participants (N = 18) screened, enrolled, and consented to the study.	7/2/2026	CCC

Feasibility Phase site-level training completed at Fourth Site	Feasibility Phase site-level training for sites participating in Feasibility Phase recruitment efforts at fourth site	7/25/2026	CCC
Study Drug and Placebo Ready for Distribution at Fourth Site	Study Drug and Placebo Ready for Distribution at Fourth Site	7/25/2026	CCC
Fourth Feasibility Phase Site Begins	Fourth Feasibility Phase Site Begins Recruitment	8/1/2026	CCC
50% (N=38) of Feasibility Phase Sample Enrolled	50% of participants (N = 38) screened, enrolled, and consented to the study.	8/15/2026	CCC
Full-Scale Study Phase Study Governance, Communication, and Data Management Plan	Provide a detailed overall study governance structure and study communication plan. The deliverable should include explicit delineation of all Clinical Coordinating Center (CCC) and DCC activities and how the data is managed.	8/31/2026	DCC
Draft Full-Scale Study Phase Study Protocol	We do not anticipate this being different than the feasibility phase protocol.	10/31/2026	DCC+CCC
Draft Full-Scale Study Phase Data Safety and Monitoring Plan	We do not anticipate this being different than the feasibility phase protocol.	10/31/2026	DCC
Stakeholder Advisory Board Meeting #3	Stakeholder Advisory Board Meeting #3	8/31/2026	CCC
Feasibilty Report Submission	Submit Interim Progress Report to PCORI	9/1/2026	DCC

References

1. Kaiser SV, Rodean J, Coon ER, Mahant S, Gill PJ, Leyenaar JK. Common Diagnoses and Costs in Pediatric Hospitalization in the US. *JAMA Pediatr*. Mar 1 2022;176(3):316-318. doi:10.1001/jamapediatrics.2021.5171
2. Gerber JS, Kronman MP, Ross RK, et al. Identifying targets for antimicrobial stewardship in children's hospitals. *Infect Control Hosp Epidemiol*. Dec 2013;34(12):1252-8. doi:10.1086/673982
3. Subcommittee On Urinary Tract Infection, American Academy of Pediatrics. Reaffirmation of AAP Clinical Practice Guideline: The Diagnosis and Management of the Initial Urinary Tract Infection in Febrile Infants and Young Children 2-24 Months of Age. *Pediatrics*. Dec 2016;138(6)doi:10.1542/peds.2016-3026
4. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. Oct 2011;53(7):e25-76. doi:10.1093/cid/cir531
5. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. Jul 15 2014;59(2):e10-52. doi:10.1093/cid/ciu444
6. American Academy of Pediatrics. *Red Book: Report on the Committee on Infectious Diseases*. 32nd ed. 2021.
7. National Institute of Health and Care Excellence. Urinary tract infection in under 16s: diagnosis and management Accessed January 19, 2024. https://www.nice.org.uk/guidance/ng224/resources/urinary-tract-infection-in-under-16s-diagnosis-and-management-pdf-66143835667141
8. National Institute of Health and Care Excellence. Pneumonia (community acquired): antimicrobial prescribing. Accessed January 19, 2024. https://www.nice.org.uk/guidance/ng138/resources/pneumonia-communityacquired-antimicrobial-prescribing-pdf-66141726069445
9. National Institute of Health and Care Excellence. Cellulitis and erysipelas: antimicrobial prescribing. Accessed January 19, 2024. https://www.nice.org.uk/guidance/ng141/resources/cellulitis-and-erysipelas-antimicrobial-prescribing-pdf-66141774778309
10. National Institute of Health and Care Excellence. Pyelonephritis (acute): antimicrobial prescribing. Accessed January 20, 2024, https://www.nice.org.uk/guidance/ng111/resources/pyelonephritis-acute-antimicrobial-prescribing-pdf-66141593379781
11. Schuler CL, Courter JD, Conneely SE, et al. Decreasing Duration of Antibiotic Prescribing for Uncomplicated Skin and Soft Tissue Infections. *Pediatrics*. Feb 2016;137(2):e20151223. doi:10.1542/peds.2015-1223
12. Hamner M, Nedved A, Austin H, et al. Improving Duration of Antibiotics for Skin and Soft-tissue Infections in Pediatric Urgent Cares. *Pediatrics*. Dec 1 2022;150(6)doi:10.1542/peds.2022-057974
13. Rossin S, Barbieri E, Cantarutti A, et al. Multistep antimicrobial stewardship intervention on antibiotic prescriptions and treatment duration in children with pneumonia. *PLoS One*. 2021;16(10):e0257993. doi:10.1371/journal.pone.0257993
14. Afolabi TM, Goodlet KJ, Fairman KA. Association of Antibiotic Treatment Duration With Recurrence of Uncomplicated Urinary Tract Infection in Pediatric Patients. *Ann Pharmacother*. Aug 2020;54(8):757-766. doi:10.1177/1060028019900650

15. Vernacchio L, Hatoun J, Patane LB, O'Donnell H, Herigon JC. Improving Short Course Treatment of Pediatric Infections: A Randomized Quality Improvement Trial. *Pediatrics*. Jan 3 2024;doi:10.1542/peds.2023-063691
16. Patangia DV, Anthony Ryan C, Dempsey E, Paul Ross R, Stanton C. Impact of antibiotics on the human microbiome and consequences for host health. *Microbiologyopen*. Feb 2022;11(1):e1260. doi:10.1002/mbo3.1260
17. Brodin P. Immune-microbe interactions early in life: A determinant of health and disease long term. *Science*. May 27 2022;376(6596):945-950. doi:10.1126/science.abk2189
18. Kwon J, Kong Y, Wade M, et al. Gastrointestinal Microbiome Disruption and Antibiotic-Associated Diarrhea in Children Receiving Antibiotic Therapy for Community-Acquired Pneumonia. *J Infect Dis*. Sep 21 2022;226(6):1109-1119. doi:10.1093/infdis/jiac082
19. Lovegrove MC, Geller AI, Fleming-Dutra KE, Shehab N, Sapiano MRP, Budnitz DS. US Emergency Department Visits for Adverse Drug Events From Antibiotics in Children, 2011-2015. *J Pediatric Infect Dis Soc*. Nov 6 2019;8(5):384-391. doi:10.1093/jpids/piy066
20. Mohanty S, Feemster K, Yu KC, Watts JA, Gupta V. Trends in Streptococcus pneumoniae Antimicrobial Resistance in US Children: A Multicenter Evaluation. *Open Forum Infect Dis*. Mar 2023;10(3):ofad098. doi:10.1093/ofid/ofad098
21. Meropol SB, Haupt AA, Debanne SM. Incidence and Outcomes of Infections Caused by Multidrug-Resistant Enterobacteriaceae in Children, 2007-2015. *J Pediatric Infect Dis Soc*. Feb 19 2018;7(1):36-45. doi:10.1093/jpids/piw093
22. David MZ, Daum RS. Update on Epidemiology and Treatment of MRSA Infections in Children. *Curr Pediatr Rep*. Sep 1 2013;1(3):170-181. doi:10.1007/s40124-013-0023-7
23. Curran J, Lo J, Leung V, et al. Estimating daily antibiotic harms: an umbrella review with individual study meta-analysis. *Clin Microbiol Infect*. Apr 2022;28(4):479-490. doi:10.1016/j.cmi.2021.10.022
24. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ*. May 18 2010;340:c2096. doi:10.1136/bmj.c2096
25. Williams DJ, Creech CB, Walter EB, et al. Short- vs Standard-Course Outpatient Antibiotic Therapy for Community-Acquired Pneumonia in Children: The SCOUT-CAP Randomized Clinical Trial. *JAMA Pediatr*. Mar 1 2022;176(3):253-261. doi:10.1001/jamapediatrics.2021.5547
26. Coon ER, McDaniel CE, Paciorkowski N, et al. Prioritization of Randomized Clinical Trial Questions for Children Hospitalized With Common Conditions: A Consensus Statement. *JAMA Netw Open*. May 1 2024;7(5):e2411259. doi:10.1001/jamanetworkopen.2024.11259
27. World Health Organization. The WHO AWaRe (Access, Watch, Reserve) Antibiotic Book. Accessed July 26, 2024, https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2022.02
28. U.S. Centers for Disease Control and Prevention. Core Elements of Antibiotic Stewardship. Accessed July 26, 2024, https://www.cdc.gov/antibiotic-use/hcp/core-elements/index.html
29. Infectious Diseases Society of America. Antimicrobial Stewardship Centers of Excellence. Accessed July 26, 2024, https://www.idsociety.org/clinical-practice/antimicrobial-stewardship/
30. Tarrant C, Krockow EM. Antibiotic overuse: managing uncertainty and mitigating against overtreatment. *BMJ Qual Saf*. Mar 2022;31(3):163-167. doi:10.1136/bmjqs-2021-013615
31. Zaoutis T, Shaikh N, Fisher BT, et al. Short-Course Therapy for Urinary Tract Infections in Children: The SCOUT Randomized Clinical Trial. *JAMA Pediatr*. Aug 1 2023;177(8):782-789. doi:10.1001/jamapediatrics.2023.1979
32. Montini G, Tessitore A, Console K, et al. Short Oral Antibiotic Therapy for Pediatric Febrile Urinary Tract Infections: A Randomized Trial. *Pediatrics*. Jan 1 2024;153(1)doi:10.1542/peds.2023-062598

33. Lee RA, Stripling JT, Spellberg B, Centor RM. Short-course antibiotics for common infections: what do we know and where do we go from here? *Clin Microbiol Infect*. Feb 2023;29(2):150-159. doi:10.1016/j.cmi.2022.08.024
34. Lee RA, Centor RM, Humphrey LL, et al. Appropriate Use of Short-Course Antibiotics in Common Infections: Best Practice Advice From the American College of Physicians. *Ann Intern Med*. Jun 2021;174(6):822-827. doi:10.7326/M20-7355
35. Fox MT, Amoah J, Hsu AJ, Herzke CA, Gerber JS, Tamma PD. Comparative Effectiveness of Antibiotic Treatment Duration in Children With Pyelonephritis. *JAMA Netw Open*. May 1 2020;3(5):e203951. doi:10.1001/jamanetworkopen.2020.3951
36. Same RG, Amoah J, Hsu AJ, et al. The Association of Antibiotic Duration With Successful Treatment of Community-Acquired Pneumonia in Children. *J Pediatric Infect Dis Soc*. Apr 3 2021;10(3):267-273. doi:10.1093/jpids/piaa055
37. McCulloh RJ, Kerns E, Flores R, et al. A National Quality Improvement Collaborative to Improve Antibiotic Use in Pediatric Infections. *Pediatrics*. May 1 2024;153(5)doi:10.1542/peds.2023-062246
38. Evans SR, Rubin D, Follmann D, et al. Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR). *Clin Infect Dis*. Sep 1 2015;61(5):800-6. doi:10.1093/cid/civ495
39. Auger KA, Shah SS, Tubbs-Cooley HL, et al. Effects of a 1-Time Nurse-Led Telephone Call After Pediatric Discharge: The H2O II Randomized Clinical Trial. *JAMA Pediatr*. Sep 1 2018;172(9):e181482. doi:10.1001/jamapediatrics.2018.1482
40. Auger KA, Simmons JM, Tubbs-Cooley HL, et al. Postdischarge Nurse Home Visits and Reuse: The Hospital to Home Outcomes (H2O) Trial. *Pediatrics*. Jul 2018;142(1)doi:10.1542/peds.2017-3919
41. Warniment A, Sauers-Ford H, Brady PW, et al. Garnering effective telehealth to help optimize multidisciplinary team engagement (GET2HOME) for children with medical complexity: Protocol for a pragmatic randomized control trial. *J Hosp Med*. Oct 2023;18(10):877-887. doi:10.1002/jhm.13192
42. Coon ER, Greene T, Fritz J, et al. A multicenter randomized trial to compare automatic versus as-needed follow-up for children hospitalized with common infections: The FAAN-C trial protocol. *J Hosp Med*. Jun 5 2024;doi:10.1002/jhm.13425
43. Edwards YA, A.; McCulloch, C.E.; Gonzales, R.; Rodean, J.; Yang, N.; Howell, E.; Goldstein, J.; Thompson, S.; Kaiser, S.V. Simultaneously Implementing Pathways (SIP) for Improving Asthma, Pneumonia, and Bronchiolitis Care for Hospitalized Children: Protocol for a Hybrid Effectiveness-Implementation, Cluster-Randomized Trial *J Hosp Med*. 2024:Epub ahead of print. . doi:10.1002/jhm.13482
44. Howard LM, Dantuluri KL, Soper N, Thomsen IP, Grijalva CG. Rapid Changes in Nasopharyngeal Antibiotic Resistance Gene Profiles After Short Courses of Antibiotics in a Pilot Study of Ambulatory Young Children. *Open Forum Infect Dis*. Nov 2021;8(11):ofab519. doi:10.1093/ofid/ofab519
45. Creswell J. *Qualitative inquiry & research design: Choosing among five approaches.* Sage; 2013.
46. Pernica JM, Harman S, Kam AJ, et al. Short-Course Antimicrobial Therapy for Pediatric Community-Acquired Pneumonia: The SAFER Randomized Clinical Trial. *JAMA Pediatr*. May 1 2021;175(5):475-482. doi:10.1001/jamapediatrics.2020.6735
47. Keren R, Shah SS, Srivastava R, et al. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. *JAMA Pediatr*. Feb 2015;169(2):120-8. doi:10.1001/jamapediatrics.2014.2822
48. Nakamura MM, Toomey SL, Zaslavsky AM, et al. Measuring pediatric hospital readmission rates to drive quality improvement. *Acad Pediatr*. Sep-Oct 2014;14(5 Suppl):S39-46. doi:10.1016/j.acap.2014.06.012

49. Auger KA, Mueller EL, Weinberg SH, et al. A Validated Method for Identifying Unplanned Pediatric Readmission. *J Pediatr*. Mar 2016;170:105-12 e1-2. doi:10.1016/j.jpeds.2015.11.051
50. KINDL. Accessed August 20, 2024, https://www.kindl.org/contacts/english/
51. Viotti F, Badia M, Orgaz MB, Ullan AM, Urzua JS. The Adaptation and Psychometric Properties of the Kid-KINDL(R) for Hospitalized Children in Chile. *J Pediatr Nurs*. Jul-Aug 2018;41:e8-e15. doi:10.1016/j.pedn.2018.02.007
52. Herzog K, Schepper F, Kamm-Thonwart R, et al. Trajectories of illness perceptions in paediatric cancer patients and their parents and associations with health-related quality of life: Results of a prospective-longitudinal study. *Psychooncology*. Mar 2024;33(3):e6332. doi:10.1002/pon.6332
53. Alamolhoda M, Farjami M, Bagheri Z, Ghanizadeh A, Jafari P. Assessing whether child and parent reports of the KINDL questionnaire measure the same constructs of quality of life in children with attention-deficit hyperactivity disorder. *Health Qual Life Outcomes*. Jan 15 2021;19(1):19. doi:10.1186/s12955-020-01649-w
54. Hartnick CJ, Zurakowski D, Haver K. Validation of a pediatric cough questionnaire. *Ear Nose Throat J*. Nov 2009;88(11):1213-7.
55. Ibrahim LF, Hopper SM, Donath S, Salvin B, Babl FE, Bryant PA. Development and Validation of a Cellulitis Risk Score: The Melbourne ASSET Score. *Pediatrics*. Feb 2019;143(2)doi:10.1542/peds.2018-1420
56. HV. MSDRHKMMH. The Assessment of Quality of Life among Early Aged Children with Bronchiolitis and Community-Acquired Pneumonia Using Qualin and PCQ Questionnaires. *Journal of Pulmonary & Respiratory Medicine*. 2021;11(3)
57. Milstone AM, Tamma PD. Does the SCOUT Trial Fall Short of Determining an Effective Treatment Duration for Pediatric Urinary Tract Infections? *JAMA Pediatr*. Aug 1 2023;177(8):756-758. doi:10.1001/jamapediatrics.2023.1976
58. Pew Research Center. *Mobile Fact Sheet*. 2024. Accessed August 20, 2024. https://www.pewresearch.org/internet/fact-sheet/mobile/?tabItem=673f63a2-da02-4836-96c6-c1d4e25c8a89
59. Buonsenso D, Sodero G, Mariani F, et al. Comparison between Short Therapy and Standard Therapy in Pediatric Patients Hospitalized with Urinary Tract Infection: A Single Center Retrospective Analysis. *Children (Basel)*. Oct 28 2022;9(11)doi:10.3390/children9111647
60. Thomson JE, Feinstein JA, Hall M, Gay JC, Butts B, Berry JG. Identification of Children With High-Intensity Neurological Impairment. *JAMA Pediatr*. Oct 1 2019;173(10):989-991. doi:10.1001/jamapediatrics.2019.2672
61. Shilling V, Young B. How do parents experience being asked to enter a child in a randomised controlled trial? *BMC Med Ethics*. Feb 16 2009;10:1. doi:10.1186/1472-6939-10-1
62. Taylor RG, Hounchell M, Ho M, Grupp-Phelan J. Factors associated with participation in research conducted in a pediatric emergency department. *Pediatr Emerg Care*. May 2015;31(5):348-52. doi:10.1097/PEC.0000000000000368
63. Sammons HM, Atkinson M, Choonara I, Stephenson T. What motivates British parents to consent for research? A questionnaire study. *BMC Pediatr*. Mar 9 2007;7:12. doi:10.1186/1471-2431-7-12
64. Nathe JM, Oskoui TT, Weiss EM. Parental Views of Facilitators and Barriers to Research Participation: Systematic Review. *Pediatrics*. Jan 1 2023;151(1)doi:10.1542/peds.2022-058067
65. Bottern J, Stage TB, Dunvald AD. Sex, racial, and ethnic diversity in clinical trials. *Clin Transl Sci*. Jun 2023;16(6):937-945. doi:10.1111/cts.13513

66. Rees CA, Stewart AM, Mehta S, et al. Reporting of Participant Race and Ethnicity in Published US Pediatric Clinical Trials From 2011 to 2020. *JAMA Pediatr*. May 1 2022;176(5):e220142. doi:10.1001/jamapediatrics.2022.0142
67. Brewster RCL, Steinberg JR, Magnani CJ, et al. Race and Ethnicity Reporting and Representation in Pediatric Clinical Trials. *Pediatrics*. Apr 1 2023;151(4)doi:10.1542/peds.2022-058552
68. Sauers-Ford HS, Gold JM, Statile AM, et al. Improving Recruitment and Retention Rates in a Randomized Controlled Trial. *Pediatrics*. May 2017;139(5)doi:10.1542/peds.2016-2770
69. Sauers HS, Beck AF, Kahn RS, Simmons JM. Increasing recruitment rates in an inpatient clinical research study using quality improvement methods. *Hosp Pediatr*. Nov 2014;4(6):335-41. doi:10.1542/hpeds.2014-0072
70. Charmaz K. *Constructing grounded theory: A practical guide through qualitative analysis.* Sage; 2006.
71. Sauers-Ford H, Statile AM, Auger KA, et al. Short-term Focused Feedback: A Model to Enhance Patient Engagement in Research and Intervention Delivery. *Med Care*. Aug 1 2021;59(Suppl 4):S364-S369. doi:10.1097/MLR.0000000000001588
72. Mbuagbaw L, Aves T, Shea B, et al. Considerations and guidance in designing equity-relevant clinical trials. *Int J Equity Health*. Jun 5 2017;16(1):93. doi:10.1186/s12939-017-0591-1
73. Greenberg RG, Gamel B, Bloom D, et al. Parents' perceived obstacles to pediatric clinical trial participation: Findings from the clinical trials transformation initiative. *Contemp Clin Trials Commun*. Mar 2018;9:33-39. doi:10.1016/j.conctc.2017.11.005
74. Bowen GA. *Sensitizing concepts.* . SAGE Publications Limited; 2020.
75. Creswell JW. Determining Validity in Qualitative Inquiry. *Theory into Practice*. 2000;39(3):124-130.
76. Pelletier JH, Rakkar J, Au AK, Fuhrman D, Clark RSB, Horvat CM. Trends in US Pediatric Hospital Admissions in 2020 Compared With the Decade Before the COVID-19 Pandemic. *JAMA Netw Open*. Feb 1 2021;4(2):e2037227. doi:10.1001/jamanetworkopen.2020.37227
77. Cabellos C, Pelegrin I, Benavent E, et al. Invasive meningococcal disease: Impact of short course therapy. A DOOR/RADAR study. *J Infect*. Nov 2017;75(5):420-425. doi:10.1016/j.jinf.2017.08.009
78. Noether GE. Sample size determination for some common nonparametric tests. . *JASA*. 1987;82:645–647.
79. Children's Hospital Association. Pediatric Health Information System. Accessed August 20, 2024, https://www.childrenshospitals.org/content/analytics/product-program/pediatric-health-information-system
80. Robinson L, Adair P, Coffey M, Harris R, Burnside G. Identifying the participant characteristics that predict recruitment and retention of participants to randomised controlled trials involving children: a systematic review. *Trials*. Jun 22 2016;17(1):294. doi:10.1186/s13063-016-1415-0
81. Watson SE, Smith P, Snowden J, et al. Facilitators and barriers to pediatric clinical trial recruitment and retention in rural and community settings: A scoping review of the literature. *Clin Transl Sci*. Apr 2022;15(4):838-853. doi:10.1111/cts.13220
82. Langley GJM, R.; Nolan, K.M.; Nolan, T.W.; Norman, C.L.; Provost, L.P. *The Improvement Guide: A Practical Approach to Enhancing Organizational Performance.* Jossey-Bass Publishers; 2009.
83. Hallberg LR. The “core category” of grounded theory: Making constant comparisons. . *International journal of qualitative studies on health and well-being*. 2006;1(3):141-148.
84. O’Connor CH, J. Intercoder reliability in qualitative research: debates and practical guidelines. 2020;19:1609406919899220.

85. Saunders B, Sim J, Kingstone T, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. *Qual Quant*. 2018;52(4):1893-1907. doi:10.1007/s11135-017-0574-8
86. Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epidemiol*. Apr 1 2017;46(2):746-755. doi:10.1093/ije/dyw320
87. Khan MS KM, Ansari ZN, Siddiqi TJ, Khan SU, Riaz IB, Asad ZUA, Mandrola J, Wason J, Warraich HJ, Stone GW, Bhatt DL, Kapadia SR, Kalra A. . Prevalence of Multiplicity and Appropriate Adjustments Among Cardiovascular Randomized Clinical Trials Published in Major Medical Journals. *JAMA Netw Open*. 2020;(3):e203082.
88. Parker RA WC. Multiple secondary outcome analyses: precise interpretation is important. . *Trials*. 2022;23(1):27.
89. Ong SWX, Petersiel N, Loewenthal MR, Daneman N, Tong SYC, Davis JS. Unlocking the DOOR-how to design, apply, analyse, and interpret desirability of outcome ranking endpoints in infectious diseases clinical trials. *Clin Microbiol Infect*. Aug 2023;29(8):1024-1030. doi:10.1016/j.cmi.2023.05.003
90. VanBuren JM, Banks RK, Kuppermann N, et al. Evaluating the desirability of outcome ranking and response adjusted for duration of antibiotic risk for clinical trials of antibiotics in pediatric pneumonia. *Am J Epidemiol*. Apr 8 2025;194(4):1090-1096. doi:10.1093/aje/kwae237
91. Williams DJ, Zhu Y, Grijalva CG, et al. Predicting Severe Pneumonia Outcomes in Children. *Pediatrics*. Oct 2016;138(4)doi:10.1542/peds.2016-1019
92. Mattoo TK, Shaikh N, Nelson CP. Contemporary Management of Urinary Tract Infection in Children. *Pediatrics*. Feb 2021;147(2)doi:10.1542/peds.2020-012138
93. Jones S, Rantell K, Stevens K, et al. Outcome at 6 months after admission for pediatric intensive care: a report of a national study of pediatric intensive care units in the United kingdom. *Pediatrics*. Nov 2006;118(5):2101-8. doi:10.1542/peds.2006-1455
94. Piper KN, Baxter KJ, McCarthy I, Raval MV. Distinguishing Children's Hospitals From Non-Children's Hospitals in Large Claims Data. *Hosp Pediatr*. Feb 2020;10(2):123-128. doi:10.1542/hpeds.2019-0218
95. Leary JC, Walsh KE, Morin RA, Schainker EG, Leyenaar JK. Quality and Safety of Pediatric Inpatient Care in Community Hospitals: A Scoping Review. *J Hosp Med*. Nov 1 2019;14(11):694-703. doi:10.12788/jhm.3268
96. Conover WJ, Iman RL. Analysis of covariance using the rank transformation. *Biometrics*. Sep 1982;38(3):715-24.
97. St George SM, Harkness AR, Rodriguez-Diaz CE, Weinstein ER, Pavia V, Hamilton AB. Applying Rapid Qualitative Analysis for Health Equity: Lessons Learned Using "EARS" With Latino Communities. *Int J Qual Methods*. Jan-Dec 2023;22doi:10.1177/16094069231164938
98. Hamilton AB, Finley EP. Qualitative methods in implementation research: An introduction. *Psychiatry Res*. Oct 2019;280:112516. doi:10.1016/j.psychres.2019.112516
99. Kaiser SV, Jennings B, Rodean J, et al. Pathways for Improving Inpatient Pediatric Asthma Care (PIPA): A Multicenter, National Study. *Pediatrics*. Jun 2020;145(6)doi:10.1542/peds.2019-3026
100. Kaiser SV, Johnson MD, Walls TA, et al. Pathways to Improve Pediatric Asthma Care: A Multisite, National Study of Emergency Department Asthma Pathway Implementation. *J Pediatr*. Aug 2020;223:100-107 e2. doi:10.1016/j.jpeds.2020.02.080
101. Ornish D, Madison C, Kivipelto M, et al. Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomized, controlled clinical trial. *Alzheimers Res Ther*. Jun 7 2024;16(1):122. doi:10.1186/s13195-024-01482-z

102. Fontil V, Khoong EC, Green BB, et al. Randomized trial protocol for remote monitoring for equity in advancing the control of hypertension in safety net systems (REACH-SNS) study. *Contemp Clin Trials*. Mar 2023;126:107112. doi:10.1016/j.cct.2023.107112
103. Nourbakhsh B, Revirajan N, Morris B, et al. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. *Lancet Neurol*. Jan 2021;20(1):38-48. doi:10.1016/S1474-4422(20)30354-9
104. Cozen AE, Carton T, Hamad R, et al. Factors associated with anxiety during the first two years of the COVID-19 pandemic in the United States: An analysis of the COVID-19 Citizen Science study. *PLoS One*. 2024;19(2):e0297922. doi:10.1371/journal.pone.0297922
105. Fontil V, Modrow MF, Cooper-DeHoff RM, et al. Improvement in Blood Pressure Control in Safety Net Clinics Receiving 2 Versions of a Scalable Quality Improvement Intervention: BP MAP A Pragmatic Cluster Randomized Trial. *J Am Heart Assoc*. Feb 7 2023;12(3):e024975. doi:10.1161/JAHA.121.024975
106. Pletcher MJ, Fontil V, Modrow MF, et al. Effectiveness of Standard vs Enhanced Self-measurement of Blood Pressure Paired With a Connected Smartphone Application: A Randomized Clinical Trial. *JAMA Intern Med*. Oct 1 2022;182(10):1025-1034. doi:10.1001/jamainternmed.2022.3355
107. National Institutes of Health. Compendium of Best Practices for Data Coordinating Centers. Accessed July 15, 2024, https://www.nhlbi.nih.gov/events/2011/compendium-best-practices-data-coordinating-centers
108. KID database. Accessed Dec 15, 2025, https://datatools.ahrq.gov/
109. BALANCE Investigators, for the Canadian Critical Care Trials Group, the Association of Medical Microbiology and Infectious Disease Canada Clinical Research Network, the Australian and New Zealand Intensive Care Society Clinical Trials Group, and the Australasian Society for Infectious Diseases Clinical Research Network, Daneman N, Rishu A, et al. Antibiotic Treatment for 7 versus 14 Days in Patients with Bloodstream Infections. *N Engl J Med*. 2025;392(11):1065-1078. doi:10.1056/NEJMoa2404991
110. Kaasch AJ, López-Cortés LE, Rodríguez-Baño J, et al. Efficacy and safety of an early oral switch in low-risk Staphylococcus aureus bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial. *Lancet Infect Dis*. 2024;24(5):523-534. doi:10.1016/S1473-3099(23)00756-9111.
111. Aguilar-Guisado M, Espigado I, Martín-Peña A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. *Lancet Haematol*. 2017;4(12):e573-e583. doi:10.1016/S2352-3026(17)30211-9112.
112. Li HK, Rombach I, Zambellas R, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. *N Engl J Med*. 2019;380(5):425-436. doi:10.1056/NEJMoa1710926