Improving CarE for Community Acquired Pneumonia (ICE-CAP)

Phase 1: Antibiotic Decision Support
Phase 2: Prognostic Decision Support

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Protocol Summary:

Children with pneumonia presenting to the ED at Monroe Carell Jr. Children's Hospital at Vanderbilt or Children's Hospital Pittsburgh at the University of Pittsburgh will be potentially eligible for study. During intervention periods, providers caring for enrolled children will be presented with a detailed decision support strategy that emphasizes management in accordance with national guideline recommendations. The anticipated study duration is 18 months for Phase 1 (P1) and 24 months for Phase 2 (P2). As this study does not include direct contact with enrolled subjects, there is no anticipated follow up.

Protocol Versions

Version	Date of Approval	Major Changes from Prior Version
1.0	Jul 15, 2018	-
2.0	Feb 8, 2019	Update study site; minor edits for clarity

1.0 Background

Pneumonia is the most common serious infection in childhood. In the United States (US), pneumonia accounts for 1-4% of all emergency department (ED) visits in children (3-28 per 1,000 US children per year)[1] and ranks among the top 3 reasons for pediatric hospitalization with >100,000 hospitalizations per year (15-22 per 100,000 US children per year)[2-5]. Pneumonia also accounts for more days of antibiotic use in US children's hospitals than any other condition.[6]

Safely reducing inappropriate antibiotic use is critical to slow the progression of antimicrobial resistance, and childhood pneumonia is a key area where substantial improvements can be made. In the 2011 Pediatric Infectious Diseases Society/Infectious Diseases Society of America (PIDS/IDSA) pneumonia guideline, appropriate use of antibiotics was an important area of emphasis.[7] For presumed bacterial pneumonia, recommendations emphasize the use of a single, narrow-spectrum antibiotic (i.e. amoxicillin or ampicillin). In children <6 years of age treated in the outpatient setting, the guideline recommended considering withholding antibiotics, recognizing that pneumonia in this population is most often caused by viruses. Both of these recommendations were graded as strong and supported by high-quality evidence.[8-10] Nonetheless, in a large database study we conducted just prior to release of the 2011 guideline, use of broad-spectrum antibiotics was very common among children hospitalized with pneumonia, with substantial differences in antibiotic selection patterns among the various hospitals.[11] In that study, use of narrow-spectrum ampicillin was rare (<5%). High rates of broad-spectrum antibiotic use were also noted in a study of children with pneumonia treated and released from US EDs, with <30% of children receiving narrow-spectrum therapy.[12]

Emergency care for childhood pneumonia, including hospitalization rates, varies widely across the nation. A study examining hospital admission rates at 35 US children's hospitals from 2009-12 showed marked differences in severity-adjusted pneumonia hospital admission rates (median 31%; range 19-69%)[13]. Extending these findings, Florin et al. detected great hospital-level variation in the use of diagnostic tests for children presenting to the ED with pneumonia.[14] They reported that high test-utilizing hospitals had a

nearly 2-fold greater odds of hospitalization compared with low test-utilizing hospitals.[14] Using the same database as Florin et al., we previously reported similar institutional variation in diagnostic test utilization in children hospitalized with pneumonia. The range across hospitals for even the most common diagnostic tests was very wide with some hospitals performing specific tests in <30% of children and others performing those same tests in >75% of children. We also demonstrated an association between high test-utilizing hospitals and increased average hospital length of stay.[11]

Provider preferences and inaccurate risk perceptions contribute to differences in hospitalization rates. Within the Intermountain Healthcare System in Utah, Dean et al. exposed large differences in admission rates (range 38-79%) among 18 individual ED providers providing care for >2,000 adults with pneumonia.[15] Differences were not explained by patient characteristics or illness severity and higher rates of hospitalization did not reduce hospital readmissions or mortality. In another multicenter study of 472 adults with pneumonia at <4% risk of 30-day mortality estimated using objective severity scores, providers overestimated the risk of mortality in 5% of outpatients (range across institutions 0-12%) and 41% of inpatients (range across institutions 36-48%).[16] These studies suggest that risk perceptions are often inaccurate, and potentially lead to unnecessary or prolonged hospitalizations and intensive therapies. Similar studies have not been performed in children because no valid prognostic tools exist to reliably predict pediatric pneumonia severity.

2.0 Rationale and Study Phases

Extensive variation in both antibiotic use and hospitalization decisions is evident among clinicians caring for children with pneumonia, with high potential for avoidable harm. In our prior study, one-third of children were hospitalized for less than 48 hours and nearly 10% less than 24 hours. Some of these hospitalizations were likely unnecessary. Most of these children also received broad-spectrum antibiotic therapy instead of the narrow-spectrum agents recommended by the national guideline. Conversely, one-third of children admitted to intensive care were initially managed on a general ward—earlier transfer for more intensive therapy may have improved outcomes for some of these children. New strategies to inform decision making are needed, and the combination of risk stratification using objective tools and clinical decision support in the ED setting are innovative and promising approaches to achieve this goal.

Phase 1: *To test the hypothesis that electronic antibiotic decision support increases guideline-concordant antibiotic use compared with usual care in the ED.*

The primary outcome is the proportion of children exclusively receiving guideline-concordant 1st line antibiotic therapy during the first 24 hours of care (Table 1). Secondary outcomes include exclusive use of concordant antibiotic therapy for the entire episode, any use of concordant antibiotic therapy during the first 24 hours of care and for the entire episode, and ED revisits and hospitalizations within 72 hours and 7 days of the index discharge.

Phase 2: *To test the hypothesis that the delivery of severity information generated by our prognostic tool leads to more appropriate site of care disposition compared to usual care.*

The primary outcome is appropriate site of care disposition (Table 2). Surveillance for subsequent ED visits and hospitalizations to our institutions as well as escalation to higher levels of care will be captured within the EHR data extracted by the decision support application. Secondary efficacy and safety outcomes include the overall site of care disposition (ED discharge, ward, ICU), and ED revisits and hospitalizations within 72 hours and 7 days of the index discharge.

In these studies, conducted at two experienced academic centers, we will implement and evaluate an EHR-based clinical decision support application to promote antibiotic use in concordance with the 2011 PIDS/IDSA guideline in a pragmatic, cluster-randomized crossover trial (P1). Next, we will incorporate risk stratification using a previously developed prognostic tool into a second EHR-based decision support application, testing its impact on site of care disposition compared to usual care in a pragmatic randomized trial (P2). In both studies, all subjects will receive standard of care. Decisions regarding management, including antibiotic selection and site of care, will be at the discretion of the treating provider and will not be restricted or altered in any way. Thus, this study poses no greater than minimal risks to participants. Due to the nature of the research, we will seek a waiver of informed consent as has been done in similar pragmatic studies at our institutions.[17-21]

3.0 Previous Studies

From 2010 to 2012, our research team at Vanderbilt collaborated with two other sites to conduct the Centers for Disease Control and Prevention (CDC) funded Etiology of Pneumonia in the Community (EPIC) Study, a prospective, population-based surveillance study of community-acquired pneumonia hospitalizations in children and adults.[2,22] We enrolled >2600 children, making EPIC the largest prospective study of pneumonia hospitalizations ever conducted in US children. Over 70% of children enrolled in EPIC had a viral pathogen detected whereas bacterial pathogens were identified in only 15% of children. Nevertheless, nearly 90% of children received antibiotics. In most cases, antibiotic treatment was discordant with the national guideline and broad-spectrum antibiotic use was common.[23] We have also evaluated the impact of the 2011 PIDS/IDSA guideline on antibiotic selection for children with pneumonia enrolled in EPIC, demonstrating only a modest reduction in the use of broad-spectrum antibiotics following publication of the guideline. Guideline-concordant use of narrow-spectrum aminopenicillins remained <20% by the end of the study, indicating a clear opportunity for further improvement.[23]

We also used data from the EPIC study to develop a prognostic tool for assessing pneumonia disease severity in children. Prognostic tools use statistical modeling to combine inputs, such as demographics, clinical variables, and results of diagnostic tests, to produce reliable and unbiased risk estimates for a specified outcome. For our prognostic tool, we focused on acute in-hospital outcomes, organized into an ordinal severity scale consisting of 3 levels: severe, moderate, and mild. Our modeling strategy, ordinal logistic regression, offers increased statistical power and precision compared to binary/multinomial logistic regression, and the resulting output allows one to simultaneously estimate probabilities for each level on the outcome scale or in combination (e.g., probability of moderate to severe and probability of severe outcomes). Predictor variables for our prognostic tool were selected a priori and also informed by clinical expertise and literature review. We focused on objectively defined variables with strong hypothesized associations with the outcome that could be rapidly ascertained at presentation in the

clinical setting. This process resulted in a pool of 20 predictors. We also created a separate, more parsimonious model restricted to 9 predictors commonly available within electronic health records (EHR).

Both models accurately identified risk for moderate or severe pneumonia, indicating strong potential to improve risk stratification. Model discrimination, which measures the degree of concordance between observed and predicted outcomes, was excellent with a c-index ranging from 0.78-0.81. Differences in model fit and quality were considered negligible, and results from the internal bootstrap validation were comparable to the primary models. In the full model, PaO_2:FiO_2 ratio (PF ratio, estimated from the SaO_2FiO_2 ratio),[24] age, heart and respiratory rates, altered mental status, temperature, chest indrawing, infiltrate pattern, and systolic blood pressure were the strongest predictors, contributing 96% of the explainable outcome variation. The EHR model retained most of these predictors (omitting altered mental status, chest indrawing, and infiltrate pattern). Nonetheless, predictive performance of the EHR model equaled that of the full model. For the full model, the median predicted risk for moderate or severe pneumonia was 18% (IQR 9-32%) and for severe pneumonia 5% (3-11%).

Prognostic tools used in adults with pneumonia improve risk stratification and clinical decision making, but these tools are underutilized, indicating a need for improved implementation strategies. A number of prognostic tools have been developed to assist providers caring for adults with pneumonia,[25-31] and most have undergone external validation.[26,32-42] The two best studied tools are the PSI and CURB-65,[30,31] which were designed to predict 30-day mortality. Newer tools (e.g., SMART-COP and SCAP)[26,27] have also been developed to predict acute in-hospital outcomes, including mechanical ventilation and shock. These tools have been used to safely increase the number of low-risk patients treated in the outpatient setting and improve guideline-concordant antibiotic management.[43-47] As a result, their use in the management of adults with pneumonia in outpatient and inpatient settings is strongly recommended.[25] Nonetheless, several studies indicate these tools are often applied incorrectly or not used at all.[15,48-50] Major barriers to clinical use include tool complexity (inability to recall parameters and inaccurate scoring or interpretation) and disruptions to provider workflow (suspension of patient care to calculate risk by hand or use of an electronic application outside of routine care).[51] Failure to validate new tools and assess their impact in new populations are also major impediments to clinical use. Each of these barriers must be carefully addressed to ensure effective implementation of new prognostic tools.

Effective decision support facilitates the adoption of new evidence into practice and helps standardize management to improve care and optimize outcomes. Clinical decision support is intended to directly impact provider decision-making to improve the quality, safety, effectiveness, and efficiency of care by steering behavior toward evidence-based care and away from unnecessary or unproven practices. The availability of comprehensive EHRs has allowed for the development of increasingly complex decision support applications, including risk stratification using real-time electronic capture of patient demographics, physiologic data, and diagnostic testing results.[17,52] In a randomized trial conducted in primary care settings comparing decision support integrated with 2 prognostic tools vs. usual care without decision support, McGinn and colleagues showed a 25% reduction in antibiotic use overall and a 50% reduction in broad-spectrum antibiotic use in adults with possible bacterial pharyngitis or pneumonia when using the decision support application.[52] The application was triggered on chief complaint and incorporated a risk calculator, which used automated and user-supplied inputs to identify risk for bacterial

pharyngitis or pneumonia, along with evidence-based treatment guidelines and order sets. In another study of adults with pneumonia presenting for emergency care within the Intermountain Healthcare System, Dean et al. showed increased guideline concordant care and reduced mortality in four different EDs using clinical decision support that included CURB-65 severity assessment and tailored recommendations for site of care, diagnostic testing, and antibiotic use compared to 3 usual care EDs.[17] *These successful examples highlight the potential for EHR-based decision support to improve care by providing useful, evidence-based guidance at the point of care as management decisions are being made.*

Both Vanderbilt and the University of Pittsburgh have extensive experience leveraging EHR data for decision support and research purposes. As an example of such capabilities, in the EPIC study, a decision support tool used in adults with pneumonia was adapted for use as a screening tool.[17] The tool used natural language processing to identify concepts suggestive of pneumonia in radiology "wet" reads in real-time and required a provider-confirmation of a pneumonia diagnosis. For EPIC, we adapted this tool to deliver electronic alerts to our enrollment teams. Importantly, a similar tool was used to identify pneumonia in the study by Dean et al. described in the preceding paragraph. A second example highly relevant to this proposal was developed by our co-investigator, Dr. Weitkamp, and involves antibiotic decision support to reduce inappropriate use of antibiotics in critically ill neonates. Importantly, the algorithm was followed in >70% of infants and led to significant reductions in antibiotic exposure.[53] Additionally, our co-investigators, Drs. Weinger and Slagle, experts in human factors engineering and user-interface design of health information technology, possess extensive experience designing and evaluating decision support applications that maximize utility and minimize potential for human error.[54-63] *These examples highlight that the investigators at Vanderbilt and the University of Pittsburgh possess the necessary skills, expertise, and institutional resources to develop and implement effective decision support applications.*

4.0 Study Design and Randomization

4.1 Study Design and Randomization (P1, EHR-based antibiotic decision support)

Effectiveness of the EHR-based antibiotic decision support application for promoting guideline-concordant antibiotic prescribing in children presenting for emergency care will be evaluated in a pragmatic, cluster randomized crossover study conducted over a period of 18 months that includes two respiratory seasons. Our institutions possess demonstrated experience in the execution of these pragmatic designs. [17-21] Crossover will occur each month in a randomly determined sequence within each hospital. To ensure balanced representation of each arm in periods of both low and high pneumonia prevalence, randomization will occur in 3 permuted blocks (size=6). The cluster-randomized crossover design also improves efficiency and reduces potential problems related to cluster imbalance when using a small number of clusters.[67] The antibiotic decision support application will be provided to those randomized to the intervention arm, whereas the control arm will receive usual care. Due to the nature of the intervention, blinding of treating providers will not be possible. Importantly, since this is a trial focused on provider behavior, all children will receive standard of care management. All treatment decisions will be made by the clinical providers and will not be restricted or altered in any way.

4.2 Study Design and Randomization (P2, EHR-based risk stratification)

We will conduct a randomized controlled trial comparing our prognostic tool (intervention arm) to usual care (control arm) over a period of 24 months. Randomization will occur at the patient level. Allocation to intervention or control will be based on medical record number (even vs. odd) or similar strategy and will be assigned automatically once a provider confirms the diagnosis of pneumonia. Importantly, all standard of care treatment options will be available and decision-making will not be restricted in any way in either group. A similar randomized trial that predicts readmission risk among all hospitalized adults using EHR inputs is currently ongoing at Vanderbilt. In that study, every adult admitted to Vanderbilt University Hospital is enrolled (under waiver of consent). Readmission risk is calculated automatically for all patients, but only displayed for a random half to determine if providing this additional information improves outcomes compared to usual care.

5.0 Inclusion/Exclusion Criteria (Phases 1 and 2)

Inclusion Criteria

1. Six months to <18 years of age
2. Radiographic evidence of pneumonia in ED
3. Provider-confirmed diagnosis of pneumonia

Exclusion Criteria (Provider query and/or automated data abstraction)

1. Children with tracheostomy, cystic fibrosis, immunosuppression
2. Inter-hospital transfers
3. Hospitalization within preceding 7 days
4. Previously enrolled within preceding 28 days
5. Provider preference for any reason

6.0 Screening and Enrollment

6.1 Screening and Enrollment (P1)

Children with pneumonia presenting to the ED at Monroe Carell Jr. Children's Hospital at Vanderbilt or Children's Hospital of Pittsburgh will be potentially eligible for study. The pneumonia radiology alert tool will be used to identify potentially eligible children in a systematic and efficient manner using natural language processing (NLP). Those who screen positive according to the radiology NLP algorithm will trigger a Best Practice Alert (BPA) or similar within the EHR which queries the provider to confirm the diagnosis of pneumonia and assesses for study inclusion/exclusion criteria. In instances where a chest radiograph is not captured via the NLP algorithm (e.g. a radiograph obtained at an outside facility), an alternative pathway is available to trigger the subsequent BPAs leading to enrollment. Due to the nature of the research, we will seek a waiver of informed consent as has been done in similar pragmatic studies at our institutions.[17-21] Thus, at this point, eligible children will be considered enrolled. During intervention periods, providers caring for enrolled children will be presented with a detailed decision support strategy that emphasizes management in accordance with national guideline recommendations. During control periods, no additional decision support will be provided.

6.2 Screening and Enrollment (P2)

Screening and enrollment procedures for P2 will be identical to P1. For children randomized to the intervention arm, providers will be presented with prognostic information regarding risk for severe disease outcomes via an EHR-based decision support strategy that emphasizes management in accordance with national guideline recommendations. During control periods, no additional decision support will be provided.

7.0 Study Procedures

7.1 EHR-based Antibiotic Decision Support (P1)

For enrolled subjects assigned to the decision support arm, providers will receive antibiotic recommendations in accordance with the 2011 PIDS/IDSA guideline, tailored to site of care and illness severity. For instance, in young children with mild illness being discharged from the ED, the support tool will offer guidance regarding when a strategy of watchful waiting might be favored over empiric amoxicillin (e.g., fully immunized toddler with upper respiratory tract symptoms). Similarly, in those being admitted to a general ward, the tool will advise consideration of oral therapy in children with good oral intake, or when to consider adjunctive therapy with a macrolide or anti-staphylococcal antibiotic. *Importantly, the tool will offer treatment recommendations only and will not proscribe a specific treatment plan.* If a provider chooses to prescribe therapy not in accordance with the national guideline, the tool will query providers regarding reasons for discrepant prescribing for later analysis.

7.2 Outcomes (P1)

Table 1. Concordant Use Definitions for 1st Line Antibiotics[1]

Disposition	<6 Years of Age	≥6 Years of Age
Home care	No antibiotics or amoxicillin	Amoxicillin
Inpatient, ward	Ampicillin/amoxicillin	Ampicillin/amoxicillin
Inpatient, ICU or complicated disease[2]	Ampicillin or ceftriaxone +/- anti-staphylococcal +/- macrolide	Ampicillin or ceftriaxone +/- anti-staphylococcal +/- macrolide

ICU, intensive care unit [1]Unless specific pathogen identified or known drug allergy [2]eg, empyema

The primary outcome is the proportion of children exclusively receiving guideline-concordant 1st line antibiotic therapy during the first 24 hours of care (Table 1). For patients discharged from the ED, this will include antibiotics received in the ED as well as antibiotic prescriptions provided at discharge. For hospitalized patients, this will include therapy received during the first 24 hours of care beginning with ED triage. A patient following treatment according to table 1 will be considered as concordant, whereas deviations from these treatments will be considered discordant.

Secondary outcomes include exclusive use of concordant antibiotic therapy for the entire episode, any use of concordant antibiotic therapy during the first 24 hours of care and for the entire episode, and ED revisits and hospitalizations within 72 hours and 7 days of the index discharge. Index visit is defined as the enrollment ED visit or hospitalization through discharge.

Exploratory outcomes include time to first antibiotic, lack of antibiotics during the first 24 hours of care and for the entire episode, and changes in antibiotics after 72 hours, and death, and for hospitalized children, delayed ICU transfer, defined as >24 hours following hospitalization.

7.3 Data Collection/Management (P1)

Data collection will be triggered by the pneumonia BPA and will be acquired directly from the EHR and stored securely for later analysis. Prior to study initiation, support analysts will conduct detailed

requirement explorations to identify necessary data elements and associated data flows, validate accuracy, and evaluate for missing data. Data to be collected includes decision support usage statistics, visit details (e.g., admission and discharge date and time, site of care, ED revisits or hospital readmissions), patient demographics (e.g., age, sex, race, insurance), medication orders and prescriptions (dose, frequency, route, and duration), laboratory testing and results, radiologic studies, and data elements from the decision support applications.

7.4 EHR-based Prognostic Decision Support (P2)

For enrolled subjects assigned to the decision support arm, providers will receive prognostic information derived using our previously validated and best performing model. The decision support application will automatically calculate predicted risk for moderate (intensive care) and severe (respiratory failure or shock) outcomes using the parameters derived from the prognostic tool's regression equation. Outcome probabilities will be integrated into the decision support application and displayed within the EHR. The support application will also report any objective criteria necessitating hospitalization (e.g., hypoxia) or potential intensive care (e.g., hypotension, SpO_2<92% despite FiO_2≥ 50%) to further inform site of care decisions. The application will also query providers regarding factors influencing site of care decisions to inform analyses describing discrepancies between risk assessments and decision-making (e.g., hospitalization of low risk children) and provider variation in risk tolerance. *Importantly, the tool will offer prognostic information only and will not proscribe a specific site of care or management plan. All site of care decisions will remain at the discretion of the treating provider.*

Table 2. Appropriate Site of Care Definitions

Disposition	Appropriate if:
Home care	No subsequent hospitalization within 24h
Inpatient, ward	Hospital length of stay ≥ 24h; or hospital length of stay < 24h but objective criteria for admission present (eg, need for supplemental oxygen); and no subsequent transfer to ICU within 24h
Inpatient, ICU	ICU length of stay ≥ 24h; or ICU length of stay < 24h but objective criteria for ICU admission present (eg, respiratory failure)

h, hours; ICU, intensive care unit

7.5 Outcomes (P2)

The primary outcome is appropriate site of care disposition (Table 2). Surveillance for subsequent ED visits and hospitalizations to our institutions as well as escalation to higher levels of care will be captured within the EHR data extracted by the decision support application. To adjudicate the appropriateness of brief hospitalizations and ICU stays (<24 hours), an investigator in both Nashville and Pittsburgh will review all hospitalizations meeting these criteria, blinded to intervention assignment.

Secondary efficacy and safety outcomes include the overall site of care disposition (ED discharge, ward, ICU), and ED revisits and hospitalizations within 72 hours and 7 days of the index discharge.

Exploratory outcomes include death, and for those hospitalized at the index visit, hospital length of stay.

7.6 Data Collection/Management (P2)

See Section 7.3

8.0 Statistical Considerations

8.1 Power and Sample Size (P1)

Based on ED and hospitalization data from our hospitals during the conduct of the EPIC study, we anticipate nearly 2000 total children with pneumonia will be evaluated annually during the conduct of these studies. Assuming conservatively that data for 750 children are enrolled in each arm, and 30% guideline-concordant antibiotic use in the usual care arm (based on our prior study of antibiotic use in the EPIC cohort)[23], we will be able to detect an absolute difference of ≥6.8% in guideline-concordant prescribing at an alpha level of 0.05 with 80% power. Effective sample size may be reduced due to the cluster randomized nature of the study (a conservative estimate for effective sample size would be around 500 children in each arm).

8.2 Analysis (P1)

Analyzing data from cluster randomized crossover trials requires accounting for correlations within clusters and time periods. As outlined by Turner et al.,[21] we will use a hierarchical and mixed effects logistic regression model, a complex analytic approach which offers flexibility regarding model assumptions and incorporation of cluster-level and individual-level covariates. We will also use a weighted, cluster-level logistic regression to compare guideline-concordant antibiotic prescribing between groups. In this analysis, data for each cluster are collapsed into a single summary measure, and the summary measures are then analyzed as if they were raw data, facilitating simple data reporting and interpretation. [21] Both methods perform well and are used frequently in the analysis for traditional cluster randomized trials without crossover. Important baseline covariates (e.g., age, sex, race, site of care, frequency of bacteremia and other pneumonia-related complications) will also be assessed and included as model covariates. Similar analyses will be conducted for the proposed secondary and exploratory outcomes using hierarchical and mixed effects logistic regression models for binary outcomes and frailty models for time to first antibiotic.

An important consideration in our analysis is the possibility of contamination effects in the usual care arm related to changes in provider behavior due to past exposures and awareness of the intervention. Such contamination would be expected to bias toward the null hypothesis. We posit that such effects will be of minor concern since 1) guideline-concordant prescribing at our institutions remains low despite the presence of both national and local practice guidelines and order sets for several years; 2) the ED is a busy environment with many providers (e.g., 40+ ED faculty plus mid-level providers and fellows/residents at Vanderbilt alone), such that repeated exposure to the intervention by any one provider would be infrequent, particularly early during the study period and during times of low pneumonia prevalence; and 3) resident physicians, the providers responsible for the majority of order entry and thus directly exposed to the intervention, rotate on a monthly schedule and only work in the ED once each year. We have designed our randomization and monthly crossover periods around these important considerations. Nevertheless, we acknowledge the potential for contamination, and we will formally evaluate for such effects in a secondary analysis by modeling the monthly proportions of guideline-concordant prescribing in each arm over the duration of the study period. We will then compare prescribing trends in both arms with a historical trend estimated from monthly proportions of guideline-concordant prescribing in the year prior to study initiation. By comparing prescribing trends in each arm to this historical trend, we will estimate both the degree of potential contamination as well as the independent impact of the intervention.

8.3 Potential Limitations and Alternative Approaches (P1)

We do not anticipate major difficulties designing or implementing our antibiotic decision support application. If challenges arise, our experienced team possesses the necessary expertise, past experience, and institutional resources to address and overcome them. Design challenges will be addressed by our usability and decision support experts to troubleshoot and develop effective solutions prior to and following implementation. Alternative analytic approaches were considered, including quasi-experimental step wedge designs and randomization at the provider or patient level. The cluster randomized monthly crossover design was selected since it is less subject to temporal bias (compared to the step wedge approach) and minimizes problems with contamination in the usual care arm (compared to provider or patient-level randomization) as outlined above. In addition to the analyses outlined above, if we fail to demonstrate meaningful outcome differences between the two arms, we will conduct exploratory analyses to elucidate reasons for lack of intervention effectiveness.

8.4 Power and Sample Size (P2)

As outlined in P1, we anticipate nearly 2000 children with pneumonia will be evaluated annually during the conduct of these studies. Assuming conservatively that data for 2000 children (1000 in each arm) are captured during the two-year study period, and 90% appropriate site of care disposition in the usual care arm (based on data from the EPIC cohort)[23], we will be able to detect an absolute difference of ≥3.4% in appropriate care disposition at an alpha level of 0.05 with 80% power.

8.5 Analysis (P2)

Logistic regression models will be performed to compare appropriate site of care disposition between the two study arms, controlling for important baseline covariates (e.g., age, season, provider type) to maximize power. Robust standard errors will be calculated to account for hospital clustering effects. We will also perform analyses to assess for interactions between two study arms and predicted risk for severe outcomes, age, provider type, and initial site of care, to identify subgroups in whom decision support may be most useful. Similar analyses will be conducted for the proposed secondary and exploratory outcomes along with cox regression model for hospital length of stay outcome.

8.6 Potential Limitations and Alternative Approaches (P2)

In contrast to our studies of antibiotic decision support, we chose to randomize at the individual level rather than monthly crossovers since potential for contamination effects is minimal (i.e. risk estimates are unique to each individual's set of circumstances and linked to a complex algebraic equation). Although we hypothesize that supplying providers with objective prognostic information will improve care decisions, this information could lead to unintended outcomes, such as increased hospitalizations in low risk children. This would be an important finding in itself, as it contrasts with prior studies in adults highlighting the usefulness of adult pneumonia severity tools, and provides valuable data regarding how risk information is interpreted and applied.

9.0 Risks to Participants

All study subjects will receive standard of care. All decisions regarding management, including antibiotic use and site of care disposition, will be at the discretion of the treating provider and will not be restricted or altered in any way by the study. This study does not involve an investigational intervention given or

administered directly to patients (i.e. no treatment assignments will be made). Therefore, this study poses no greater than minimal risk to study participants. Vanderbilt is at the forefront of these pragmatic, minimal risk clinical trial designs, and our study team benefits greatly from the experiences and expertise of our colleagues who have completed similar studies under waiver of informed consent. The potential benefit of this study would come through more effective therapy.

The study coordinator, with PI oversight, is responsible for ensuring protocol compliance, data integrity, and participant safety. This protocol presents minimal risks to participants and adverse events or other problems are not anticipated. In the unlikely event that such events occur, unanticipated problems involving risks to subjects or others will be reported immediately to the PI and responsible IRBs, and in writing within 5 days to the IRB and any appropriate funding and regulatory agencies. The PI will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project through regular study meetings. Annual reports will be submitted to the responsible IRBs summarizing study progress, adverse events, complaints about the research or withdrawals, and any protocol violations.

Although the study poses no greater than minimal risk to human subjects, we have appointed an independent data and safety monitoring board (DSMB) due to the inclusion of children and the multi-center nature of the study. The DSMB is comprised of three individuals with expertise relevant to the study, including biostatistics, and prior experience serving in this capacity. The DSMB will be independent of the study team and will conduct formal data and safety evaluations at least every six months. During these meetings, the DSMB will assess study progress, including subject accrual and retention, data quality, and subject safety in a confidential manner. The DSMB will make recommendations regarding whether the study should continue unchanged or require modification/amendment. Based on the findings of the data and safety monitor's reports, the PI, associated IRBs, and any other appropriate funding or regulatory agencies have the authority to stop or suspend the study or require modifications.

10.0 Privacy/Confidentiality Issues

Privacy and confidentiality is of the highest priority, and all efforts will be made to keep personal information and research records private throughout these studies. Records and documents pertaining to the conduct of this study will be kept in HIPPA-compliant, secure, password protected databases or in locked files accessible only by a limited number of study personnel. All patient data will be coded using a unique study ID. No PHI will be shared outside of the key study personnel at each institution and no PHI will be shared between institutions. The information from the research study may be published using aggregate results; however, no individual subject will be identified.

11.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants

The PI is responsible for monitoring the data, assuring protocol compliance, and conducting safety reviews. Adverse events or other problems are not anticipated. In the unlikely event that such events occur, unanticipated problems involving risks to subjects or others will be reported immediately to the PI and responsible IRBs, and in writing within 5 days to the IRB and any appropriate funding and regulatory

agencies. The PI will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project through regular study meetings. Annual reports will be submitted to the responsible IRBs summarizing study progress, adverse events, complaints about the research or withdrawals, and any protocol violations.

12.0 Study Withdrawal/Discontinuation

The investigators may choose to withdraw a subject if it is judged to be in the participant's best interest, or if the subject no longer meets eligibility criteria (see Section 5.0). Due to the observational nature of the study, there are no formal interim analyses or planned halting criteria.

13.0 Follow-Up and Record Retention

The anticipated study duration is 24 months for P1 and 24 months for P2. As this study does not include direct contact with enrolled subjects, there is no anticipated follow up. Records will be maintained in accordance with IRB, institutional, and sponsor policies.

14.0 References

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