Clinical Trial Transformation Initiative (CTTI)

Prospective Observational Study of the Risk Factors for Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HABP/VABP)

Protocol Number: CTTI_001

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Protocol Version:	*2.1 (Amendment 1)*
Principal Investigator:	*Vance Fowler, MD, MHS* Duke University Medical Center

Signature Page

The signature below documents the review and approval of this protocol and provides the necessary assurances that this study will be conducted according to the protocol (per undersigned participating study Arm), including all statements regarding confidentiality, and according to national, regional, and local legal and regulatory requirements.

The CTTI/PTN Risk Factors for HABP/VABP Study includes two arms - an Adult (Arm 1) and a Pediatric (Arm 2). An institution may participate either in Arm 1 only, Arm 2 only, or both Arm 1 and 2. Each arm will have a separate Principal Investigator. The signature below indicates in which arm of the protocol the principal investigator is participating.

Site Principal Investigator Name (Print)	Adult (Arm 1)
Signature	Date
Site Principal Investigator Name (Print)	Pediatric (Arm 2)
Signature	Date

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Protocol change history /summary:

	Version 1.0 (12/17/2015)	**Version 2.1 (4/15/2016)**
Protocol version	N/A. Original version	Amendment #1
Study population	Adult (>= 18 years old) only	Adult and Pediatric
# Patients	6850 Adults	6850 Adults (Arm 1) and 1000 Pediatric (Arm 2)
# study sites	45	Added 10 Pediatric sites
Funding Sponsor	FDA	FDA and NICHD
Protocol Chair	Dr. Vance Fowler	Added Dr. Danny Benjamin as PTN Chair
Appendix B (Pediatric supplement)	N/A	Included
Interim Analysis	The interim analysis will occur after 500 high-risk CRFs are completed or 3 months after all U.S. sites are activated, whichever occurs first.	The interim analysis will occur three months after 50% of US sites have begun enrolling patients.

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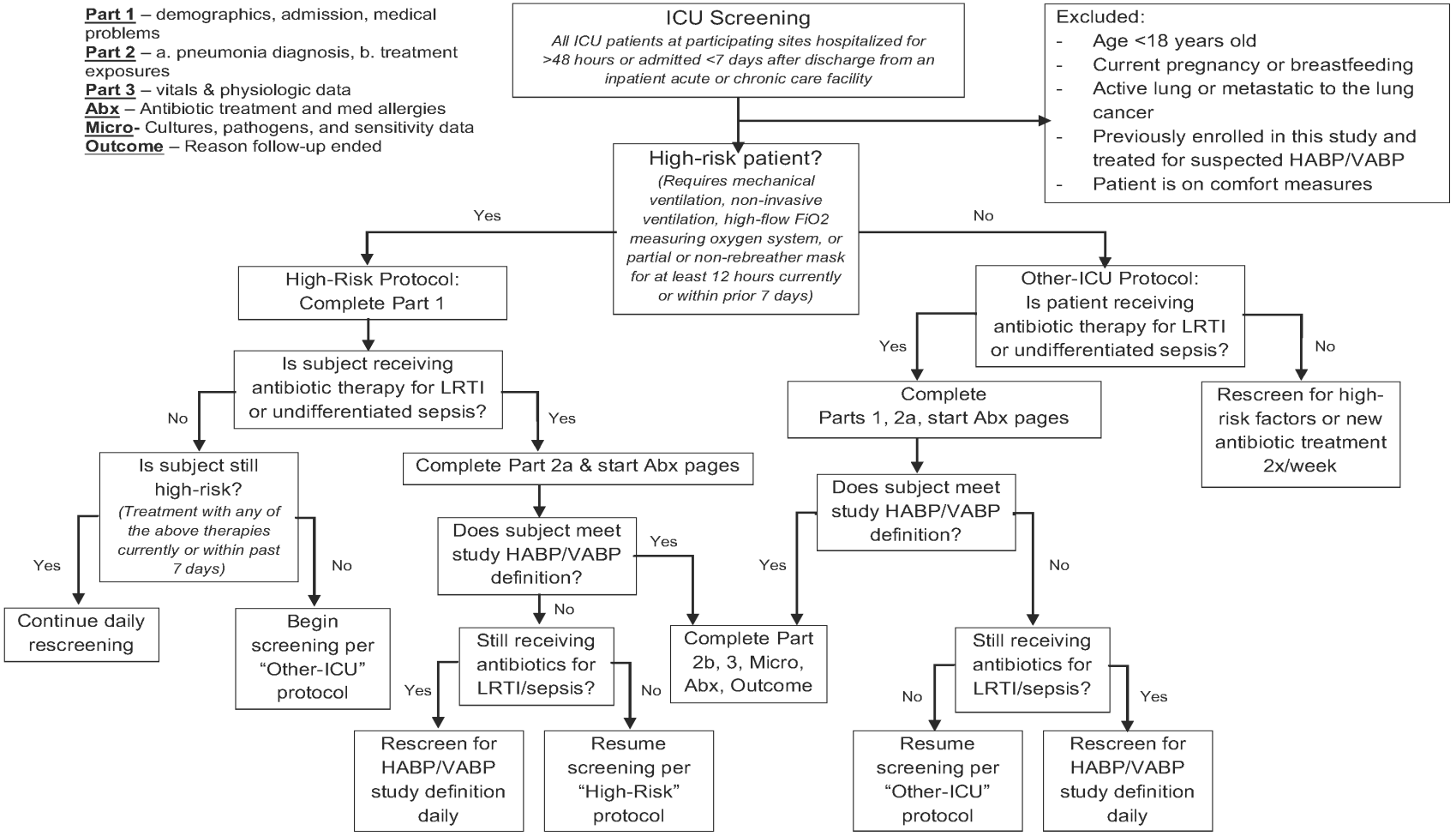
List of Abbreviations

BiPAP	Bilevel Positive Airway Pressure
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CTTI	Clinical Trials Transformation Initiative
DCRI	Duke Clinical Research Institute
EDC	Electronic Data Capture
FDA	U.S. Food and Drug Administration
FiO2	Fraction of Inspired Oxygen
HABP	Hospital-Acquired Bacterial Pneumonia
ICU	Intensive Care Unit
IRB	Institutional Review Board
LPM	Liters Per Minute
LRTI	Lower Respiratory Tract Infection
MRSA	Methicillin-Resistant *Staphylococcus aureus*
NICHD	National Institute of Child Health and Human Development
PTN	Pediatric Trials Network
VABP	Ventilator-Associated Bacterial Pneumonia

Protocol Synopsis

Protocol Title	Prospective Observational Study of the Risk Factors for Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HABP/VABP)
Study Design	Prospective, multi-center, observational study
Primary Study Objectives	• Estimate the rates of hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP) developing in intensive care unit (ICU) patients considered high risk for pneumonia, as defined by treatment with one or more of the following respiratory modalities for at least 12 hours, either currently or within the prior 7 days in patients age ≥18 year old (Arm 1)*: – Invasive mechanical ventilation – Noninvasive ventilation (bilevel positive airway pressure [BiPAP] or continuous positive airway pressure [CPAP] for any indication other than obstructive sleep apnea) – High-flow, supplemental oxygen therapy via nasal cannula. Only include systems using an air/oxygen blender capable of delivering a precise fraction of inspired oxygen [FiO2] level, not just a flow in liters per minute (LPM) – High flow supplemental oxygen therapy delivering at least 50% FiO2 via aerosol facemask or tracheostomy collar (mask). Only include systems using an air/oxygen blender capable of delivering a precise FiO2 level, not just a flow in LPM. – Supplemental oxygen therapy delivered via either partial or non-rebreather face mask. * For patients age <18 year old (Arm 2), see Appendix B • Estimate the proportion of patients diagnosed with HABP/VABP who would be eligible for enrollment in a clinical trial of antibacterial therapy for HABP/VABP per U.S. Food and Drug Administration (FDA) draft guidance document criteria.
Study Population	Arm 1: Adult (≥18 years) patients admitted to ICUs Arm 2: Pediatric (<18 years) patients admitted to ICUs or intermediate care unit
Number of Subjects	Arm 1: 6850 ICU patients meeting high-risk criteria Arm 2: ~1000 pediatric (<18 years) patients
Number of Sites	Arm 1: 45 total: 30 in the United States, 15 outside the United States Arm 2: ~ 10 sites in the United States
Clinical Samples	None
Estimated Start of Enrollment	January 30, 2016
Estimated Time to Completion	Up to 12 months of enrollment

Risk Factors for HABP/VABP Study Flowchart (Arm 1: age ≥18 years old)



1.0 Background and Scientific Rationale

1.1 Background Information

Clinical trials to evaluate the efficacy and safety of new antibacterial drugs for hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) are challenging to conduct and expensive, and there are a very limited number of clinical trials of new drugs for this indication in progress or planned. Evaluating new antibacterial drugs for efficacy in HABP/VABP is important, as a number of antibacterial drugs with demonstrated efficacy in the treatment of other serious bacterial infections have demonstrated limitations when studied in HABP/VABP. In addition, patients with infections caused by multi-drug resistant Gram-negative bacteria often present with HABP/VABP.[1]

The Clinical Trial Transformation Initiative (CTTI) is a collaborative organization that seeks to improve the quality and efficiency of clinical trials. The CTTI Streamlining HABP/VABP Trials Project includes a number of collaborative efforts to better understand the challenges of conducting HABP/VABP trials and address these challenges through streamlining the operational processes and building efficiencies for data collection in HABP/VABP trials.[2] A data gathering and mapping project conducted in collaboration with the Tufts Center for the Study of Drug Development found that the cost of screen failures, as well as screen failure rates, are the main drivers of cost for a Phase 3 HABP/VABP trial.[3] HABP/VABP Phase 3 trials are generally non-inferiority trials. To address the concern of bias toward non-inferiority, FDA Draft Guidance[4] recommends that patients who have received effective antibacterial drug therapy for HABP/VABP for a continuous duration of more than 24 hours during the previous 72 hours be excluded from HABP/VABP clinical trials. In a guided discussion with experienced research coordinators conducted by CTTI, this recommended exclusion criteria was noted as a significant challenge to enrollment as care standards in the intensive care unit often lead to antibacterial drugs being administered as soon as pneumonia is suspected. In addition, patients are often quite ill and unable to provide informed consent themselves, so legally authorized representatives must be identified and contacted. Other necessary enrollment procedures such as laboratory tests and other procedures to meet inclusion/exclusion criteria, randomization, and obtaining study drug from the pharmacy can add to the time between administration of antibacterial drugs and study enrollment. Strategies to address these feasibility concerns while ensuring that trial interpretability will not be limited by a bias toward non-inferiority are needed.

A HABP/VABP pilot study, incorporating many of the recommendations from the CTTI Streamlining HABP/VABP Trials Project, is planned. The primary objective is to conduct a study that will lead to improved HABP/VABP clinical trial feasibility. The proposed design of the future pilot study is a randomized trial comparing early enrollment and traditional enrollment strategies. The early enrollment strategy (treatment arm) will include approaching AND consenting patients at high risk for developing pneumonia, many before pneumonia symptoms develop. The rationale of this early enrollment strategy is to identify and enroll high-risk patients at the time they meet criteria for a diagnosis of HABP/VABP and before they have received more than 24 hours of effective antibacterial therapy.

1.2 Scientific Rationale

One of the challenges in planning the HABP/VABP pilot study is determining which patients to approach for early enrollment. A group of patients at risk for pneumonia is required, but selecting criteria based on existing literature will involve a tradeoff between sensitivity and specificity. Approaching only the highest risk patients (e.g., those on a ventilator for a pre-specified length of time) would likely yield a relatively high percentage of patients who go on to develop pneumonia.[5] The drawbacks of this approach include 1) not including a mix of VABP and non-VABP HABP; 2) exclusion of a large group of other patients who go on to develop

pneumonia in the hospital in absence of the highest risk factors; and 3) increased likelihood of exclusion due to current use of antibiotics. Using a more inclusive approach, such as enrolling patients with a history of aspiration or with chronic lung disease, would increase the total number of patients who ultimately develop pneumonia, but would decrease the proportion of enrolled patients that develop pneumonia. If the proportion of patients developing pneumonia is too low, it is possible that the time, effort, and money required to conduct a study using an early enrollment strategy would not result in a meaningful increase in number of patients enrolled who ultimately meet study criteria for antibacterial therapy for HABP/VABP. Therefore, this risk factor study will be conducted to better define the population at highest risk for developing HABP/VABP.

2.0 Hypotheses

2.1 Primary Hypothesis

- At least 5% of patients considered high risk for developing nosocomial pneumonia will ultimately be diagnosed with HABP/VABP during an intensive care unit (ICU) stay. High-risk patients are those admitted to an ICU who are treated with one or more of the following respiratory modalities for at least 12 hours (Arm 1) or 24 hours (Arm 2), either currently or within the prior 7 days: invasive mechanical ventilation; noninvasive mechanical ventilation for any indication other than obstructive sleep apnea; or supplemental oxygen therapy with a partial or non-rebreather mask, high-flow nasal cannula (a system that uses an air/oxygen blender and delivers a precise fraction of inspired oxygen [FiO2] level, not just a flow in liters per minute [LPM]), or high flow supplemental oxygen therapy delivering at least 50% FiO2 via aerosol facemask or tracheostomy collar (mask).

- At least 75% of patients diagnosed with HABP/VABP during an ICU admission would meet the inclusion and exclusion criteria outlined in the FDA draft guidance document for HABP/VABP drug development for a clinical trial of antibacterial therapy for HABP/VABP.

3.0 Objectives

3.1 Primary Objectives (Arm 1: age ≥18 years old):

a. Estimate the rates of HABP/VABP diagnosis in ICU patients considered high risk for pneumonia. High risk is defined by treatment with one or more of the following respiratory modalities for at least 12 hours, currently or within the prior 7 days:

   i. Invasive mechanical ventilation

   ii. Noninvasive ventilation (bilevel positive airway pressure [BiPAP] or continuous positive airway pressure [CPAP] for any indication other than obstructive sleep apnea)

   iii. High-flow, supplemental oxygen therapy via nasal cannula. Only include systems using an air/oxygen blender capable of delivering a precise FiO2 level, not just a flow in LPM.

   iv. High flow supplemental oxygen therapy delivering at least 50% FiO2 via aerosol facemask or tracheostomy collar (mask). Only include systems using an air/oxygen blender capable of delivering a precise FiO2 level, not just a flow in LPM.

   v. Supplemental oxygen therapy delivered via either partial or non-rebreather face mask

b. Estimate the proportion of patients diagnosed with HABP/VABP who would be eligible for enrollment in a clinical trial of antibacterial therapy for HABP/VABP per FDA draft guidance document criteria.

   i. Diagnosed is defined as fulfilling study HABP/VABP diagnostic criteria.

   ii. Eligible for enrollment will be defined as: Subject fulfills study HABP/VABP diagnostic criteria, and the time at which these diagnostic criteria were met is less than 24 hours after the first dose of antibiotics for HABP/VABP.

Please see Appendix B for Arm 2 (age <18 years old) information

3.2 Key Secondary Objective

a. In patients treated with respiratory modalities classified as high risk, identify demographic factors, comorbid medical illnesses, and treatment exposures that are associated with an increased risk of HABP/VABP development during ICU admission.

3.3 Secondary Objectives

a. Estimate the proportion of patients treated for HABP/VABP who would be eligible for enrollment in a clinical trial of antibacterial therapy for HABP/VABP per FDA draft guidance document criteria.

   i. Treated is defined as received antibiotics for suspected HABP/VABP.

   ii. Eligible for enrollment will be defined as: Subject fulfills study HABP/VABP diagnostic criteria, and the time at which these diagnostic criteria were met is less than 24 hours after the first dose of antibiotics for HABP/VABP.

b. Estimate the proportion of patients diagnosed with HABP/VABP who would otherwise meet FDA phase 3 clinical trial inclusion criteria but would be excluded from enrollment due to treatment with >24 hours, >36 hours, or >48 hours of effective antibiotics prior to pneumonia diagnosis.

   i. Determine the most common reasons for administration of antibacterial therapy prior to patients meeting the diagnosis of HABP/VABP per FDA draft guidance document criteria.

c. Estimate the proportion of patients treated for HABP/VABP who have lower respiratory tract cultures collected either on the day antibiotics are started for pneumonia treatment or within the prior 48 hours.

   i. Determine the proportion of lower respiratory tract cultures for which gram stain results are reported prior to the initiation of antibacterial therapy for HABP/VABP.

   ii. Determine the proportion of patients with HABP/VABP for which gram stain results are available within 24 hours of initiation of antibacterial therapy for HABP/VABP.

d. Estimate the proportion of patients treated for HABP/VABP for which a causative bacterial pathogen is identified.

e. Determine the most common bacterial causes of HABP/VABP among patients with positive lower respiratory tract culture.

f. Determine the incidence of the following types of antibacterial resistance among relevant pathogens:

   i. Methicillin resistance among *S. aureus* HABP/VABP lower respiratory tract isolates

   ii. Extended-spectrum beta-lactamase production among gram-negative organisms

   iii. Carbapenem resistance among gram-negative organisms

   iv. Fluoroquinolone resistance among gram-negative organisms

g. Determine the most common initial antibiotics prescribed for the treatment of HABP/VABP.

   i. Determine the proportion of patients treated with an initial antibacterial active against methicillin-resistant *Staphylococcus aureus* (MRSA).

   ii. Determine the proportion of patients with HABP/VABP treated with at least 1 initial anti-pseudomonal antibiotic (within 24 hours of HABP/VABP antibiotic initiation).

   iii. Determine the proportion of patients with HABP/VABP treated with 2 or more initial anti-pseudomonal antibiotics (within 24 hours of HABP/VABP antibiotic initiation).

h. Determine the proportion of patients with HABP/VABP for whom antibiotic therapy was changed because the initial regimen was either inactive or ineffective against the pathogen isolated on lower respiratory tract culture.

i. Determine the proportion of patients with HABP/VABP for whom antibiotic therapy was changed because of clinical deterioration or lack of clinical improvement.

j. Determine the frequency with which all antibacterials prescribed for HABP/VABP treatment are discontinued within 24 hours after final negative lower respiratory tract culture.

k. Determine the frequency with which antibacterials prescribed for HABP/VABP treatment are changed to narrow the antibacterial spectrum within 24 hours of positive (and negative) lower respiratory tract culture results.

l. Determine the average and median number of days a subject is followed in the risk factor study.

m. Estimate the proportion of subjects for which a causative viral pathogen is identified. (Arm 2 only)

n. Estimate the proportion of subjects for which normal respiratory flora is identified on lower respiratory tract cultures (Arm 2 only)

4.0 Study Design

This is a prospective, multi-center, observational study of patients - admitted to ICUs. Patients will be enrolled into 2 Arms based on their age – Arm 1: ≥18 years old, Arm 2: <18 years old. Generally, all patients admitted to the ICU for any indication will be considered at risk for developing HABP/VABP. A subset of the at-risk patients treated with select respiratory modalities

for at least 12 hours (Arm 1) or 24 hours (Arm 2) will be considered high risk for the development of HABP/VABP, will have baseline data collected, and will be screened daily for antibiotic treatment for suspected pneumonia. Patients <120 days old will be considered high risk if treated with a select respiratory modality for at least 5 days. Patients not meeting high-risk criteria, "other-ICU patients", will be screened twice weekly for antibiotic treatment for suspected pneumonia.

Once a high-risk subject or other-ICU patient is treated with antibiotics for either a lower respiratory tract infection (LRTI) or undifferentiated sepsis, additional clinical information will be recorded from the subject's medical record. All subjects treated with antibiotics for either indication will subsequently be screened for the development of pneumonia, as defined by the FDA draft guidance document for drug development in HABP/VABP. Subjects who meet the FDA draft guidance definition of pneumonia will have vitals and physiologic data collected and will be followed for 4 days after pneumonia is diagnosed to capture the results of any microbiologic testing and changes to initial antibiotic therapy.

All observational data will be collected from the subject's electronic health record and recorded in a secure electronic case report form. No information on outcomes, such as vital status, discharge destination, or length of stay will be collected. The data collected in this risk factor study will be used to better define the ICU population at highest risk for developing HABP/VABP.

4.1 Inclusion Criteria (Arm 1: age ≥18 years old)

- Admission to participating ICU
- Hospitalized for >48 hours or admitted <7 days after discharge from an inpatient acute or chronic care facility

Please see Appendix B for Arm 2 (age <18 years old) information

4.1.1 High-Risk Inclusion (Arm 1)

Treated with one or more of the following respiratory modalities for at least 12 hours, either currently or within the prior 7 days:

- Invasive mechanical ventilation
- Noninvasive ventilation (BiPAP or CPAP for any indication other than obstructive sleep apnea)
- High-flow, supplemental oxygen therapy via nasal cannula. Only include systems that using an air/oxygen blender capable of delivering a precise FiO2 level, not just a flow in LPM.
- High flow supplemental oxygen therapy delivering at least 50% FiO2 via aerosol facemask or tracheostomy collar (mask). Only include systems using an air/oxygen blender capable of delivering a precise FiO2 level, not just a flow in LPM.
- Supplemental oxygen therapy delivered via either partial or non-rebreather face mask

Please see Appendix B for Arm 2 information

4.1.2 Other-ICU Inclusion (Arm 1)

All patients who meet eligibility criteria in 4.1, but do not fulfill high-risk criteria in 4.1.1, and are receiving an antibiotic for treatment of LRTI or undifferentiated sepsis.

Please see Appendix B for Arm 2 information

4.2 Exclusion Criteria (Arm 1)

- Age <18 years old
- Pregnancy (current) or breastfeeding
- Lung cancer or another malignancy metastatic to the lungs (currently receiving treatment)
- Patient previously enrolled and treated for suspected HABP or VABP (More than CRF Part 1 was previously completed)
- Patient is on comfort measures (e.g. would not receive antibiotics)

Please see Appendix B for Arm 2 information

4.3 Co-enrollment Guidelines

Co-enrollment in other clinical trials or studies is permitted except for protocols that would violate the exclusion criteria.

4.4 Study Discontinuation

This study may be terminated at any time by the principal investigator in consultation with CTTI and/or the FDA.

5.0 Study Procedures

5.1 Recruitment Plan

This study will collect data on subjects who meet protocol-specified high-risk criteria. In addition, data will be collected on subjects not meeting high-risk criteria but who are treated with antibiotics for LRTI or undifferentiated sepsis for which HABP/VABP is considered in the differential diagnosis.

- Arm 1: approximately 6850 patients ≥18 years old
- Arm 2: approximately 1000 patients < 18 years old

Sections 5.2 through 5.5 below apply to Arm 1. Please see Appendix B for Arm 2 information

5.2 Enrollment (Arm 1)

All patients admitted to a study site ICU who have been hospitalized for at least 48 hours or discharged from an inpatient acute or chronic care facility within the prior 7 days will be screened for study inclusion. If any exclusion criterion is present, the patient will be recorded as a “screening failure” in the screening log and no further data will be collected.

If the patient satisfies the study enrollment criteria, he/she will be enrolled in the study. The subject will be counted as an inclusion in the screening log, and he/she will also be registered in the electronic data capture (EDC) system. For each enrolled subject, the types of respiratory support received at the time of enrollment and within the previous 7 days will be recorded. Those subjects receiving one or more of the modalities of respiratory support described in section 4.1.1. for at least 12 hours will be followed per the “High-Risk” protocol.

All other ICU patients, meeting eligibility criteria in 4.1, but not receiving respiratory support via one of the modalities in 4.1.1 or receiving for less than 12 hours will be followed according to the “Other-ICU” protocol. Other-ICU patients are enrolled only if they receive antibiotic therapy for LRTI or undifferentiated sepsis.

5.3 High-Risk Protocol (Arm 1)

Demographic, admission, and medical problems will be recorded for subjects meeting criteria for "high-risk" on the day of enrollment. High-risk subjects will be followed daily for the initiation of antibiotic therapy for either the treatment of LRTI or undifferentiated sepsis for which HABP/VABP is considered in the differential diagnosis. Antibiotics prescribed and evaluation for the study definition of pneumonia will be completed for subjects treated with antibiotics for either of these indications. If the study criteria for HABP/VABP are present, treatment exposures and microbiology will then be completed, and the subject will be followed for an additional 4 days as described in Section 5.5. Subjects treated with antibiotics for either LRTI or undifferentiated sepsis but not meeting criteria for HABP/VABP will be reevaluated daily for the fulfillment of HABP/VABP study criteria. If antibiotics for LRTI or undifferentiated sepsis are discontinued, screening per the High-Risk protocol will resume.

Subjects who have not met the study criteria for HABP/VABP will be followed daily per the High-Risk protocol until they have not received support from at least one respiratory modality listed in the high-risk criteria within the past 7 days. If a subject remains in the ICU beyond this time period, they will then be followed per the Other-ICU protocol until discharged from the ICU or transitioned to comfort measures and are no longer being treated with antibiotics. If support with a respiratory modality included in the "high-risk" criteria is later required, the subject will then be followed per the High-Risk protocol again.

5.4 Other-ICU Protocol (Arm 1)

Patients not meeting the "high-risk" criteria will be screened at least twice weekly for treatment with an antibiotic for either LRTI or undifferentiated sepsis for which HABP/VABP is considered in the differential diagnosis. Demographic, admission, medical problems, and antibiotics prescribed will be completed for subjects treated with antibiotics for either of these indications. Evaluation of the study definition of pneumonia will occur. If the study criteria for HABP/VABP are present, treatment exposures and microbiology will then be completed, and the subject will be followed for an additional 4 days as described in Section 5.5. Subjects treated with antibiotics for either LRTI or undifferentiated sepsis but not meeting criteria for HABP/VABP will be reevaluated daily for the fulfillment of HABP/VABP study criteria until antibiotics for LRTI or undifferentiated sepsis are discontinued. For those other-ICU patients who never receive antibiotic treatment for LRTI or undifferentiated sepsis during their ICU stay, no information will be collected.

Subjects who have not met the study criteria for HABP/VABP will be followed per the Other-ICU protocol until discharged from the ICU or transitioned to comfort measures and are no longer being treated with antibiotics. Subjects originally assigned to the Other-ICU protocol who later require support with a respiratory modality described in section 4.1.1. for at least 12 hours will be subsequently followed per the High-Risk protocol.

5.5 Study Completion (Arm 1)

Subjects developing HABP/VABP will be followed for 4 days beyond the initial fulfillment of HABP/VABP study criteria to collect microbiologic and antibacterial treatment data. After 4 days, the patient will no longer be followed in the risk factor study.

Subjects who do not develop HABP/VABP will be followed until discharge from the ICU. Or, follow-up will end if the subject is transitioned to comfort measures and are no longer being treated with antibiotics. At the end of follow up, treatment exposures will be collected using the most abnormal values/events from the ICU stay.

6.0 Statistical Analysis Plan (Arm 1)

Please see Arm 2 (< 18 years old) information in Appendix B.

6.1 General Considerations

All continuous variables will be summarized using descriptive statistics, including number of observations, number of missing observations, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum. All categorical variables will be summarized using frequency counts and percentages.

No missing data imputation will be performed. All statistical tests will be two-sided and interpreted at the 5% level of significance without correction for multiple comparisons.

All analyses will be performed in SAS 9.2 or higher.

6.2 Endpoints

The primary endpoint is the development of FDA-defined HABP/VABP.

6.3 Sample Size

Due to the exploratory nature of this study, no power calculations are performed.

A sample size of 6850 high-risk patents was chosen based on an estimate of the number of patients that can feasibly be enrolled at 45 sites over 12 months, and it is believed that this number will provide a meaningful number of patients who develop HABP/VABP. This number assumes enrollment of one new high-risk patient per business day per site and the months of participation per site will range from 3-12 months.

The sample size will provide reasonable estimates and exact 95% confidence intervals for the rate of HABP/VABP development (see Table 1 above). If the estimated rate of HABP/VABP is 5%, then the margin of error will be less than 1%.

Table **1: Exact confidence intervals for estimated rates of HABP/VABP development for 100%, 90%, and 80% of planned sample size.**

	Exact 95% Confidence Intervals		
Estimated Rate of HABP/VABP	**N=6850**	**N=6165**	**N=5480**
1%	(0.78% - 1.27%)	(0.77% - 1.29%)	(0.76% - 1.30%)
3%	(2.62% - 3.44%)	(2.59% - 3.46%)	(2.57% - 3.50%)
5%	(4.50% - 5.55%)	(4.48% - 5.59%)	(4.44% - 5.61%)
7%	(6.41% - 7.64%)	(6.38% - 7.67%)	(6.35% - 7.72%)
9%	(8.34% - 9.71%)	(8.30% - 9.74%)	(8.27% - 9.80%)

6.4 FINAL Analysis

6.4.1 Analysis Populations

The following analysis populations will be defined:

- The high-risk population (ICU subjects who meet the predefined high-risk criteria)
- *The treated population (subjects given antibiotics to treat possible HABP/VABP)*

6.4.2 The HABP/VABP population (subjects meeting diagnostic criteria for HABP/VABP)
Primary Analyses

- Estimate the rate of HABP/VABP diagnosis in ICU subjects who meet the predetermined high-risk criteria.

- Estimate the proportion of ICU subjects diagnosed with HABP/VABP who would be eligible for enrollment in a clinical trial of antibacterial therapy for HABP/VABP per FDA draft guidance on HABP/VABP.

The estimated rates will be presented as well as its exact 95% confidence interval.

6.4.3 Key Secondary Analysis

The key secondary analysis will be:

- Assess the risk factors, comorbid medical illnesses, and treatment exposures associated with the development of HABP/VABP in ICU subjects at high-risk for developing pneumonia using a logistic regression model with age, sex, height (cm), weight (kg), ICU type, admission source, hospital length of stay at the time of screening (calendar days), ICU length of stay at the time of screening, ICU admission diagnosis, aspiration risk, medical history, type and duration of ventilation, enteral nutrition, medications, and other therapies of interest as factors.

Estimated proportions will be presented as well as their 95% confidence intervals.

Odds ratios, 95% confidence intervals and p-values will be reported for each factor in the regression model.

Summary statistics will also be presented for all factors included in the regression model.

6.4.4 Secondary Analysis

The following summaries will be conducted in the treated population:

- Estimate the proportion of ICU subjects who would be eligible for enrollment in a clinical trial of antibacterial therapy for HABP/VABP per FDA draft guidance document criteria.

- Estimate the proportion of subjects who develop HABP/VABP.

- Estimate the proportion of subjects who have lower respiratory tract cultures collected within 48 hours preceding treatment of pneumonia with antibiotics.

- Estimate the proportion of subjects for which a causative bacterial pathogen is identified on lower respiratory tract cultures.

- Summarize prescribed initial antibiotics.

- Estimate the proportion of subjects treated within 24 hours of HABP/VABP antibiotic initiation with an initial antibacterial agent active against MRSA, the proportion treated with at least 1 initial antibacterial agent active against *Pseudomonas aeruginosa*, and the proportion treated with at least 2 initial antibacterials active against *Pseudomonas aeruginosa.*

The following summaries will be conducted for subjects in the HABP/VABP population:

- Estimate the proportion of subjects who meet clinical trial inclusion criteria but would be excluded from enrollment due to *effectively* being treated for pneumonia within 24 hours, 36 hours, or 48 hours preceding pneumonia diagnosis.
- Estimate the proportion of subjects for which gram stain results are available within 24 hours preceding initiation of antibacterial therapy for HABP/VABP.
- Estimate the proportion of subjects treated with at least 1 initial anti-pseudomonal antibiotic within 24 hours of initial HABP/VABP antibiotic treatment.
- Estimate the proportion of subjects treated with at least 2 initial anti-pseudomonal antibiotics within 24 hours of initial HABP/VABP antibiotic treatment.
- Estimate the proportion of subjects for whom antibiotic therapy was changed because the initial regimen was either inactive or ineffective against the pathogen isolated on lower respiratory tract culture.
- Estimate the proportion of subjects for whom antibiotic therapy was changed because of clinical deterioration or lack of clinical improvement.

The following summaries will be conducted for subjects in the HABP/VABP population who have lower respiratory cultures collected:

- Estimate the proportion of gram stain results reported prior to the start of antibacterial therapy.
- Estimate the rate of HABP/VABP antibacterial discontinuation within 24 hours after final negative lower respiratory tract culture.
- Estimate the rate at which HABP/VABP antibacterials are changed within 24 hours of lower respiratory tract culture results to narrow the antibacterial spectrum.

The following summaries will be conducted for subjects in the HABP/VABP population who have positive lower respiratory cultures:

- Summarize the bacterial pathogens of HABP/VABP.
- Summarize the types of antibacterial resistance by pathogen.

All estimated proportions and rates will be presented with their exact 95% confidence intervals. All summaries will be presented as frequency counts and percentages.

6.5 Baseline Summaries

The high-risk population will be summarized according to the following factors measured at the time of high-risk determination:

- Invasive mechanical ventilation
- Noninvasive ventilation
- High-flow, supplemental oxygen therapy via nasal cannula.
- High flow supplemental oxygen therapy delivering at least 50% FiO2 via aerosol facemask or tracheostomy collar (mask)
- Supplemental oxygen therapy delivered via either partial or non-rebreather face mask

- Demographics: age, sex, height (cm), weight (kg), ICU type, admission source, hospital length of stay at the time of screening (calendar days), ICU length of stay at the time of screening, identification of legally authorized representative or medical proxy

- Medical problems: reason for hospital and ICU admission, aspiration risk, medical history, and drug allergies

- Treatment exposures: type and duration of ventilation, enteral nutrition, medications, and other therapies of interest

6.6 Interim Analysis

One interim analysis will be conducted during the study. The primary purpose of the interim analysis is to assess futility by investigating the primary objectives and the first two secondary objectives (3.1a-b, 3.2a, and 3.3a). The interim analysis will occur three months after 50% of US sites have begun enrolling patients.

The following analyses will be conducted on the high-risk population:

1. Estimate the rate of HABP/VABP development as well as its exact 95% confidence interval. If the exact 95% confidence interval for the pneumonia rate in high-risk subjects does not include 5%, the feasibility of continuing the risk factor study and/or an amendment to expand the high-risk definition will be discussed.

2. Assess the risk factors, comorbid medical illnesses, and treatment exposures associated with the development of HABP/VABP in ICU subjects at high-risk for developing pneumonia using a logistic regression model with age, sex, height (cm), weight (kg), ICU type, admission source, hospital length of stay at the time of screening (calendar days), ICU length of stay at the time of screening, ICU admission diagnosis, aspiration risk, medical history, type and duration of ventilation, enteral nutrition, medications, and other therapies of interest as factors.

The following analysis will be conducted on the HABP/VABP population: estimate the proportion of subjects, as well as its exact 95% confidence interval, who would be eligible for enrollment in a clinical trial of antibacterial therapy for HABP/VABP per FDA guidance document criteria.

The following analysis will be conducted on the treated population: estimate the proportion of subjects, as well as its exact 95% confidence interval, who would be eligible for enrollment in a clinical trial of antibacterial therapy for HABP/VABP per FDA guidance document criteria

7.0 Ethics and Regulatory

7.1 Ethical Standards

The investigator will ensure that the study will be conducted in accordance with all applicable national, regional, and local regulations. This study will request a waiver of informed consent, consistent with CFR Title 45 part 46.116(d). The study does not involve direct interaction with human subjects. The medical records of patients admitted to the ICU will be screened and data collected from those records according this protocol. The patients will not be approached to obtain information, no intervention is being tested, and no samples or specimens are being collected. Therefore, the study should be considered no more than minimal risk, and the waiver will not adversely affect the rights and welfare of the patients observed.

This research could not practicably be carried out without the waiver of consent since the most critically ill patients, like the ICU patients, are very problematic to consent. This risk factor study requires screening of the medical records of all ICU patients, and data collection on a large

number of patients meeting high-risk characteristics and/or receiving antibiotics to obtain a complete picture of HABP/VABP development in ICUs. Studies in a different critically ill population, one with MRSA bloodstream infections, showed that the mortality risk of patients with MRSA is considerably lower in studies that required informed consent[6] relative to those that do not.[7] Hence, requiring informed consent would systematically bias the study towards less severely infected patients. Less severely ill high-risk patients are also less likely develop pneumonia. If the number of high-risk patients identified is too low, the proportion developing pneumonia will be too small to provide meaningful information.

7.2 Data Confidentiality

The study documentation, data, and all other information generated by this study will be maintained in a secure manner and will be kept confidential as required by law.

Duke Clinical Research Institute's (DCRI) configured the EDC database (eClinical OS data) that will be hosted by Merge, which uses a Peak 10 datacenter located in Morrisville, NC. Database access will be limited to study personnel who are issued a unique user identification and password. Data will be entered via a web-based interface at each site by study personnel. No information concerning the study or the data will be released to any third party without prior written approval of the sponsor. Study records may be reviewed in order to meet federal or state regulations. Reviewers may include the IRBs or the the DCRI.

7.2.1 Quality Control and Quality Assurance

The local site principal investigator will ensure that study personnel are appropriately trained and applicable documentations are maintained.

The DCRI will implement a Quality Plan to ensure that protocol training and data quality and data security measures are being undertaken.

7.2.2 Source Documents and Access to Source Data

All study monitoring will be performed centrally via the electronic study database. If necessary, a site monitoring visit will be arranged by the DCRI.

7.3 Data Handling and Record Keeping

7.3.1 Data Capture Methods

This study will use a web-based e-CRF database configured by the DCRI. The investigator's site staff, who will be entering data, will receive training on the system, after which each person will be given access to the study database.

7.3.2 Data Editing and Audit Trail

eClinical OS maintains an audit trail that consists of creation and/or modification date and time, identification of the user that created/changed the record, the device where the data were added or changed, and the reason for the change if applicable. Data changes do not obscure previously recorded data.

If incomplete or inaccurate data are found, a data clarification request will be generated and distributed to clinical centers for a response. Clinical centers will resolve data inconsistencies and errors and enter all corrections and changes into the study EDC database.

8.0 Publication Policy

Following completion of the study, the results of this research will be written up in a manuscript to be submitted to a scientific journal. As part of the publication of results, CTTI will make the de-identified data from this study, and the underlying code and research provenance available not only in summary form but also via a web platform—with appropriate data governance and security—for other researchers to review. Prior to submission, it will undergo review by CTTI's Publication Committee, a subcommittee of the Executive Committee. The Executive Committee includes distinguished U.S. and international thought leaders in government, academia, industry, and patient advocacy who are experienced at envisioning and facilitating improvements in health care and medical research systems (http://www.ctti-clinicaltrials.org/who-we-are/organizational-structure/executive-committee). The purpose of the Publication Committee review is to foster the quality of CTTI products. The Publication Committee reviews papers to be submitted to peer-reviewed journals and posters to be presented at professional meetings. The primary decision on content stays with the author, unless the paper or poster represents an official CTTI position, which can only be established by the Executive Committee.

9.0 References

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2. Streamlining HABP/VABP Trials. (n.d.). Retrieved October 20, 2015, from http://www.ctti-clinicaltrials.org/what-we-do/ctti-projects/habpvabp-trials.

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6. Fowler VG Jr, Olsen MK, Corey GR, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. *Arch Intern Med*. 2003;163:2066-2072.

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APPENDIX A: DATA COLLECTION SCHEDULE (Arm 1)

Event	Screen-ing	High-Risk Criteria Met	Other-ICU (Not Meeting High-Risk Criteria)	High-Risk Protocol with Pneumonia Symptoms or Antibiotics Started for any LRTI or Undifferentiated Sepsis	Other-ICU Protocol with Antibiotics Started for LRTI or Undifferentiated Sepsis	Meets HABP or VABP Definition (in Either High-Risk or Other-ICU Group)	Lower Respira-tory Tract Cultures Obtained	Full CRF Complete or Condition Met to Stop Data Collection
Review eligibility criteria	X							
Daily status worksheet		X						
Twice weekly status worksheet			X					
Collect: demographics, admission, medical problems		X			X			
Evaluate clinical signs/symptoms of pneumonia (HABP/VABP definition)				X	X			
Collect Treatment Exposures						X		X (In those not meeting HABP or VABP definition)
Collect Antibiotics				X	X	X		
Collect: microbiology							X	
Collect Study Outcomes Page								X

CRF, case report form; HABP, hospital-acquired bacterial pneumonia; LRTI, lower respiratory tract infection; ICU, intensive care unit; VABP, ventilator-associated bacterial pneumonia.

Appendix B: Supplement for pediatric subjects (Arm 2: <18 years old)

1. Study Objectives:

1.1. Primary Objectives:

a. Estimate the rates of HABP/VABP diagnosis in pediatric patients considered high risk for pneumonia. High risk is defined in section 2.1 of this Appendix.

1.2. Secondary Objectives (In addition to Arm 1 items):

a. Estimate the proportion of subjects for which a causative viral pathogen is identified

b. Estimate the proportion of subjects for which normal respiratory flora is identified on lower respiratory tract cultures

2. Inclusion Criteria

- < 18 years old
- Admission to participating ICU or intermediate care unit
- Hospitalized for >48 hours or admitted <7 days after discharge from an inpatient acute or chronic care facility

Note: Children and infants with pulmonary and cardiac anomalies are eligible to participate.

2.1. High-Risk Inclusion

Subjects ≥120 days old and <18 years old:
Currently treated with one or more of the following respiratory modalities for at least 24 hours:

a. Invasive mechanical ventilation via endotracheal intubation
b. New initiation of mechanical ventilation, BiPAP or CPAP via tracheostomy
c. Noninvasive ventilation (BiPAP or CPAP for any indication other than obstructive sleep apnea)
d. High-flow, supplemental oxygen therapy delivering at least 1.5LMP with 100% FiO2 via nasal cannula when delivered using an air/oxygen blender capable of delivering a precise FiO2 level, not just a flow in LPM
e. High flow supplemental oxygen therapy delivering at least 50% FiO2 via aerosol facemask or tracheostomy collar (mask) when delivered using an air/oxygen blender capable of delivering a precise FiO2 level, not just a flow in LPM
f. Supplemental oxygen therapy delivered via either partial or non-rebreather face mask

Subjects <120 days old:
Currently treated with mechanical ventilation via endotracheal intubation for at least 5 days

2.2. Standard-Risk Inclusion

All patients who meet eligibility criteria in Appendix B Section 2, but do not fulfill high-risk criteria in Appendix B Section 2.1, and are receiving an antibiotic for treatment of LRTI or undifferentiated sepsis.

3. Exclusion Criteria

- Known pregnancy (current) or breastfeeding
- Lung cancer or another malignancy metastatic to the lungs (currently receiving treatment)
- Patient previously enrolled and treated for suspected HABP or VABP (More than Pediatric CRF Part 1 was previously completed)
- Patient is on comfort measures (e.g. would not receive antibiotics)

4. Co-enrollment Guidelines

Co-enrollment in other clinical trials or studies is permitted except for protocols that would violate the exclusion criteria.

5. Study Discontinuation

This study may be terminated at any time by the principal investigator in consultation with CTTI and/or the FDA.

6. Study Procedures

6.1. Recruitment Plan

This study will collect data on pediatric subjects who meet protocol-specified high-risk criteria. In addition, data will be collected on subjects not meeting high-risk criteria but who are treated with antibiotics for LRTI or undifferentiated sepsis for which HABP/VABP is considered in the differential diagnosis. Approximately 1000 subjects will be recruited.

6.2. Enrollment

All patients admitted to a study site ICU or intermediate care unit who have been hospitalized for at least 48 hours or discharged from an inpatient acute or chronic care facility within the prior 7 days will be screened for study inclusion. If any exclusion criterion is present, the patient will be recorded as a “screening failure” in the screening log and no further data will be collected.

If the patient satisfies the study enrollment criteria, he/she will be enrolled in the study. The subject will be counted as an inclusion in the screening log, and he/she will also be registered in the electronic data capture (EDC) system. For each enrolled subject, the types of respiratory support received at the time of enrollment and within the previous 7 days will be recorded. Those subjects receiving one or more of the modalities of respiratory support described in section Appendix B Section 2.1. for at least 24 hours will be followed per the “High-Risk” protocol.

All other patients, meeting eligibility criteria in Appendix B Section 2, but not receiving respiratory support via one of the modalities in Appendix B Section 2.1 or receiving for less than 24 hours will be followed according to the “Standard-risk ” protocol. Standard-risk patients are enrolled only if they receive antibiotic therapy for LRTI or undifferentiated sepsis.

6.3. High-Risk Protocol

Demographic, admission, and medical problems will be recorded for subjects meeting criteria for “high-risk” on the day of enrollment. High-risk subjects will be followed or be flagged by the electronic medical record daily for the initiation of antibiotic therapy for either the treatment of LRTI or undifferentiated sepsis for which HABP/VABP is considered in the differential diagnosis. Antibiotics prescribed and evaluation for the study definition of pneumonia will be completed for subjects treated with antibiotics for either of these indications. If the study criteria for HABP/VABP are present, treatment exposures and microbiology will then be completed, and the subject will be followed for an additional 4 days as described in Appendix B Section 6.5. Subjects treated with antibiotics for either LRTI or undifferentiated sepsis but not meeting criteria for HABP/VABP will be reevaluated daily for the fulfillment of HABP/VABP study criteria. If antibiotics for LRTI or undifferentiated sepsis are discontinued, screening per the High-Risk protocol will resume.

Subjects who have not met the study criteria for HABP/VABP will be followed daily per the High-Risk protocol until they have not received support from at least one respiratory modality listed in the high-risk criteria within the past 7 days. If a subject remains in the ICU or intermediate care unit beyond this time period, they will then be followed per the standard-risk protocol until discharged from the ICU or intermediate care unit or transitioned to comfort measures and are no longer being treated with antibiotics. If support with a respiratory modality included in the “high-risk” criteria is later required, the subject will then be followed per the High-Risk protocol again.

6.4. Standard-risk Protocol

Patients not meeting the “high-risk” criteria will be screened at least twice weekly or be flagged by the electronic medical record for the initiation of treatment with an antibiotic for either LRTI or undifferentiated sepsis for which HABP/VABP is considered in the differential diagnosis. Demographic, admission, medical problems, and antibiotics prescribed will be completed for subjects treated with antibiotics for either of these indications. Evaluation of the study definition of pneumonia will occur. If the study criteria for HABP/VABP are present, treatment exposures and microbiology will then be completed, and the subject will be followed for an additional 4 days as described in Appendix B Section 6.5. Subjects treated with antibiotics for either LRTI or undifferentiated sepsis but not meeting criteria for HABP/VABP will be reevaluated daily for the fulfillment of HABP/VABP study criteria until antibiotics for LRTI or undifferentiated sepsis are discontinued. For those standard-risk patients who never receive antibiotic treatment for LRTI or undifferentiated sepsis during their ICU or intermediate care unit stay, no information will be collected.

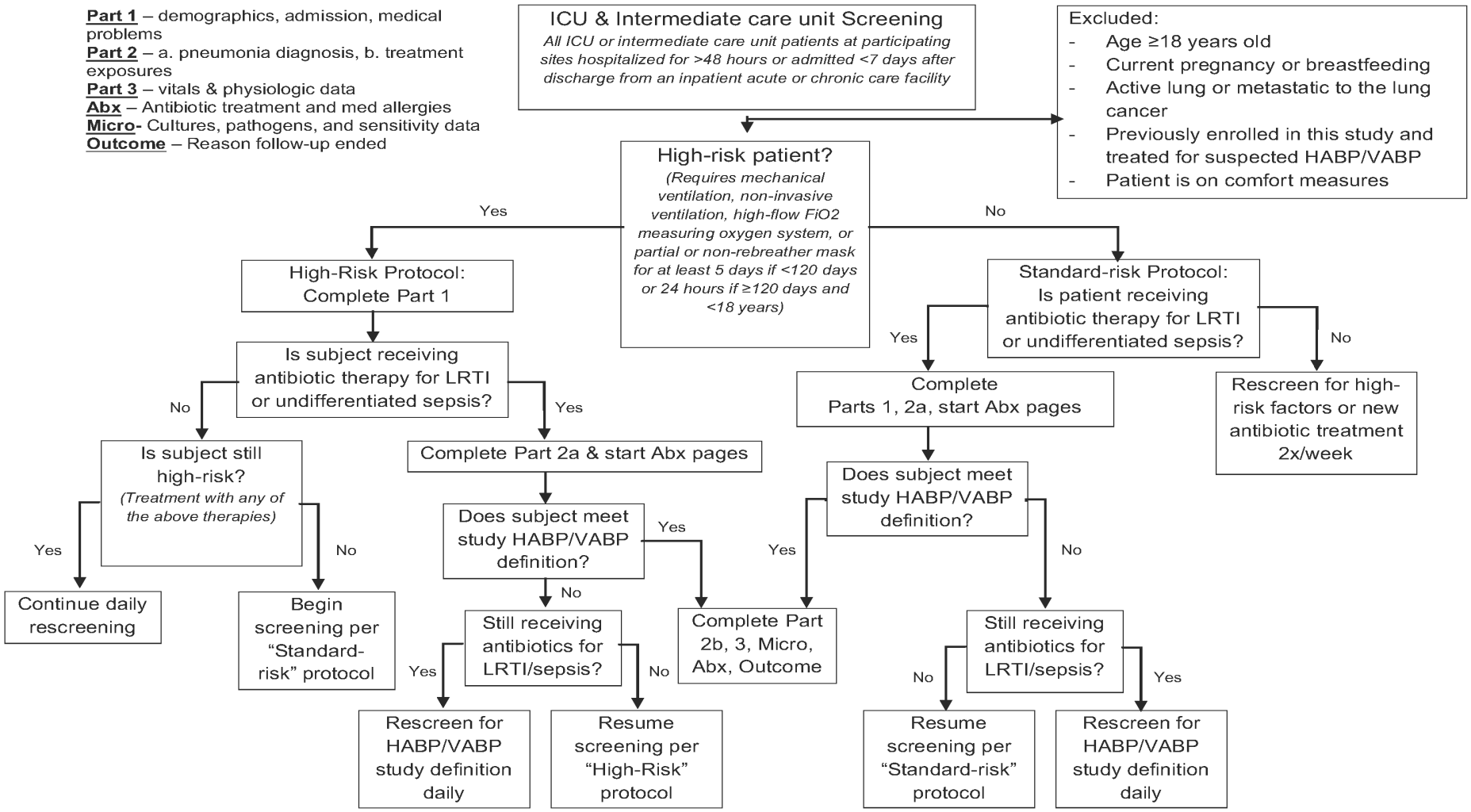
Subjects who have not met the study criteria for HABP/VABP will be followed per the standard-risk protocol until discharged from the ICU or intermediate care unit or transitioned to comfort measures and are no longer being treated with antibiotics. Subjects originally assigned to the standard-risk protocol who later require support with a respiratory modality described in Appendix B Section 2.1 for at least 24 hours if ≥120 days old or for at least 5 days if <120 days old will be subsequently followed per the High-Risk protocol.

6.5. Study Completion

Subjects developing HABP/VABP will be followed for 4 days beyond the initial fulfillment of HABP/VABP study criteria to collect microbiologic and antibacterial treatment data. After 4 days, the patient will no longer be followed in the risk factor study.

Subjects who do not develop HABP/VABP will be followed until discharge from the ICU or intermediate care unit. Or, follow-up will end if the subject is transitioned to comfort measures and are no longer being treated with antibiotics. At the end of follow up, treatment exposures will be collected using the most abnormal values/events from the ICU or intermediate care unit stay.

Risk Factors for HABP/VABP Study Flowchart (Arm 2: age <18 years **old)**



7. Statistical Analysis Plan

7.1. General Considerations

All continuous variables will be summarized using descriptive statistics, including number of observations, number of missing observations, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum. All categorical variables will be summarized using frequency counts and percentages.

No missing data imputation will be performed. All statistical tests will be two-sided and interpreted at the 5% level of significance without correction for multiple comparisons.

All analyses will be performed in SAS 9.2 or higher.

7.2. Endpoints

The primary endpoint is the development of FDA-defined HABP/VABP. HABP/VABP is defined as all below criteria are met:

a. Chest radiograph showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia within 48 hours of all other diagnostic criteria being present

b. New onset or worsening cough, dyspnea, tachypnea (respiratory rate >60 breaths per minute for children <1 year old, >40 breaths per minute for children ages 1-3 years, >30 breaths per minute for children ages 4-12 years, >20 breaths per minute for children >12 years), OR expectorated sputum production OR new requirement for invasive mechanical ventilation OR hypoxemia (partial pressure of oxygen <60 millimeters of mercury measure by arterial blood gas or worsening (decrease >10%) of the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) or pulse oximetry reading of <90% or new supplemental oxygen requirement or greater than 50% increase in supplemental oxygen requirement for patients on chronic supplemental oxygen therapy) OR need for acute changes (≥20% increase in FiO2 or ≥3cmH20 increase in PEEP over the “baseline daily minimum), after 2 days of stability in ventilator support OR new onset of suctioned respiratory secretions.

c. Systemic inflammation: body temperature ≥38 degrees Celsius or ≤35 degrees Celsius OR leukocytosis (total peripheral white blood cell count ≥10,000 cells/cubic millimeter) OR leukopenia, (total peripheral white blood cell count ≤4,500 cells/cubic millimeter) OR greater than 15% immature neutrophils (bands) noted on peripheral blood film OR a C-reactive protein ≥5 times the upper limit of normal.

d. Timing: Signs/symptoms of pneumonia first noted >48 hours after hospital admission OR signs/symptoms of pneumonia first noted >48 hours after initiation of mechanical ventilation

7.3. Sample Size

Due to the exploratory nature of this study, no power calculations are performed.

A sample size of 1000 - pediatric patents was chosen based on an estimate of the number of patients that can feasibly be enrolled at 10 sites over 12 months, and it is believed that this number will provide a meaningful number of patients who develop HABP/VABP.

7.4. Final Analysis

7.4.1. Analysis Populations

The following analysis populations will be defined:

- The high-risk pediatric population ≥120 days old but <18 years old (subjects who meet the predefined high-risk criteria)
- The high-risk pediatric population <120 days old (subjects who meet the predefined high-risk criteria)
- The treated pediatric population ≥120 days old but <18 years old (subjects given antibiotics to treat possible HABP/VABP)
- The treated pediatric population <120 days old (subjects given antibiotics to treat possible HABP/VABP)
- The HABP/VABP pediatric population ≥120 days old but <18 years old (subjects meeting diagnostic criteria for HABP/VABP)
- The HABP/VABP pediatric population <120 days old (subjects meeting diagnostic criteria for HABP/VABP)

7.4.2. Primary Analyses

- Estimate the rate of HABP/VABP diagnosis in pediatric subjects who meet the predetermined high-risk criteria.
- Estimate the proportion of pediatric subjects diagnosed with HABP/VABP who would be eligible for enrollment in a clinical trial of antibacterial therapy for HABP/VABP per FDA draft guidance on HABP/VABP.

The estimated rates will be presented as well as its exact 95% confidence interval.

7.4.3. Key Secondary Analysis

The key secondary analysis will be:

- Assess the risk factors, comorbid medical illnesses, and treatment exposures associated with the development of HABP/VABP in pediatric subjects at high-risk for developing pneumonia using a logistic regression model with age, sex, height (cm), weight (kg), hospital admission type, admission source, hospital length of stay at the time of screening (calendar days),hospital length of stay at the time of screening, hospital admission diagnosis, aspiration risk, medical history, type and duration of ventilation, enteral nutrition, medications, and other therapies of interest as factors.

Estimated proportions will be presented as well as their 95% confidence intervals.

Odds ratios, 95% confidence intervals and p-values will be reported for each factor in the regression model.

Summary statistics will also be presented for all factors included in the regression model.

7.4.4. Secondary Analysis

The following summaries will be conducted in the treated population:

- Estimate the proportion of subjects who would be eligible for enrollment in a clinical trial of antibacterial therapy for HABP/VABP per FDA draft guidance document criteria.
- Estimate the proportion of subjects who develop HABP/VABP.
- Estimate the proportion of subjects who have lower respiratory tract cultures collected within 48 hours preceding treatment of pneumonia with antibiotics.
- Estimate the proportion of subjects for which a causative bacterial pathogen is identified on lower respiratory tract cultures.
- Estimate the proportion of subjects for which a causative viral pathogen is identified.
- Estimate the proportion of subjects for which normal respiratory flora is identified on lower respiratory tract cultures
- Summarize prescribed initial antibiotics.
- Estimate the proportion of subjects treated within 24 hours of HABP/VABP antibiotic initiation with an initial antibacterial agent active against MRSA, the proportion treated with at least 1 initial antibacterial agent active against *Pseudomonas aeruginosa*, and the proportion treated with at least 2 initial antibacterials active against *Pseudomonas aeruginosa.*
- Estimate the sensitivity, specificity and positive and negative predictive values of C-reactive protein, procalcitonin and leukocytosis in the diagnosis of HABP/VABP.

The following summaries will be conducted for subjects in the HABP/VABP population:

- Estimate the proportion of subjects who meet clinical trial inclusion criteria but would be excluded from enrollment in an FDA phase 3 trial due to *effectively* being treated for pneumonia within 24 hours, 36 hours, or 48 hours preceding pneumonia diagnosis.
- Estimate the proportion of subjects for which gram stain results are available within 24 hours preceding initiation of antibacterial therapy for HABP/VABP.
- Estimate the proportion of subjects treated with at least 1 initial anti-pseudomonal antibiotic within 24 hours of initial HABP/VABP antibiotic treatment.
- Estimate the proportion of subjects treated with at least 2 initial anti-pseudomonal antibiotics within 24 hours of initial HABP/VABP antibiotic treatment.
- Estimate the proportion of subjects for whom antibiotic therapy was changed because the initial regimen was either inactive or ineffective against the pathogen isolated on lower respiratory tract culture.
- Estimate the proportion of subjects for whom antibiotic therapy was changed because of clinical deterioration or lack of clinical improvement.

The following summaries will be conducted for subjects in the HABP/VABP population who have lower respiratory cultures collected:

- Estimate the proportion of gram stain results reported prior to the start of antibacterial therapy.

- Estimate the rate of HABP/VABP antibacterial discontinuation within 24 hours after final negative lower respiratory tract culture.
- Estimate the rate at which HABP/VABP antibacterials are changed within 24 hours of lower respiratory tract culture results to narrow the antibacterial spectrum.
- Estimate the rate at which HABP/VABP antibacterials are changed within 24 hours of lower respiratory tract culture results to broaden the antibacterial spectrum.

The following summaries will be conducted for subjects in the HABP/VABP population who have positive lower respiratory cultures:

- Summarize the bacterial pathogens of HABP/VABP.
- Summarize the types of antibacterial resistance by pathogen.
- Estimate the proportion of study sites in which MRSA was identified on ≥1 lower respiratory tract culture.
- Estimate the proportion of study sites in which an ESBL-producing Gram negative bacillus was identified on ≥1 lower respiratory tract culture.
- Estimate the proportion of study sites in which an carbapenemase-producing Gram negative bacillus was identified on ≥1 lower respiratory tract culture.

All estimated proportions and rates will be presented with their exact 95% confidence intervals. All summaries will be presented as frequency counts and percentages.

7.5. Baseline Summaries

The high-risk population will be summarized according to the following factors measured at the time of high-risk determination:

- Invasive mechanical ventilation
- Noninvasive ventilation
- High-flow, supplemental oxygen therapy via nasal cannula.
- High flow supplemental oxygen therapy delivering at least 50% FiO2 via aerosol facemask or tracheostomy collar (mask)
- Supplemental oxygen therapy delivered via either partial or non-rebreather face mask
- Demographics: age, sex, height (cm), weight (kg), hospital admission type, admission source, hospital length of stay at the time of screening (calendar days), hospital length of stay at the time of screening, identification of legally authorized representative or medical proxy
- Medical problems: reason for hospital and ICU admission, aspiration risk, medical history, and drug allergies
- Treatment exposures: type and duration of ventilation, enteral nutrition, medications, and other therapies of interest

7.6. Interim Analysis

One interim analysis will be conducted during the study. The primary purpose of the interim analysis is to assess futility by investigating the primary objectives and the first two secondary objectives (1.1a-b, 1.2a, and 1.2b). The interim analysis will occur after 50 pediatric high-risk CRFs are completed or 3 months after all pediatric sites are activated, whichever occurs first. The following analyses will be conducted on the high-risk population:

a. Estimate the rate of HABP/VABP development as well as its exact 95% confidence interval. If the exact 95% confidence interval for the pneumonia rate in high-risk subjects does not include 5%, the feasibility of continuing the risk factor study and/or an amendment to expand the high-risk definition will be discussed.

b. Assess the risk factors, comorbid medical illnesses, and treatment exposures associated with the development of HABP/VABP in subjects at high-risk for developing pneumonia using a logistic regression model with age, sex, height (cm), weight (kg), hospital admission type, admission source, hospital length of stay at the time of screening (calendar days), hospital length of stay at the time of screening, hospital admission diagnosis, aspiration risk, medical history, type and duration of ventilation, enteral nutrition, medications, and other therapies of interest as factors.

The following analysis will be conducted on the HABP/VABP population: estimate the proportion of subjects, as well as its exact 95% confidence interval, who would be eligible for enrollment in a clinical trial of antibacterial therapy for HABP/VABP per FDA guidance document criteria.

The following analysis will be conducted on the treated population: estimate the proportion of subjects, as well as its exact 95% confidence interval, who would be eligible for enrollment in a clinical trial of antibacterial therapy for HABP/VABP per FDA guidance document criteria.

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