Procalcitonin to Reduce Antibiotic Use in Pediatric Pneumonia (P-RAPP)
PECARN Protocol Number 047

Pediatric Emergency Care Applied Research Network
National Heart, Lung and Blood Institute

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PROTOCOL TITLE:

Procalcitonin to Reduce Antibiotic Use in Pediatric Pneumonia

Short Title: P-RAPP
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Lead Investigator and Author:
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Ann and Robert H. Lurie Children's Hospital of Chicago

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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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Abstract

Although viruses are the leading cause of community-acquired pneumonia (CAP) in young children, antibiotics are prescribed for most children with CAP. Antibiotic overuse has substantial societal and individual consequences, including promotion of antimicrobial resistance, antibiotic-associated side effects and severe complications. Procalcitonin (PCT) is a biomarker that is elevated in the serum of patients with bacterial infections but is not typically elevated in patients with viral infections. A low PCT level has been shown to have a high negative predictive value for detection of children with CAP caused by typical bacteria. Similarly, PCT algorithms have decreased antibiotic use without increasing adverse events in adults and children; however, clinicians may be hesitant to use PCT, as the clinical efficacy and safety of avoiding antibiotics in outpatient children with low-risk clinical characteristics and low PCT levels has not been evaluated. The overall objective of this work is to test the hypothesis that low-risk children 12-71 months of age managed as outpatients with CAP and PCT levels <0.25 ng/mL treated with placebo have similar clinical response to those treated with antibiotics, with fewer adverse effects, through a large-scale, multi-institutional randomized trial (RCT). Given the complexities of conducting an RCT of this nature, the overall objective of this R34 protocol is to evaluate the feasibility and finalize the methods of a future large-scale trial through a 3-site pilot feasibility trial. We will implement and establish feasibility of all study procedures by conducting a 3-site pilot trial of amoxicillin vs placebo in low-risk children with CAP and PCT levels <0.25 ng/mL. We will enroll and randomize 36 children at 3 participating sites. This pilot trial will provide necessary data to plan the large-scale definitive trial, including assessment of facilitators and barriers of study participation, estimating enrollment and attrition rates, evaluating study procedures and interventions in a real-world setting, and determining adherence rates. In addition, we will demonstrate the ability to collect outcomes important to the future RCT, including clinical response, symptom resolution, adverse events and quality of life. The subsequent large RCT will be significant, as it will definitively address whether antibiotics are beneficial in low-risk children with CAP, representing an innovative departure from the status quo by shifting from empirical antibiotic use for all children with CAP to a targeted approach.

1 Study Summary

This pilot study will evaluate study processes and feasibility of a future large-scale clinical trial that proposes to test whether low-risk children managed as outpatients with community-acquired pneumonia (CAP) and procalcitonin (PCT) levels <0.25 ng/mL treated with placebo (i.e., no antibiotics) have a similar clinical response, with fewer adverse effects, compared with those treated with antibiotics.

1.1 Hypotheses

The hypothesis of this pilot study is that we will enroll and randomize at least 2 children per site per month and successfully conduct all study procedures, demonstrating the feasibility of conducting a subsequent large-scale clinical efficacy trial of antibiotics vs. placebo in low-risk children with CAP.

[redacted]

Pilot trials are designed with procedures similar to full-scale trials but with smaller patient enrollment to assess the feasibility and fill important knowledge gaps to inform a subsequent large-scale definitive trial. The overall objective of this pilot trial is to evaluate and finalize all trial procedures and study outcomes necessary for the development of a subsequent phase III trial evaluating antibiotics vs. placebo in low-risk children with CAP and PCT levels <0.25 ng/mL, while assessing the feasibility of study design and procedures. Knowledge gained from these pilot studies will also inform future trials of children with CAP. To achieve this overall objective, we will pursue the following specific aim:

Specific Aim 1: To demonstrate the feasibility to efficiently and effectively enroll low-risk children with CAP and PCT levels <0.25 into a multicenter RCT evaluating antibiotics vs. placebo, while refining study procedures for the subsequent large-scale clinical trial.

2 Background

3 Participant Eligibility, Accrual and Study Duration

3.1 Eligibility criteria.

Eligible participants will be identified by study staff. Inclusion criteria are:

1. Age 12–71 months; and
2. Diagnosis of CAP, defined using established criteria:
   (a) Signs and symptoms of lower respiratory tract infection (LRTI), defined as one or more of the following:
      · new or different cough; or
      · new or different sputum production; or
      · chest pain; or
      · dyspnea/shortness of breath; or
      · documented tachypnea; or
      · abnormal findings consistent with LRTI on physical examination (e.g., crackles/rales, rhonchi, wheezing) and
   (b) Fever, defined as temperature ≥38°C, and
   (c) ED clinician diagnosis of CAP, including intention to treat with antibiotics, and
   (d) Chest radiography suspicious for CAP.[4]
3. Intention to treat as an outpatient after ED visit.

Exclusion criteria are:

1. Hospitalization within one month preceding study visit; or
2. Sustained oxygen saturations <90% with appropriate waveform on oximeter; or
3. Incomplete immunization status (<2 doses of Hib and pneumococcal vaccines); or
4. Chronic complex medical conditions (chronic heart disease, chronic lung disease (not including asthma), congenital airway or lung malformations, cystic fibrosis, chronic renal disease, protein-losing enteropathy, genetic syndromes, neurocognitive deficits, or metabolic disorders); or
5. Conditions that compromise the immune system (HIV, primary immunodeficiency, asplenia, sickle cell disease, receipt of hematopoietic stem cell or solid organ transplant, immunosuppressive agents, daily corticosteroids for more than 7 consecutive days in past 14 days) ; or
6. Systemic antibiotic receipt within the previous two weeks of CAP diagnosis; or
7. Radiographic findings of complicated pneumonia (moderate-to-large pleural effusion, empyema, abscess, necrotic lung disease); or
8. Pneumonia known to be due to bacterial source at the time of enrollment, as documented by blood culture or PCR if available, or another clear source of bacterial infection requiring immediate antibiotics; or

9. Toxic clinical appearance, sepsis, or critical illness as determined by clinical team at ED presentation; or
10. Diagnosed with pneumonia in the previous three months; or
11. Provider diagnosis of bronchitis, or aspiration pneumonia; or
12. Severe drug allergy to amoxicillin; or
13. Any other condition that in the judgement of investigators or the clinical team could affect safety of the subject; or
14. No access to a telephone or video technology for follow-up; or
15. Current enrollment in another clinical trial of an investigational agent; or
16. Previous enrollment in this trial; or
17. Parent/guardian non-English or non-Spanish speaking; or
18. Known allergy to milk and/or red dye.

Note: To be eligible for stage 2 randomization, the subject must have a PCT level<0.25ng/mL.

3.2 Participant Accrual and Study Duration

This trial will enroll over a 6-month period and take place at 3 sites that are or were sites in the Pediatric Emergency Care Applied Research Network (PECARN), a federally funded network of 18 pediatric EDs that have an established and successful history of completing large-scale clinical trials in the ED. The randomized trial (stage 2) will enroll 36 patients in total (2 patients per month, per site).

4 Study Design

This pilot clinical trial is a 3-site, randomized, placebo-controlled, double-blinded trial assessing the feasibility of comparing amoxicillin to placebo in children 12 months to <6 years of age who present to the ED with CAP, a PCT<0.25 ng/mL, and who will be treated as outpatients.

5 Study Procedures

5.1 Screening and Enrollment

Clinical research coordinators (CRCs) at participating EDs will screen potentially eligible patients with respiratory tract symptoms and discuss eligibility with the treating attending physician. If thought to be eligible and a diagnosis of CAP is presumed by the treating physician, the CRC will approach the patient to complete screening procedures. As outlined in the Trial Flow Diagram figure 1 on page 15. The informed consent process will consist of two stages.

- **Stage 1: Baseline Characteristics and Serum Procalcitonin Levels**

  Informed consent will be obtained for the initial data collection and PCT in eligible patients. Potential participants will be informed that if eligibility criteria are met during the first phase, they will be approached to further discuss the randomized trial. The RCT will be introduced during stage 1 and participants will not be enrolled in stage 1 unless they express an interest to participate in stage 2 (the RCT).

  Participants consenting during stage 1 will have the following procedures performed:

  1. baseline characteristics, including severity factors, will be ascertained,
  2. blood will be collected for real-time PCT testing,and
  3. data collected from the electronic health record (EHR) will be retained for additional observational studies.

  If PCT concentration is ≥0.25 ng/mL, participation will end and no further trial procedures will occur. If the PCT is <0.25 ng/mL then the participant will proceed to the randomized trial (stage 2).

- **Stage 2: Randomized Trial of Amoxicillin vs. Placebo with PCT <0.25 ng/mL**

  If PCT concentration is <0.25 ng/mL, stage 2 of informed consent, with procedures specific to the RCT, will be obtained. As part of enrollment, a standardized letter will be given to families and shared with primary care pediatricians, when feasible, explaining the study, including its rationale, and any emergency contacts and procedures if clinical deterioration should occur.

  Participants consenting to the following study procedures during stage 2:

  1. randomization to receive either oral amoxicillin or placebo for a standard course (7 days),
  2. daily symptom diary during days 1-7 and,
  3. a nasal swab collection in the ED at the time of the study visit, and one home collection between days 7–25 after the study visit and,
  4. telephone or video-based follow-up at 7 and 21 days following randomization.

  The DCC will prepare enrollment reports to monitor the screening and enrollment at each site to assess site performance and, if necessary, take corrective action.

5.1.1 Procalcitonin

We will employ the B·R·A·H·M·S PCT assay for this trial. This assay requires <0.5 mL of blood with a turnaround time of 30-60 minutes. As such, 0.5-1 mL of whole blood will be collected from the patient. [redacted]

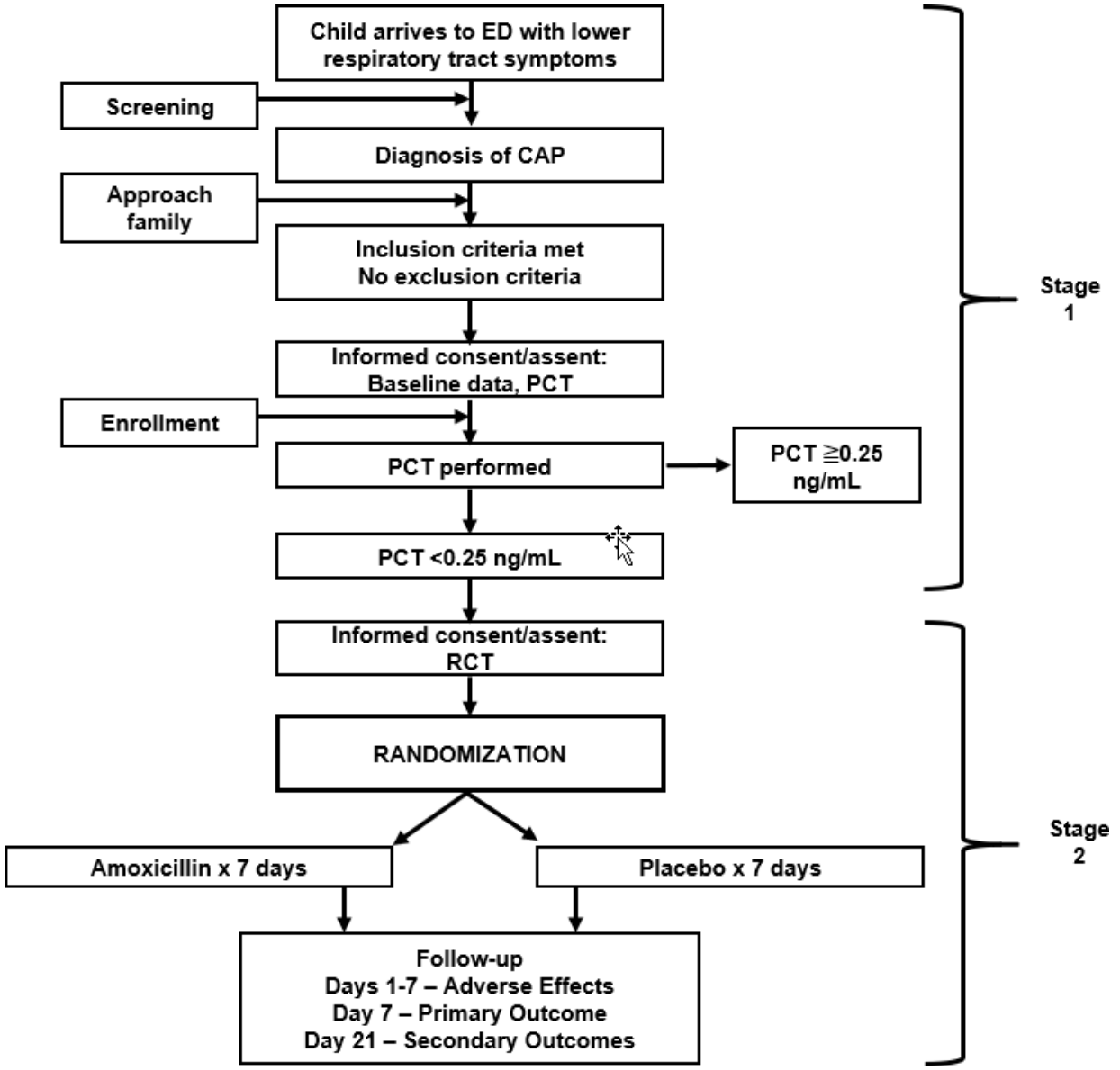


Figure 1: Trial Flow Diagram

[redacted] n this trial, the PCT concentration will not be revealed to the participants or any member of the clinical care team unless it is <0.25 ng/mL to allow for randomization. The PCT assay will be performed using the validated assay used for clinical care at each site.

5.2 Randomization

After enrollment and confirmation of a PCT less than 0.25 ng/mL, patients will be randomized to a 7-day course of either amoxicillin (80-100 mg/kg divided BID up to 4,000 mg/day) or placebo. Randomization to amoxicillin or placebo will be at a 1:1 ratio with block sizes of 2 and 4. Patients will be stratified by clinical site and randomization will be performed through an online system.

5.2.1 Blinding

As a double-blind clinical trial, the study patients and their parents/guardians, investigators and study staff will be blinded to study treatment assignment for the duration of the study. At the data coordinating center, only the study biostatisticians and the DSMB will be unblinded, as necessary, to treatment assignment.

5.3 Study Drug Administration

5.3.1 Central Pharmacy and Distribution

Local investigational drug pharmacies will use the same formulation of amoxicillin across all study sites. Sites will be provided with matching placebo from a central pharmacy.

5.3.2 Preparation, Storage & Labeling

Site pharmacies at each institution will store study drug and dispense as needed. Study medications will both be liquid and will resemble each other with regards to appearance, flavor, consistency and packaging. Study products will be labeled with numerical codes that will maintain allocation concealment. Site investigational pharmacies will be provided with the randomization scheme. The pharmacy will aliquot amoxicillin and placebo into blinded bottles based on randomization scheme.

5.3.3 Unblinding Procedures

In general, immediate unblinding will not occur in this protocol. The exception is if there is life-threatening anaphylaxis, which is a rare occurrence with amoxicillin (1 in 100,000). If this rare

situation does occur, unblinding will occur within 12 hours after presentation with anaphylaxis in order to guide further decision regarding the study agent or other antibiotics. If a patient presents to primary care or the ED and has concerns for non-fatal allergic reaction or for other concerns that require decisions around antibiotics, the treating clinicians will be told to assume the patient received amoxicillin and treat accordingly. Thirty days after randomization, the patients will have the option of a delayed unblinding at the requests of the clinical teams (e.g., primary care physician) or the parents because knowledge of the study drug could be important to future patient care.

5.3.4 Discontinuation of Study Drug

Discontinuation of study drug may occur at the discretion of the clinical team. The participant's parent/guardian may opt to discontinue the study drug, but remain in the study, therefore this will NOT be considered a study withdrawal. See Section 5.6 on the next page

5.4 Follow-up

5.4.1 Daily Follow-up

The guardians of participants will be asked to complete a daily symptom diary, using an online data collection form, during the first 7 days after the initial ED study visit. The follow-up will assess patient condition, clinical response, signs or symptoms of clinical deterioration and other adverse effects.

5.4.2 Day 7 Follow-up

The primary outcome will be assessed at day 7 (±2 days), using video chat technology that is standard on most smart phones, tablets, and computers. Video follow-up will be performed by site clinician investigators. In the rare case that a mobile device or computer with video chat technology is not available to the family, the day 7 follow-up will occur by telephone or text through an online system.

5.4.3 Day 21 Follow-up

A final follow-up,performed by site research staff, by telephone call, will occur at Day 21 (±2 days) to assess overall disease course and secondary outcomes.

5.5 Data Collection

5.5.1 Baseline Data

At baseline, demographics, medical history and history of current illness will be obtained from all participants during stage 1 (pre-randomization). Vital signs will be obtained and a brief physical examination will be performed.

5.5.2 Follow-up Assessment(s)

After the initial ED visit, patients will be sent a data collection form to record symptoms on daily basis for 6 days via an online data collection form. Follow-up assessments will be completed via telehealth visit or telephone for days 7 and 21. Follow-up visits will collect data regarding symptoms, adverse events and return to medical care, in addition to assessing adherence to study procedures (i.e., medication adherence and daily symptom diary completion). If there is concern for adverse events or deterioration that may warrant medical care, the participant's caregiver have been instructed to contact their primary care physician, emergency department, or call 911 as indicated.

5.5.3 Schedule of Evaluations

Day 7: We will use video chat technology to assess the primary outcome (clinical response, adverse effects), as described above.

Day 21: A final telephone call or text will assess secondary outcomes, overall disease course, in addition to surveying the parents/guardians of the participants about their attitudes and beliefs regarding antibiotic use after participating in the trial.

For a detailed schedule of evaluations, please refer to table 1 on page 19.

5.6 Withdrawal from Study

Parents may withdraw their child from participation in this study at any time without prejudice to their care. If the parent/guardian expresses interest in withdrawing from participation, the study staff will discuss the process with them, confirm their specific wishes, and review safety information. If complete withdrawal of consent is received in writing from the parent, the study team will not collect new information about their child, and they will be withdrawn from the research study. The study team will preserve and use any information that has already been collected, as needed to maintain the integrity of the research. There are no penalties nor benefits lost to the patient if the parent/guardian decides to withdraw.

The participant may also be withdrawn from the study at the discretion of the investigator. The investigator or the sponsor may also withdraw participants who violate the study plan, to protect the

Evaluation	**Baseline**	**Days +1 to +6**	**Day +7**	**Day +21**
Screening and Eligibility	X			
Consent: Stage 1	X			
Demographics/Baseline Information	X			
Medical History	X			
Physical Examination	X			
Procalcitonin	X			
Consent: Stage 2	X			
Randomization	X			
Nasal Swab	X			
Adverse Events		X	X	X
Daily Symptom Diary		X		
Primary Outcome(DOOR)			X	
Telehealth Evaluation			X	
Secondary Outcomes			X	X
Home Nasal Swab			X	X
Parental Survey (Attitudes/Beliefs/Feasibility)				X
End of Study				X

Table 1: Schedule of Evaluations

participant for reasons of safety or for administrative reasons. If a physician takes the patient off of the study drug for any reason, they will not be considered withdrawn unless there is a specific parental or investigator request to withdraw from the study. It will be documented whether or not each participant completes the clinical study. For the sake of this trial, a participant will only be considered withdrawn if the withdraw occurs after randomization into the trial.

5.7 Participant Compensation

A tiered incentive structure will be used to account for time and effort in participating in this study, with a total of $100 being provided for completion of all study procedures. Participating sites may choose to add parking reimbursement, and/or provide age-appropriate crayons, coloring pages and/or books to keep participants occupied during the wait time.

6 Data Analysis

The hypothesis of this pilot study is that we will enroll and randomize at least 2 children per site per month and successfully conduct all study procedures, demonstrating the feasibility of conducting a subsequent large-scale clinical efficacy trial of antibiotics vs. placebo in low-risk children with CAP.

[redacted]

[redacted]

[redacted]

[redacted]

6.2 Feasibility Outcome Analysis

The primary outcome in this pilot study is the enrollment rate per site per month. We will divide the total number of participants enrolled by the total number of months that active enrollment was occurring across sites. A 95% confidence interval will be created for this rate. We will summarize this outcome using descriptive statistics.

Secondary outcomes of the pilot study include:

1. Consent and drop-out rates between the two stages of consent
2. Parental attitudes and beliefs about trial procedures

3. Feasibility and usability of video chat follow-up
4. Lost to follow-up rates

These outcomes will be summarized in a similar fashion to the primary outcome.

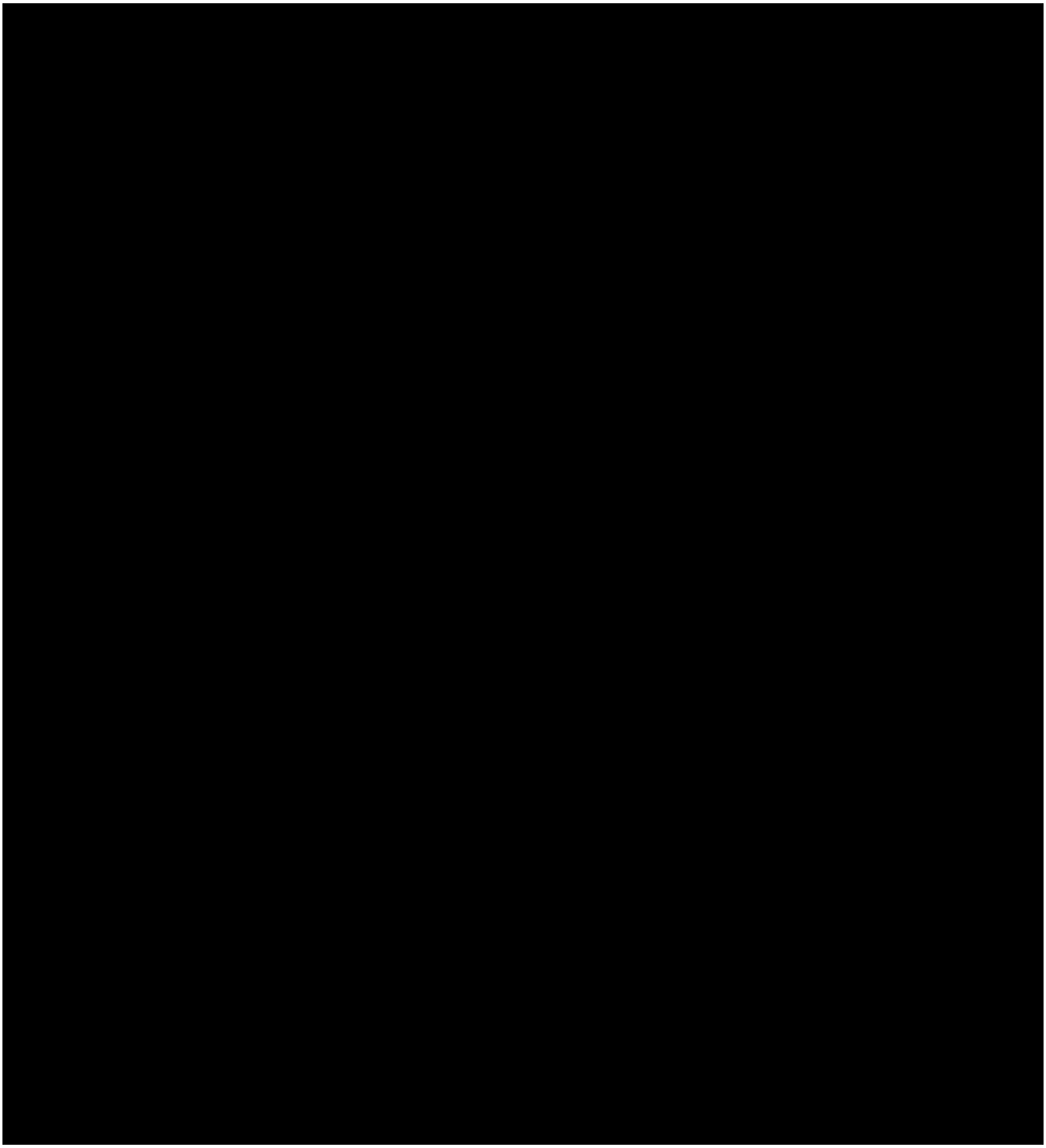
[redacted]

Summaries of these events will be produced by arm. Continuous values will be summarized with medians (IQR) or means (SD). Categorical values will be summarized with counts and percentages. No statistical inferences between arms will be made.

In addition to these analyses, we will survey ED clinicians to refine study inclusion/exclusion criteria, including the development of specific chest radiograph criteria and outcome determination.

6.3 Sample Size Calculations and Statistical Power

[redacted]



7 Data Management

7.1 Clinical Site Data Management

Each clinical site will maintain study records in secure locations that may include password protected electronic files or locked filing cabinets. The site will maintain an Essential Documents Binder, which may be in paper or electronic form. Copies of all informed consent documents will be kept on file and be available for site monitoring inspection (on site or remote).

7.2 Data Coordinating Center

7.2.1 Data Center Description

Overview The Data Coordinating Center (DCC) in the Department of Pediatrics at the University of Utah School of Medicine provides data coordination and management services for a variety of national research networks. Anchoring these services is a state-of-the-art, energy efficient data center. The data center facility supports more than 3500 users around the country and provides a secure, reliable, enterprise-wide infrastructure for delivering mission critical DCC systems and services.

Facility, Hardware, Storage, Data Backup and System Availability The data center was built using industry standards and energy efficient cooling solutions. The data center is cooled by Liquid Cooling Package (LCP) inline cooling technology, providing the desired efficiency, redundancy and the modularity. The LCP utilizes a hot/cold aisle design that allows for even air distribution to minimize hot spots. The data center's electrical power system contains an uninterruptible power supply (UPS) with a diesel backup generator. The data center is protected with an FM-200 backed fire suppression system, which provides waterless fire suppression without leaving behind residue or particulate. Enhanced security measures are implemented to safeguard the equipment and the data within in it. Security measures are enforced 24 hours a day, 7 days a week, 365 days a year by a combination of on-premise security guards, University police officers and video surveillance.

The data center has a virtualized environment. This environment consists of more than 415 virtual servers across 25 host servers. Virtualization provides key advantages: High availability (HA) – in the event of hardware failure, virtual machines (VM) automatically restart on healthy resources, minimizing impact to end-users; Flexible infrastructure – compute and storage is seamlessly scaled as current needs change; Rapid deployment – new resources are provisioned on-demand.

Production servers running mission critical applications are clustered and configured for failover events across multiple clusters. Entire servers are backed-up to a dedicated infrastructure. The backup repositories are encrypted-at-rest using AES-256. The storage area networking (SAN) applications, clusters, and switch-to-switch links are highly redundant. Incremental backups of data

occur Monday through Friday. A full data backup occurs weekly. Full backups are sent off-site on a weekly basis to a secure secondary location. The data center currently manages over 125 terabytes (TB) of data.

Information systems are available 24/7/365 unless a scheduled maintenance period or mitigation of an unexpected event is required. Critical systems availability has exceeded 99.9% for the past 5 years.

Security, Support, Encryption and Confidentiality The data center coordinates the network infrastructure and security with University Information Technology (UIT) at the University of Utah. This provides us with robust firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Centralized authentication and communication over public networks are encrypted using transport layer security (TLS) and/or virtual private network (VPN) technologies. Direct access to data center machines is only available while physically on premise or via a VPN client.

All network traffic is monitored for intrusion attempts. Security scans are regularly run against data center servers and IT staff are notified of intrusion alerts. Security is maintained with Windows user/group domain-level security. Users are required to change their passwords every 90 days. All files are protected at user/group levels and database security is handled in a similar manner with group-level access to databases, tables, and views. Finally, all laptops used by faculty and staff in the DCC are whole-disk encrypted.

The data center uses monitoring tools to continuously monitor applications and servers. Environmental and network systems are also monitored to ensure up-time. System Administrators are on-call 24/7/365 to respond to urgent events.

All personnel involved with the DCC have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act (HIPAA) education. We require all users to sign specific agreements concerning security, confidentiality, and use our information systems before access is provided.

7.3 Electronic Data Capture System

The Data Coordinating Center (DCC) will develop an electronic data capture system for this trial. Currently the DCC uses multiple applications, such as OpenClinica or REDCap, and will elect to use the most appropriate application at the time of implementation of the study. Data will be entered by each clinical site.

The DCC will use an electronic discrepancy management system to notify sites of inconsistent or erroneous data entry, which will be corrected by the clinical site. The discrepancy management system maintains an audit trail of all discrepancy resolution.

7.4 Study Monitoring

The investigators recognize the importance of ensuring data of excellent quality. Study monitoring is critical to this process. Monitoring has been a very effective tool for maintaining data quality in previous PECARN studies, and we will use this process to ensure excellent quality data in the proposed study. The DCC uses risk-based methods to identify and correct problems that may arise at sites. The risk-based approach to monitoring focuses on oversight activities and preventing or mitigating key risks to data quality, as well as to processes critical to human participant protection and integrity of the trial or study.

Study monitors must be provided with appropriate access to study materials and the medical records for study participants. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the study monitor's review of data in the electronic medical record.

7.4.1 Site Monitoring Plan

A supplemental study-specific risk-based monitoring plan, separate from the protocol, will be completed which outlines specific criteria for monitoring. This plan may include the number of planned site visits, criteria for focused visits, additional visits or remote monitoring, a plan for medical record review and a follow up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g., sample of all participants within a site; key data or all data), the schedule of visits, how they are reported and a time frame to resolve any issues found.

Site monitoring visits may be performed in-person or remotely by a trained site monitor during the study period to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. Interim visits will take place depending on grant budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. It is anticipated that the study monitoring visits for this protocol will consist of a site initiation visit (prior to patient enrollment), interim visit, and a close out visit. The site initiation may take place as group training made up of site investigators and research assistants.

7.4.2 Remote Monitoring

Remote monitoring involves detailed review of the data entered by the Clinical Center and consultations with the Clinical Center investigator and/or research coordinator to review safety and data quality. This may require uploading copies of medical records, patient study files, regulatory documentation, or other source documents for the monitor to review. Alternatively, other methods, such as remotely viewing source documentation, may be utilized. This helps assure protocol compliance and accurate data collection. The Data Coordinating Center may conduct more remote

monitoring activities early in the trial to assure protocol compliance and identify any training issues that may exist. Remote monitoring documents will be retained in accordance with federal requirements. Safety of participants will be monitored and ensured in accordance with the Data and Safety Monitoring Board (DSMB) plan.

7.4.3 Pharmacy Monitoring

Each Clinical Center pharmacy must maintain adequate records of all dispensed study drug. Since the study will use a central pharmacy to distribute study medication to each site's local pharmacy, adequate records at that location must be maintained as well. Monitoring will take place at both the central pharmacy and the clinical center pharmacies to ensure adequate storage and drug accountability records, as well as adherence to appropriate dispensing and destruction procedures.

7.5 Record Access

The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the Data Coordinating Center, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives (when applicable) of the Food and Drug Administration (FDA), NIH, other Federal funders or study sponsors, and the Institutional Review Board (IRB) for each study site.

8 Protection of Human Participants

8.1 Institutional Review Board (IRB) Approval

A Central IRB (CIRB) will be used for this study. The University of Utah IRB will serve as the IRB of record. Study sites will rely on the University of Utah IRB to act as central IRB. The Data Coordinating Center and each clinical center must obtain IRB approval prior to participating in the study.

The Data Coordinating Center will track IRB approval status at all participating centers and will not permit participant enrollment without documentation of initial CIRB approval and local review sign-off. The Data Coordinating Center will also track the maintenance of that approval throughout subsequent years of the project.

8.2 Informed Consent

Parental Permission

Participants who are eligible for this study are younger than 18 years, and written permission from a parent or legal guardian will be required for participation. After determining that a subject is eligible, the site investigator or designee will approach the parent or legal guardian to offer participation for their child in the study. The parent or legal guardian will be informed about the objectives of the study and the potential risks and benefits of participation. Eligible subjects will only be enrolled if their parent or guardian provides permission for their child to participate.

8.3 Potential Risks

The potential risk of receiving placebo is that clinical outcomes may not be equivalent to amoxicillin therapy. Specifically, the proportion of children with adequate clinical response or symptom resolution may be lower in children who receive placebo. Adequate clinical response, as defined above, is lack of a visit to a clinic, acute care setting, ED or hospitalization due to persistent or worsening pneumonia, as defined by receipt of a new antibiotic for pneumonia or treatment for pneumonia complications. Included in this would be lack of need for additional antibiotic therapy, additional contacts with the healthcare system, or surgical procedures for worsening pneumonia. Symptom resolution is defined as absence of fever, tachypnea (respiratory rate <50 breaths/minute in children aged <24 months and >40 breaths/minute in those aged 24-71 months), work of breathing (i.e., retractions, grunting or flaring) and moderate to severe cough (i.e., frequent coughing fits more than 3-4 times per hour that is interfering with sleep).

The magnitude of this risk is not well established, although a randomized trial of amoxicillin vs placebo in 1126 young children with fast-breathing pneumonia in Malawi found that at Day 4, 93% of children who received placebo and 97% of those receiving amoxicillin did not experience treatment failure with no differences in the groups by Day 14. There were no deaths in either study group in this study. Additional data comes from a trial that used PCT to guide antibiotic decisions in children. In one trial of 319 children hospitalized with CAP, 21 children with mild CAP and 3 with severe CAP who had PCT<0.25 ng/mL were never treated with antibiotics – none experienced respiratory problems, and all were considered cured during follow-up.[42] These data suggest that the degree of risk is small, however there are no similar trials in the U.S. We are limiting our study population to a very low risk group of children based on:

(a) inclusion/exclusion criteria that exclude children with any disease severity greater than mild,

(b) the use of very low PCT levels to include patients, which provides an objective measure of a very low risk of serious bacterial infection using previously studied outcomes using PCT, and

(c) concordance with evidence supporting national CAP guidelines that most infections in the study age group are viral and routine antibiotics are not recommended in children well enough to be managed as outpatients.

The degree of risk will, nevertheless, be fully evaluated during this pilot trial, and the subsequent large-scale trial.

In addition, amoxicillin is known to have several potential adverse effects. Common side effects include rash, diarrhea, nauseas, vomiting and mucocutaneous candidiasis. Rare side effects (<1% prevalence) include:

- Cardiovascular: hypersensitivity angiitis (rash)
- Central nervous system: agitation, anxiety, behavioral changes, confusion, dizziness, headache, hyperactivity (reversible), insomnia, seizure
- Dermatologic: acute generalized exanthematous pustulosis (blistering skin reaction), erythema multiforme (rash-like skin reaction), exfoliative dermatitis (peeling skin reaction), Stevens-Johnson syndrome (blistering and peeling skin reaction), toxic epidermal necrolysis (severe blistering and peeling skin reaction), urticarial (hives)
- Gastrointestinal: dental discoloration (brown, yellow, or gray; rare), hemorrhagic colitis (bloody diarrhea), melanoglossia (black tongue), pseudomembranous colitis (swelling/irritation of the colon)
- Genitourinary: crystalluria (cloudy urine)
- Hematologic & oncologic: agranulocytosis (low white blood cell count), anemia (low red blood cell count), eosinophilia (high eosinophils, a type of white blood cell), hemolytic anemia (low red blood cell count), leukopenia (low white blood cell count), thrombocytopenia (low platelet count), thrombocytopenic purpura (clotting disorder that causes bleeding)
- Hepatic: cholestatic hepatitis (blocked bile duct), cholestatic jaundice (yellowing of the skin), hepatitis-acute cytolytic (liver inflammation), increased hepatic enzymes
- Hypersensitivity: anaphylaxis (severe allergic reaction)
- Immunologic: serum sickness-like reaction (a type of allergic reaction)

Amoxicillin is an approved drug with a long prescribing history and is considered first-line therapy in children with CAP for whom antibiotics are warranted. The risk of these effects is no greater in this trial than the current practice of providing amoxicillin to most children with CAP and may be less in this trial due to vigilant monitoring of study participants.

8.4 Protections Against Potential Risks

As noted above, our study is limited to a low-risk population of children with CAP for whom antibiotics are not routinely recommended by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America and whose PCT levels suggest a low risk of bacterial infection. In addition to our careful choice of inclusion and exclusion criteria, several safeguards will be implemented during the trial to protect against potential risks.

1. First, documentation will be provided to participants with detailed instructions on reasons to return to medical care.

2. Second, contact with participants will be attempted on day 7 (±2 days) and on day 21 (±2 days) after the study ED visit to collect data regarding symptoms, side effects, adverse events and return to medical care, in addition to assessing adherence to study procedures (i.e., medication adherence and daily symptom diary completion).

3. Third, a video telehealth visit will be initiated, when possible, on or around day 7 to assess the primary outcome. If use of video technology is not available or feasible, a telephone call will occur for this follow-up encounter. This will include an assessment of, clinical course, side effects, adverse effects and other risk concerns.

4. Fourth, a safety monitoring plan and data safety monitoring board will be established for this trial to assess and address risk concerns.

The only personnel who will have access to identifiable private information will be the research personnel (a site principal investigator and a research coordinator) at the study site where the participant was enrolled and the study's principal investigator. Data collection will be electronic; using password protected computing devices that wirelessly transmit data to a secure network drive. These devices will be kept in locked cabinets, in locked suites when not in use. Each participant will be assigned a unique patient identifier for purposes of analysis, and this will be used to link any paper records to an electronic research record within the analytic database. Study site personnel will be responsible for entering the data through the electronic interface into a secure, web-based data management system hosted at the PECARN DCC; thus, the analytic database will be maintained in a secure encrypted HIPAA compliant computing system. Most research results will be presented in aggregate fashion. HIPAA identifiers will be stripped from findings that reference individual participants. While the majority of the data will be stored electronically, there is a chance that we will need to retain some information on paper records. All paper research records with patient identifiers, if any, will be kept at the site from which they were obtained in locked cabinets, in a locked office, within a locked office suite. Patient identifiers will not be part of the analytic database. Any paper participant records will be destroyed upon completion of analysis. Due to these precautions the likelihood of a loss of privacy or confidentially is very minimal.

8.5 Potential Benefits

Potential benefits to the individual child include avoidance of potentially unnecessary antibiotics, a lower risk of an adverse event or effect associated with antibiotic therapy (e.g., diarrhea, rash, allergy mislabeling, C. difficile infection), and a lower risk of colonization with antibiotic resistant bacteria. Potential population-level societal benefits if the future clinical trial is successful include a lower prevalence of colonization with pathogenic antibiotic-resistant bacteria in children with CAP. This lower colonization rate offers a lower colonization risk among the larger population given the transmissibility of pathogenic bacteria across all persons regardless of whether or not they are treated with antibiotics.

8.6 Risk Benefit Assessment

Due to the prospect of direct benefit to patients, the risk-benefit ratio seems favorable to patients, parents and providers.

9 Data and Safety Monitoring Plan

9.1 Data Safety Monitoring Board (DSMB)

The study will have a Data Safety Monitoring Board (DSMB). The DSMB will have a charter, will approve the protocol prior to implementation, and will review interim analyses as applicable. The purpose of the DSMB is to advise the sponsors and Principal Investigator(s) regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the study protocol, assessments of data quality, performance of individual Clinical Center, review of serious adverse events and other subject safety issues, and review of formal interim statistical analyses of treatment efficacy.

Participant safety data will be reviewed on a regular basis. Study halting rules will be developed, and further study enrollment will be halted for DSMB review and recommendation if any halting events are reported.

9.2 Safety Monitoring

This protocol has extensive safety monitoring in place. The study site investigators will be responsible for close safety monitoring of all children participating in the study, and for alerting the protocol team if unexpected concerns arise. All children will undergo a targeted physical exam at screening and enrollment to ensure that children are medically stable and do not demonstrate any exclusion criteria. For the first 6 days of the study, participants will complete a daily online survey to monitor their health and ensure study adherence. During days 7 and 21, study staff will perform follow-up via telehealth, or telephone. Every effort will be made to trace all children in the study for the final outcome assessment. The day 7 primary outcome will be a telehealth visit, whenever possible, allowing the site study clinician to visualize the child during the telehealth examination. Participants' caregivers will be been instructed to contact their primary care provider, return to the ED or call 911 should symptoms worsen. Any SAE's will be collected by site study staff. (See section, 9.3 on the following page). As needed, children in the study may be evaluated at interim visits and/or referred for additional care. In the case of a life-threatening event, they will be instructed to seek immediate emergency care. These "safety net" procedures are intended to identify all instances of potential treatment failure and clinical relapse so that those children failing treatment can be provided appropriate antibiotics and clinical care.

9.3 Adverse Event Reporting

The site investigator is responsible for evaluating all adverse events at their Clinical Center and ensuring that they are properly reported. Specified adverse events that occur during this study will be recorded. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment will be documented. The safety profile of amoxicillin is well established, and this trial is not powered to detect new, unknown safety effects, therefore, there will be no additional AE collection outside of the daily symptom diary during this study. All serious adverse events (SAE) will be collected and recorded. The investigative team anticipates AEs, both severe and non-severe, to occur among enrolled children at a similar rate as untoward medical events occur in comparable pediatric populations outside of a research setting.

AEs that the study team expects may occur during the research include, but are not limited to: adverse reactions to amoxicillin (e.g., skin rash), progression of pneumonia-related symptoms (e.g., work of breathing), and onset of other common and uncommon childhood illnesses (e.g., diarrhea). Research staff will obtain information about side effects from scheduled follow-up contacts.

9.3.1 Definition of Adverse Event and Serious Adverse Event

Adverse Event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom.

Serious Adverse Event (SAE): A serious adverse event (SAE) for this population is an adverse event that:

- results in death; or
- is life-threatening (the patient was, in the view of the site investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect; or
- any other event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

In addition to the SAEs listed above, the following serious adverse events (SAE) will be collected as part of this protocol:

- death that is not trauma or accident-related,
- anaphylaxis,
- laryngospasm or bronchospasm within 1 day of treatment initiation,
- Stevens-Johnson Syndrome,
- severe erythema multiforme, or

- toxic epidermal necrolysis.

All SAEs will be assessed for severity and causal relationship by a physician member of the study team, recorded on the appropriate SAE report form, follow through to resolution by study physician and reviewed by safety monitor and IRB.

A data safety monitoring board (DSMB) will be convened for this study. Participant safety data will be reviewed on a regular basis. Study halting rules will be developed, and further study enrollment will be halted for DSMB review and recommendation if any halting events are reported.

9.3.2 Classification of an Adverse Event (Relatedness, Severity, and Expectedness

Relatedness: The suspected relationship between study interventions and any adverse event will be determined by the site investigator using the criteria below. *Relatedness must be assessed by an investigator and may **not** be assessed by a research coordinator.*

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

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 participant's clinical state, therapeutic interventions, or concomitant drugs administered to the participant.

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 participant's clinical state, therapeutic interventions, or concomitant drugs administered to the participant.

Severity: The severity, which is a measure of intensity, of clinical adverse events and laboratory abnormalities will be recorded by the site investigator and categorized. The following guidelines will be used to describe severity.

Mild: The event requires minimal or no treatment and does not interfere with the participant's daily activities.

Moderate: The event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: The event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Expectedness of the Event: All adverse events, including serious adverse events, will be evaluated as to whether their occurrence was expected or unexpected. An AE 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.

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 participant's clinical state immediately prior to the event.

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.

Treatment or Action Taken: For each adverse event, the site investigator will record whether an intervention was required:

- Medical or surgical procedure
- Concomitant medication: started, changed, or discontinued
- Other, specify
- No action taken

Outcome of Event: Finally, the site investigator will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with permanent sequelae
- Symptoms persist

9.3.3 Time Period for Adverse Events

For purposes of this study, all SAEs will be recorded from randomization through 21 days after randomization. Specifically, events that occur following parental permission to participate in the study, but prior to actual randomization, are *not* adverse events. These should be recorded as baseline conditions.

9.3.4 Data Collection Procedures for Adverse Events

After patient randomization, all serious adverse events will be assessed for relatedness, severity, and expectedness, as well as their duration and any treatment prescribed. Any medical condition present at the time of randomization, recorded in the patient's baseline history at study entry, which remains

unchanged or improves (unless the clinician feels it is clinically relevant), will not be recorded as an adverse event at subsequent evaluations. However, worsening of a medical condition that was present at the time of randomization will be considered a new adverse event and reported if on the list of solicited adverse events.

Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the Data Coordinating Center as this requires specific training.

9.3.5 Unanticipated Problems (UP)

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related or possibly related to participation in the study, and suggest that the research places participants at a greater risk of harm than was previously known or recognized. The site investigator will report unanticipated problems to the DCC within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report these unanticipated problems to the NHLBI Program Official or Project Officer in an expedited manner (as close to 24 hours as possible). In accordance with local IRB requirements, the site investigator may be required to report such unanticipated problems to the IRB in addition to notifying the Data Coordinating Center. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and NHLBI staff cannot be reached expeditiously, the DCC will notify the study principal investigator (Dr. Florin) and all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NHLBI staff after discussion with the DSMB.

9.3.6 Monitoring Serious Adverse Events

A qualified physician will be designated to fulfill the function of the medical monitor for this study. Site investigators and/or research coordinators will report serious adverse events to the DCC within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the DCC within 3 working days of the event, and the medical monitor will assess all serious adverse events reported from site investigators.

For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The medical monitor will sign off on each SAE report after review. All SAE reports will be retained at the DCC, and all SAE reports will be available for review by DSMB members and NHLBI staff. The SAE reporting process may be incorporated into the Electronic Data Capture (EDC) System in use for the study.

In the unlikely event that the medical monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, NHLBI staff and the DSMB chairperson will be immediately consulted. If these individuals concur with the judgment of the medical monitor, or

if the NHLBI staff and the DSMB chairperson cannot be reached expeditiously, the DCC will notify the study principal investigator (Dr.Florin) and all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NHLBI staff after discussion with the DSMB.

In accordance with local IRB requirements, the site investigator may be required to report such events to the IRB in addition to notifying the Data Coordinating Center.

After notification of the NHLBI Program Official or Project Officer, and the DSMB chairperson, of *serious, unexpected, and study-related* adverse events or unanticipated problems (UP), decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to the study investigator (Dr. Florin) and all clinical investigators, who will be instructed to report this to their local IRB.

The DSMB will review all adverse events (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The Data Coordinating Center will prepare a Summary Report of Adverse Events for the DSMB meetings, classified with the MedDRA coding system.

9.3.7 Follow-up of Serious, Unexpected and Related Adverse Events

All serious, unexpected and related adverse events, that are unresolved at the time of the patient's termination from the study or discharge from the hospital, will be followed by the Clinical Center investigators until the events are resolved, participant is lost to follow-up, the adverse event is otherwise explained or has stabilized, or 30 days have passed from the time of last study dose.

10 Study Training

10.1 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics and Good Clinical Practice. The training will also provide in depth explanations regarding study procedures, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring, and the informed consent process. A manual of operations will be provided to each investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically. The Data Coordinating Center, in collaboration with the study investigator (Dr. Florin), will be the main contact for study questions.

11 Regulatory Considerations

11.1 Food and Drug Administration

The Food and Drug Administration has deemed that an investigational device exemption (IDE) or investigational new drug (IND) exemption is not required for this pilot trial, as procalcitonin is being used in an FDA-approved manner and amoxicillin is the current first-line standard of care for pediatric pneumonia. The FDA deemed this study a non-significant risk (NSR) study, thus an IDE application is not required.

11.2 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth and date of admission. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de–identified, and will exclude these specific dates.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

For purposes of the DCC handling potential protected health information (PHI) and producing the de–identified research data sets that will be used for analyses, all study sites have been offered a Business Associate Agreement with the University of Utah. Copies of executed Business Associate Agreements are maintained at the DCC.

11.3 Inclusion of Women and Minorities

There will be no exclusion of patients based on gender, race, or ethnicity.

11.4 ClinicalTrials.gov Requirements

This trial will be registered at ClinicalTrials.gov in accordance with Federal regulations.

11.5 Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all

[redacted]