PROcalcitonin impact on antibiotic reduction, adver**S**e events and **AV**oidable healthcar**E** costs (ProSAVE): a RCT

Version 18

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Signature Page

Short title: ProSAVE

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1 GENERAL INFORMATION

1.1 Responsibilities

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1.2 Compliance Statement

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

Principal Investigator: _____
Print/Type Name

Signed: _____ Date: _____

1.3 List of Abbreviations

Abbreviation	Term
AB	Antibiotic
ADE	Adverse Drug Events
ADR	Adverse Drug Reaction
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AHRQ	Agency for Healthcare Quality and Research
ALT	Alanine transaminase
AST	Aspartate aminotransferase
CAE30	Composite Adverse Events until Day 30 (Primary Endpoint)
CAP	Community Acquired Pneumonia
CBC	Complete Blood Cell Count
CDC	Centers for Disease Control
CDI	Clostridium difficile infection
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CURB 65	Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years of age and older
DOT	Days of Therapy
EC	Ethics Committee
ED	Emergency Department
GCP	Good Clinical Practice
GDH	Glutamate dehydrogenase
(HO) CDI	Healthcare facility-onset Clostridium difficile infection

IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IDN	Integrated Delivery Network
IRB	Institutional Review Board
LOS	Length of stay
LRTI	Lower respiratory tract infection
NAAT	Nucleic acid amplification test
NI	Non-inferiority
PCT	Procalcitonin
prescribedABx	Antibiotics prescribed at discharge for pneumonia treatment
RCT	Randomized controlled trial
shortABx	Short treatment of pneumonia with antibiotics (less than 4 days)
SOFA	Sequential organ failure assessment
qSOFA	Quick sequential organ failure assessment
ULN	Upper limit of normal

1.4 Protocol Synopsis

Title	**PRO**calcitonin impact on antibiotic reduction, Clo**S**tridium difficile infection and **AV**oidable healthcar**E** costs (ProSAVE): A RCT
Acronym	ProSAVE
Principal investigator	**Michael K. Mansour, MD, PhD** Associate Professor Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA
Sponsor	B·R·A·H·M·S GmbH Neuendorfstrasse 25 16761 Hennigsdorf, Germany
Background	Antimicrobial resistance is one of our most serious health threats. Infections from resistant bacteria are now too common, and some pathogens have even become resistant to multiple types or classes of antibiotics (antimicrobials used to treat bacterial infections).[1,2] The binary issue is that when antibiotics are prescribed appropriately to treat bacterial infection, they are effective and should be prescribed without delay. However, 50% of the time antibiotics are misused or prescribed without proper indication. Lower respiratory tract infections (LRTI) are among the most frequent indications for antibiotics and pose a significant risk for excessive exposure to antibiotics and increase incidence of CDI. Delay or lack of pathogen identification and non-specific clinical and radiographic findings often leave clinicians with insufficient evidence to make definitive decisions regarding the need for antibiotics. The Infectious Disease Society of America (IDSA) recommends improving antibiotic prescribing practices as an essential action. [3] Several novel biomarkers have been proposed as a complementary strategy to evaluate the severity of bacterial infection, differentiate viral from bacterial etiologies, and improve antibiotic therapy decisions. Procalcitonin (PCT), a pro-inflammatory cytokine that is nearly undetectable in health and up regulated in response to endotoxemia, offers significantly more sensitive and specific prediction of bacterial infection. Trials comparing PCT-guided antibiotic algorithms to standard management show a significant reduction in antibiotic exposure without an increase in mortality or treatment failure. [4,5,6] . Despite this strong evidence from multiple studies a recent prospective multicentric interventional trial in the US fell short of demonstrating antibiotic reductions by PCT-guided antibiotic management. [7] Amongst other limitations the authors of that study concluded that successful implementation of PCT may require closer educational oversight. As such, this study will compare effectiveness and safety of antibiotic prescription

	guided by a PCT-algorithm via a stewardship team over standard guidelines in hospitalized adult patients with suspected or confirmed pneumonia.
Indication	Adult patients with suspected pneumonia at time of admission to or while admitted to the ED, general ward, intermediate care unit, or ICU.
Primary Objective	Determine the difference in antibiotic exposure and healthcare cost and assess safety by comparing antibiotic prescription guided by a (i) PCT algorithm + stewardship team (intervention) or (ii) standard guidelines (control) in hospitalized patients with suspected or confirmed LRTI.
Study Design	Prospective, multi-center, randomized-controlled interventional trial
Enrolling Wards	ED, admitted floor and ICU teams
Intervention	Addition of previously validated PCT algorithms to clinical assessment to guide the discontinuation of antibiotics in patients with suspected or confirmed pneumonia.
Primary Endpoint	Proportion of patients with short treatment of pneumonia with antibiotics (less than 4 days, "shortABx")
Secondary Endpoints	1. Composite safety adverse event rate at 30 days (CAE30). The composite endpoint includes: a. All-cause in-hospital mortality b. All-cause mortality after discharge (as available) c. Hospital readmission d. Septic shock (vasopressor use for > 1 h) e. Mechanical ventilation (via endotracheal tube for respiratory failure) f. Required dialysis g. Lung abscess/empyema 2. Antibiotic exposure at discharge 3. Antibiotic duration 4. Days of Therapy per 1000 patient days (inclusive of antibiotics prescribed at discharge) 5. Antibiotic days prescribed at discharge 6. Treatment or readmission for CDI until day 30 after enrollment 7. LOS in hospital until Day 30 8. LOS on ICU until Day 30 9. ICU admission until Day 30
Exploratory Endpoints	All the single variables of the safety endpoint CAE30, see 3.2. "Composite adverse events until day 30"
Healthcare Economic Endpoints	Costs associated with primary hospitalization, readmission for CDI, and loss of function • Cost of Antibiotics (total cost of antibiotics per patient inclusive of antibiotic, tubing, IV bag, discharge antibiotic prescription) • Cost of Procalcitonin • Total per patient cost (including blood cultures and mechanical ventilation days)

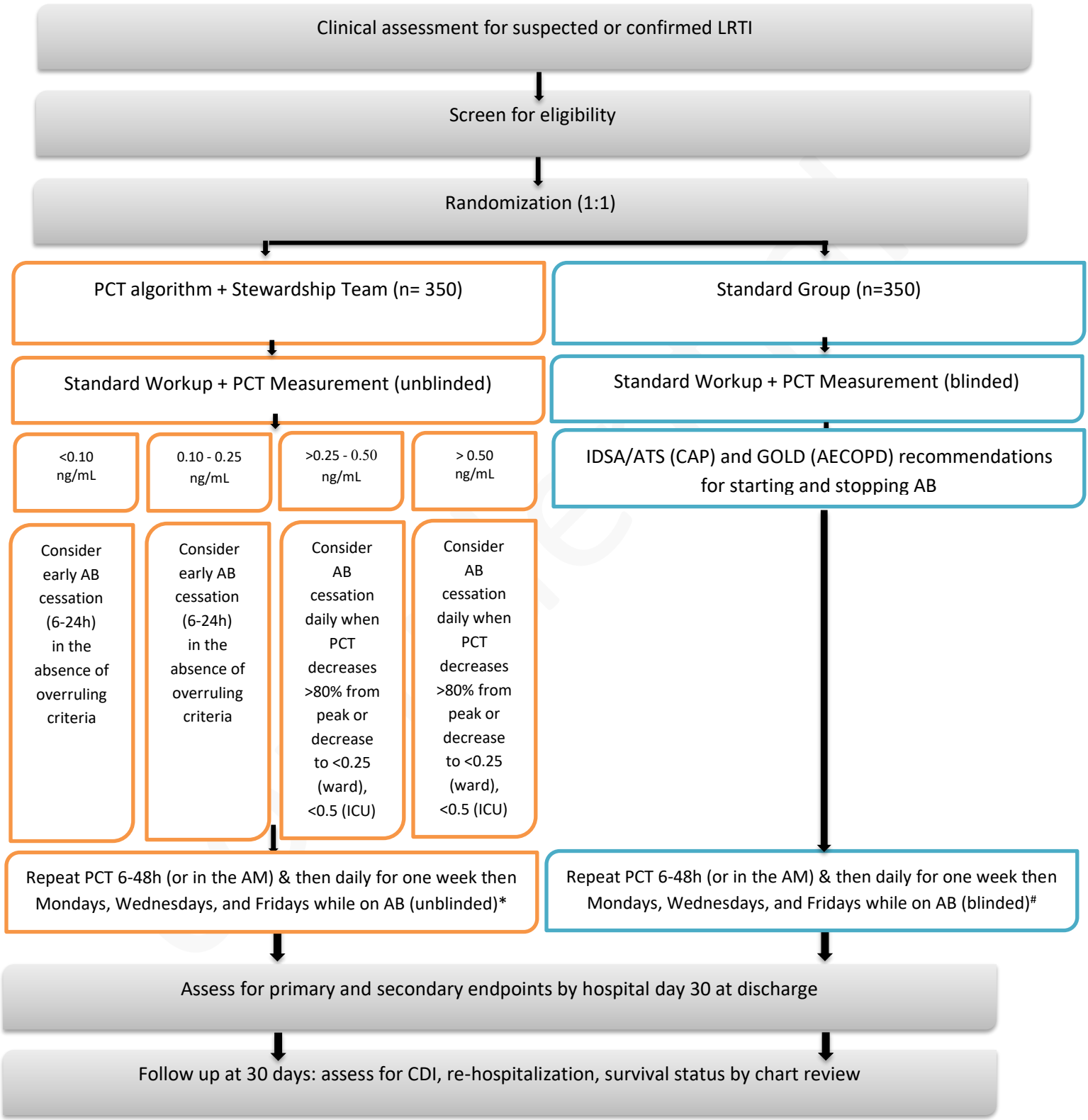
	• Antibiotic ADRs (e.g. CDI) • AB days difference plus prescriptions avoided infection adverse event incidence modeling[29] • Cost of readmissions
Inclusion Criteria	- Hospitalized adult patients ≥ 18 years of age - Suspected or confirmed LRTI pneumonia <28 days at time of admission to the hospital (ED) who are prescribed antibiotics - Minimum of 2 (two) blood samples available for PCT value assessment between 6 and 48 hours apart.
Exclusion Criteria	- Patient has tested positive for SARS-CoV-2 - Patients who are not admitted to the hospital - Patients admitted to home health - Major surgeries, defined as any procedure in which an incision is made with the exception of superficial procedures (eyes, cornea, skin, dental procedures), organs removed, or normal anatomy altered (e.g. open thoracic, abdominal and/or major orthopedic surgery), in the past 1 month or expected surgical procedure or patient receiving antibiotics for surgical prophylaxis - Known Pregnancy - Primary and acquired cell-mediated immune deficiency (HIV with CD4 <350 cells/mm^3; receipt of systemic chemotherapy and/or biologics in the past 3 months for reasons other than malignancy) - Active metastatic cancer or neuroendocrine tumor or liquid tumor and/or on check point inhibitors within 3 months or has signs of mucositis (e.g. mouth lesions or intestinal bleeding). - Neutropenia (<1,500 ANC) - Patients with cystic fibrosis - Infection where long courses of antibiotics are the standard of care (> 2 weeks) other than anti-inflammatory reasons - Concomitant non-pulmonary bacterial infection that requires antibiotic therapy based on an active medical team decision - Antibiotics given for non-infectious indications (e.g. rifaximin for hepatic encephalopathy) - Patients receiving dialysis - Patients with solid organ transplant, bone marrow transplant or stem cell transplant recipient - ST elevation myocardial infarction - Prior enrollment into this study within 30 days. - Patient experiencing major trauma defined as any injury that could cause prolonged disability and/or an Injury Severity Score >15, and/or burns or patient under extracorporal circulation confirmed by a second research staff member. - Patient with acute viral hepatitis and/or decompensated severe liver cirrhosis (Child-Pugh Class C).

	- Patient with prolonged or severe cardiogenic shock defined as decreased cardiac output leading to end organ injury (e.g. severe hypotension or AKI or oliguria or altered mental status or cool extremities or respiratory distress AND evidence of metabolic acidosis on lab testing), - Patient with pancreatitis, chemical pneumonitis or heat stroke - Active infection with invasive fungal pathogen (e.g. candidiasis, aspergillosis) or plasmodium falciparum malaria or mycobacteria - Patient under treatment with OKT3 antibodies, OK-432, interleukins, TNF-alpha and other drugs stimulating the release of pro-inflammatory cytokines or resulting in anaphylaxis. - Patient is under hospice care - Patient with ventilator-associated pneumonia - Patients with untreated, active, and symptomatic autoimmune disease - Patients actively enrolled in other clinical trial involving immunomodulatory therapy - Patients with empyema, abscess, or cavitary/necrotizing pneumonia
Sample Size	Bayesian adaptive design with interim analyses after enrollment of 200, 350, 550 and 650 patients and a maximum number of 700 patients (350 per study arm)
Study Sites	1. Massachusetts General Hospital, Department of Medicine, Boston, MA, USA 2. North Shore Medical Center, Department of Medicine, Salem, MA, USA 3. Martha's Vineyard Hospital, Department of Medicine, Oak Bluffs, MA, USA 4. Grady Memorial Hospital, Department of Medicine, Atlanta, GA, USA 5. Charlotte Hungerford Hospital, Department of Medicine, Torrington, CT, USA
Study Duration	15-24 months depending on patient recruitment per adaptive study design (see statistics section below) and 30 days follow-up.
Safety Considerations	Multiple RCTs evaluating the addition of PCT algorithms to clinical management have shown a safe decrease in antibiotic exposure in LRTI and sepsis. Antibiotic discontinuation will be determined by clinician interpretation of standard clinical, laboratory and radiology parameters along with the addition of a PCT algorithm to guide antibiotic decisions. Patients will not receive a direct investigational intervention in this study. All recommendations outlined in the ICH guidelines for Good Clinical Practice will be adhered to throughout this study. Data Monitoring Committee (DMC) includes infectious disease experts. The DMC can meet at a frequency of their choice with a minimum of two meetings during study period at 350 and 550 patients.

	An unblinded biostatistician will be available to answer any queries of the DMC. In addition to safety datasets of the respective number of enrolled patients, safety-relevant results of interim analyses about the safety endpoint CAE30 will also be provided to the DMC, see Section 8.10.
Test product	The Elecsys B·R·A·H·M·S PCT™ immunoassay or Abbott Alinity will be used to determine PCT concentrations in leftover specimen of routine blood draws from patients with pneumonia.
Statistical Methodology	For the primary study endpoint "short antibiotic treatments" (proportion of patients with short antibiotic treatment of pneumonia less than 4 days, "shortABx") the hypotheses for statistical inference are as follows: **H0:** The probability of patients with short antibiotic treatments of pneumonia is smaller or equal in the PCT arm versus the control arm. **H1:** The probability of patients with short antibiotic treatments of pneumonia is greater in the PCT arm than in the control arm. For the first secondary study endpoint "composite adverse events until day 30" ("CAE30") the hypotheses for statistical inference are as follows: **H0:** PCT arm is inferior to control arm in composite safety adverse event rate at day 30. **H1:** PCT arm is not inferior to control arm in composite safety adverse event rate at day 30. For the second secondary study endpoint "proportion of patients with antibiotic exposure at discharge") ("prescribedABx") the hypotheses for statistical inference are as follows: **H0:** The probability of patients with antibiotic exposure at discharge is greater or equal in the PCT arm versus the control arm. **H1:** The probability of patients with short antibiotic treatment of pneumonia is smaller in the PCT arm than in the control arm. The analysis of the study endpoints shortABx, CAE30 and prescribedABx will be conducted with Bayesian methodology: Differences in proportions between study arms will be assessed on the basis of posterior probabilities assuming binomially distributed events and uninformative uniform priors. Type-1 error is controlled at 2.5%. The endpoints shortABx and prescribedABx will be tested for superiority. Superiority is specified by more than 98.5% [1] posterior probability for less antibiotic exposure in the PCT arm than in the control arm, i.e., more

	frequent short antibiotic treatments in the PCT arm versus the control arm (shortABx) and less frequent antibiotic exposure at discharge in the PCT arm versus the control arm (prescribedABx). The endpoint CAE30 will be tested for non-inferiority. Non-inferiority is specified by 98.5% [1] posterior probability for a smaller CAE30 probability of patients of the PCT arm than the CAE30 probability of patients of the control arm plus 10% non-inferiority (NI) margin. <u>For further secondary and exploratory endpoints:</u> Distributions of numerical variables will be visualized for all patients and separately for PCT and control arm. Study arm-specific distributions will be compared with each other by statistical tests (e.g. Wilcoxon rank-sum tests), and by comparing descriptive summary measures (e.g. group medians and means). 2 x 2 contingency tables will be reported for counts stratified according to study arm (PCT, control) and endpoint level (true/false). Associations between study arms and endpoints will be analyzed by statistical tests (e.g. chi-square test or Fisher's exact test). Proportions and two-sided 95% confidence intervals or Bayesian 95% credible intervals will be computed for all patients and separately for PCT and control arm. <u>Health Economic Evaluation:</u> The clinical outcomes of the study will be analyzed from a health economic hospital perspective, extrapolation to third party payer remains optional. Clinical data and local cost data will be processed in the previously published/under publication Health Economic Model (Janne C Mewes et. al., The cost impact of PCT-guided antibiotic stewardship versus usual care for hospitalized patients with suspected sepsis or lower respiratory tract infections in the US: a health economic model analysis). All available information will be used in the model. Missing/confidential cost data will be substituted with publicly available data and highlighted accordingly. All findings will be discussed in the local hospital context as well as how these compare to the overall situation in the United States.

1.5 Treatment Decision Flowchart



***LRTI PCT Algorithm (Appendix A)**
#Please see section 4.2

1.6 Study Plan

	Between presentation and enrollment day	Screening/ Enrollment day	Per Protocol until discharge (as available)	Hospital Discharge	Day 30
Medical History	**x**				
Routine Clinical Assessment	**x**	**x**	**x**		
Standard laboratory evaluation	**x**	**x**	**x**		
Inclusion/Exclusion		**x**			
PCT measurement	**x**	**x**	**x***		
Document presence or absence of safety endpoints and antibiotic prescription				**x**	**x**
Follow-up via chart review/public record: readmission, survival status					**x**
Follow-up via chart review: Readmission for CDI					**x**

*PCT measurement only until antibiotics are stopped or patient becomes ineligible

2 BACKGROUND

Antimicrobial resistance is one of our most serious health threats. Infections from resistant bacteria are now too common, and some pathogens have even become resistant to multiple types or classes of antibiotics (antimicrobials used to treat bacterial infections).[1,2] The binary issue is that when antibiotics are prescribed appropriately to treat bacterial infection, they are effective and should be prescribed without delay. However, 50% of the time antibiotics are misused or prescribed without proper indication.

Lower respiratory tract infections (LRTI) are among the most frequent indications for antibiotics and pose a significant risk for excessive exposure to antibiotics and increase incidence of CDI. Delay or lack of pathogen identification and non-specific clinical and radiographic findings often leave clinicians with insufficient evidence to make definitive decisions regarding the need for antibiotics. The Infectious Disease Society of America (IDSA) recommends improving antibiotic prescribing practices as an essential action. [3]

Several novel biomarkers have been proposed as a complementary strategy to evaluate the severity of bacterial infection, differentiate viral from bacterial etiologies, and improve antibiotic therapy decisions. Procalcitonin (PCT), a pro-inflammatory cytokine that is nearly undetectable in health and up regulated in response to endotoxemia, offers significantly more sensitive and specific prediction of bacterial infection. Trials comparing PCT-guided antibiotic algorithms to standard management show a significant reduction in antibiotic exposure without an increase in mortality or treatment failure [4,5,6].

Despite this strong evidence from multiple studies a recent prospective multicentric interventional trial in the US fell short of demonstrating antibiotic reductions by PCT-guided antibiotic management. [7] Amongst other limitations the authors of that study concluded that successful implementation of PCT may require closer educational oversight. As such, this study will compare effectiveness and safety of antibiotic prescription guided by a PCT-algorithm via a stewardship team over standard guidelines in hospitalized adult patients with suspected or confirmed pneumonia.

3 TRIAL OBJECTIVES

3.1 Primary Objective

Determine the difference in antibiotic exposure and healthcare cost and assess safety by comparing antibiotic prescription guided by a (i) PCT algorithm + stewardship team (intervention) or (ii) standard guidelines (control) in hospitalized patients with suspected or confirmed pneumonia.

3.2 Primary Endpoint

The primary study endpoint is the superiority endpoint short antibiotic treatments (proportion of patients with short treatment of pneumonia with antibiotics less than 4 days, “shortABx”).

3.3 Secondary Endpoints

The secondary study endpoints are as follows:

1. Safety non-inferiority endpoint: Composite safety adverse event rate at 30 days (CAE30). The composite endpoint includes:
   a. All-cause in-hospital mortality
   b. All-cause mortality after discharge (as available)
   c. Hospital readmission
   d. Septic shock (vasopressor use for > 1 h)
   e. Mechanical ventilation (via endotracheal tube for respiratory failure)
   f. Required dialysis
   g. Lung abscess/empyema/cavitation/necrotizing pneumonia

In the case a patient is enrolled with mechanical ventilation, such an event is not considered to be an adverse event due to its occurrence before randomization. If the patient is then extubated during their hospital stay, re-intubation is only classified as an adverse event if it occurs at least 24 hours post extubation.

In the case a patient is enrolled with septic shock, such an event is not considered to be an adverse event due to its occurrence before randomization. If the patient then has a resolved septic shock during their hospital stay, developing a new septic shock is only classified as an adverse event if it occurs at least 24 hours post resolution of the initial septic shock.

In the case a patient develops a safety adverse event at any point on the day of enrollment post randomization, such an event will be classified as an adverse event.

2. Antibiotic exposure at discharge (superiority endpoint)
3. Days of Therapy per 1000 patient days (inclusive of antibiotics prescribed at discharge)
4. LOS in hospital until Day 30
5. LOS on ICU until Day 30
6. ICU admission until Day 30

3.4 Exploratory Endpoints

1. Treatment or readmission for CDI until day 30 after enrollment
2. All the single variables of the safety endpoint CAE30, see 3.2.“Composite adverse events until day 30”

4 STUDY DESCRIPTION

4.1 Study Design

The study will be conducted as a prospective, randomized controlled, multicenter, interventional trial whereby individual patients will be evaluated for eligibility and then randomized to one of two arms:

(i) Antibiotic prescription guided by a **PCT algorithm and stewardship team** (PCT arm): antibiotic treatment recommendations will be made by the stewardship team. The stewardship team will discuss PCT algorithm overruling with the primary care team.

(ii) antibiotic prescription guided by **current guidelines** (control arm): treating clinicians will be blinded to PCT results and antibiotic treatment decisions will be at the discretion of the treating clinician based on standard of care guidelines.

Antibiotic exposure (duration and DOT), safety outcomes and associated healthcare costs will be compared between groups throughout enrollment and follow up.

Screening, (D0) Baseline and (D1) PCT measurement

Patients will be consecutively screened for eligibility one day after their admission to an inpatient bed. Research staff will be responsible for screening admissions and antibiotic orders for potential enrollment and randomization. A dedicated stewardship team at each site will implement the intervention algorithm. The stewardship team will ensure PCT results and appropriate algorithm interventions are addressed (via phone, email, messaging system, or in person) with the primary provider as well as document assigned protocol adherence and deviations.

Upon review of inclusion/exclusion criteria, study subjects will be randomized 1:1 into one of two groups: (i) PCT algorithm + stewardship team arm or (ii) the standard care arm. PCT results will be unblinded in the (i) *PCT algorithm + stewardship team arm* and blinded in the (ii) *standard care group*.

Potential subjects resulting from the initial EPIC screen are not considered subjects. Subjects are defined as those who meet criteria for entry into the study. Non-eligible subjects are those who have met an exclusion criterion at some point during the study.

Upon randomization, the research staff will send a welcome message to both the standard of care and intervention teams. Enrollment PCT values consist of one value from the day of randomization (D1) and one value from a previous day 6-48 hours prior (D0). All PCT measurements throughout the study should be obtained using discarded blood from routine lab work. All PCT values ordered by the study team for patients in the intervention arm will be released in EPIC, while those of the standard of care arm will be suppressed.

After the PCT results are available, the stewardship team will review both the D0 and D1 results as a pair and provide an antibiotic recommendation (PCT intervention arm only) using the stewardship team recommendation template to the primary provider service on enrollment day. If the stewardship team is discordant with the PCT algorithm (see section 1.5 for algorithm), they will be sent a discordance survey (see Appendix G). If the primary team is discordant with the stewardship recommendations, a reason for discordance survey will be sent out and recorded in REDCap (see Appendix H). Patient information will be recorded in REDCap for both the intervention and standard of care arms.

(D2+) Daily PCT measurements

For patients who are still eligible and on antibiotics, PCT should be measured daily for one week and then Monday, Wednesday, and Friday in both arms. If there are no results on a Monday, the PCT will be measured on Tuesday, Wednesday, and Friday. If there are no results on a Wednesday, the PCT will be measured on Monday, Thursday, and Friday.

For PCT arm patients, the stewardship team will review available PCT results and provide an antibiotic recommendation to the primary provider service on the same calendar day. Antibiotic monitoring and/or discontinuation will be guided by clinical assessment (medical history, physical exam, imaging and standard laboratory evaluations) as well as the PCT algorithm (Appendix A, LRTI) and pre-defined overruling criteria (Appendix A, 11.2). If the stewardship team is discordant with the PCT algorithm, a discordance survey will be requested (Appendix G). In case of discordance between the primary team and the stewardship team, a discordance survey will also be requested (Appendix H).

The stewardship team will provide a recommendation every day (Monday-Friday) that the patient has a PCT result. Patients will not receive recommendations on weekends, holidays or pre-planned absences. If the stewardship team wants to repeat the same recommendation for multiple days in a row, they must indicate in their communication to the team that this is a standing recommendation and the medical team will not receive further communications until the stewardship team decides to change their recommendation. If the medical team changes, the new medical team will receive a recommendation.

In both arms, selection of antibiotic agent, dosing and route of administration will be at the discretion of the treating clinician.

For patients in the control arm, PCT results will be blinded to the stewardship and primary service team. Select research staff will be unblinded to the PCT values and will record them into REDCap. Antibiotic monitoring and/or discontinuation will be guided by standard care guidelines including clinical assessment (medical history, physical exam, and imaging and standard laboratory evaluations).

4.2 Study Population

Hospitalized adult patients with suspected or confirmed pneumonia at time of admission or while admitted to the ED who are prescribed antibiotics (including septic patients with respiratory focus).

Studies show that PCT is not affected by certain cancers so those patients will be included. Several studies have shown that PCT is a promising and reliable infection marker in patients with cancer[30,31]. Neuroendocrine tumors and the presence of metastases have been linked to false positive PCT values[32,33]. Thus, metastatic cancer, liquid tumors, neuroendocrine tumors and unstable patients who are on check point inhibitors or experiencing mucositis (e.g. mouth lesions or intestinal bleeds) will not be included.

4.2.1 Inclusion Criteria

- Hospitalized adult patients ≥ 18 years of age

- Suspected or confirmed LRTI pneumonia <28 days at time of admission to the hospital (ED) who are prescribed antibiotics.
- Minimum of 2 (two) blood samples available for PCT value assessment between 6 and 48 hours apart.

4.2.2 Exclusion Criteria

- Patient has tested positive for SARS-CoV-2
- Patients who are not admitted to the hospital
- Patients admitted to home health
- Major surgeries, defined as any procedure in which an incision is made with the exception of superficial procedures (eyes, cornea, skin, dental procedures), organs removed, or normal anatomy altered (e.g. open thoracic, abdominal and/or major orthopedic surgery), in the past 1 month or expected surgical procedure or patient receiving antibiotics for surgical prophylaxis
- Known Pregnancy
- Primary and acquired cell-mediated immune deficiency (HIV with CD4 <350 cells/mm^3; with receipt of systemic chemotherapy and/or biologics in the past 3 months for reasons other than malignancy)
- Active metastatic cancer or neuroendocrine tumor or liquid tumor and/or on check point inhibitors within 3 months or has signs of mucositis (e.g. mouth lesions or intestinal bleeding).
- Neutropenia (<1,500 ANC)
- Patients with cystic fibrosis
- Infection where long courses of antibiotics are the standard of care (more than 2 weeks) other than for anti-inflammatory reasons
- Concomitant non-pulmonary bacterial infection that requires antibiotic therapy based on an active medical team decision.
- Antibiotics given for non-infectious indications (e.g. rifaximin for hepatic encephalopathy)
- Patients receiving dialysis
- Patients with solid organ transplant, bone marrow transplant or stem cell transplant recipient
- ST elevation myocardial infarction
- Prior enrollment into this study within 30 days
- Patient experiencing major trauma defined as any injury that could cause prolonged disability and/or an Injury Severity Score >15, and/or burns or patient under extracorporal circulation confirmed by a second research staff member.
- Patient with acute viral hepatitis and/or decompensated severe liver cirrhosis (Child-Pugh Class C).
- Patient with prolonged or severe cardiogenic shock defined as decreased cardiac output leading to end organ injury (e.g. severe hypotension or AKI or oliguria or altered mental status or cool extremities or respiratory distress AND evidence of metabolic acidosis on lab testing).
- Patient with pancreatitis, chemical pneumonitis or heat stroke
- Active infection with invasive fungal pathogen (e.g. candidiasis, aspergillosis) or plasmodium falciparum malaria or mycobacteria

- Patient under treatment with OKT3 antibodies, OK-432, interleukins, TNF-alpha and other drugs stimulating the release of pro-inflammatory cytokines or resulting in anaphylaxis.
- Patient is under hospice care
- Patient with ventilator-associated pneumonia
- Patients with untreated, active, and symptomatic autoimmune disease
- Patients actively enrolled in other clinical trial involving immunomodulatory therapy.
- Patient with empyema, abscess, or cavitary/necrotizing pneumonia

4.2.3 Definition of suspected or confirmed LRTI

-Pneumonia requires one respiratory symptom plus one finding during auscultation or one sign of infection evidenced by core temperature of 38C, shivering, or a leukocyte count greater than 12,000u/µL or less than 4,000u/µL independent of antibiotic pretreatment.

- **pneumonia** will be defined as a new infiltrate on chest radiograph as defined by the IDSA/ATS 2007 CAP Guidelines.

4.2.4 Definition of treatment or readmission for CDI

- Treatment for CDI which consists of oral vancomycin, fidaxomicin, or oral or IV metronidazole or fecal microbiota transplantation
- Hospital re-admission within 30 days after enrollment coded for a primary diagnosis of CDI using ICD-10

4.2.5 Definition 'until day 30'

Day 30 is defined as the thirtieth calendar day after ED or hospital admission.

4.2.6 Monthly patient report

A report with the names and dates of birth of all Mass General Brigham enrolled patients will be created in REDCap every month. This report will be checked to make sure there are no duplicate patients enrolled at different sites within 30 days of the patient's original enrollment.

4.2.7 Cross checking charts

Information entered in REDCap by research staff will be subject to detailed cross check by one of the other unblinded study coordinators. Select study coordinators will be checking information from another site using EPIC.

Information to be cross-checked includes:

Admission date
Discharge Date
PCT values
Composite adverse events
Antibiotics names (enrollment and daily)
Antibiotics doses

Discharge antibiotics names
Discharge antibiotics doses
Discharge antibiotics duration
Survival at day 30

In the case of errors in 3 different sections and/or a 15% error of all values, all information related to the enrolled subject will be cross-checked by the study coordinator.

4.3 Estimated Study Duration and Study Centers

Start of enrollment Feb 2021

Last patient out Jun 2023

1. Massachusetts General Hospital, Department of Medicine, Boston, MA, USA
2. North Shore Medical Center, Department of Medicine, Salem, MA, USA
3. Martha's Vineyard Hospital, Department of Medicine, Oak Bluffs, MA, USA
4. Grady Memorial Hospital, Department of Medicine, Atlanta, GA, USA
5. Charlotte Hungerford Hospital, Department of Medicine, Torrington, CT, USA
6. Texas Health Harris Methodist Hospital-Fort Worth, Department of Pharmacy, Fort Worth, TX, USA

5 BLOOD SAMPLING

5.1 Collection of specimen

Left over serum from daily routine sampling will be collected in every study patient (intervention and control) and PCT will be measured. Samples should be processed according to clinics' standard operating procedures to gain serum.

5.2 Handling of specimen and labeling of PCT measurements

All sample processing should occur at room temperature (RT) at the time points specified in section 4.1. Samples should be processed according to the Elecsys B·R·A·H·M·S PCT™ or Abbott Alinity package insert, depending on site.

All samples will be coded in the eCRF using a unique study identifier.

6 RANDOMIZATION AND MEASUREMENT OF PROCALCITONIN

6.1 Randomization

Admitted patients will be screened, and eligible patients will be randomly assigned in a 1:1 ratio to the (i) PCT algorithm + stewardship team arm or (ii) the standard care arm.

6.2 Procalcitonin (PCT) Measurement

Procalcitonin will be measured with the Elecsys B·R·A·H·M·S PCT™ assay or Abbott Alinity and site personnel will be responsible for PCT measurements according to standard hospital procedure.

PCT results will be unblinded in the PCT arm (i.e. antibiotic management guided by the PCT algorithm + stewardship team) and blinded in the control arm (i.e. antibiotic management guided by standard of care). Research staff will enter PCT results in the eCRF (REDCap) and also ensure that the stewardship team views the results and makes a recommendation for PCT arm patients at the time frames specified in section 4.1.

Every site will have an SOP or delegation log with all key personnel listed including the core lab director/manager who will have confirmed that their site has PCT testing validated and ready for use.

If during the hospital course, patients meet an enrollment ineligibility criterion (e.g., developed a non-pulmonary infection, had to undergo a major surgery…), PCT levels will stop being measured and no further intervention from the stewardship team will be made. However, patients will continue to be monitored.

7 STUDY DATA

Data from the participating patients will be collected in electronic Case Report Forms ("CRF") (see 9.4 Case Report Form). These clinical parameters will be collected to determine the clinical status of the patients.

7.1 Clinical Data Collection

The following clinical parameters will be collected in the corresponding eCRFs:

- **Socio-demographics at baseline PCT measurement D0 only** (age, gender, race, weight)
- **Hospitalization Details** (Enrollment date, time, number of days in the ICU, number of days in the general ward, number of mechanical ventilation days; admission date, time, diagnosis; discharge date, time diagnosis; ICU admission, date, time, reason for ICU and hospital admission)
- **Medical History** (history of present illness, list of chronic conditions)
- **Clinical Assessment** (date, time, physical exam, chief complaint, suspected site of infection, PSI, CURB 65 score)

- **Vital Signs at rest** (heart rate, respiratory rate, blood pressure, $SpO_{2,}$)
- **Imaging Results for each image ordered while enrolled** (Chest radiograph, Chest CT: Date, time, results summary)
- **Laboratory Values included in the standard care of a patient hospitalized with suspected infection, daily as available** (date, time of blood draw; Complete Blood Count (CBC), serum creatinine, aspartate aminotransferase (AST), alanine transaminase (ALT) and serum total bilirubin, C-reactive Protein (CRP), lactate, # of blood cultures taken per patient, blood and sputum culture results (date/time, infecting pathogen), urine legionella and/or urine pneumococcus (if available), Procalcitonin (PCT))
- **Antibiotic Therapy** (agent, dosing, date and time at start and stop). More specifically, each agent will be documented daily as being started, continued or stopped including date and time of start and stop.
- **Antibiotic Therapy Decision Rationale at start/stop** (reasons for starting, stopping and/or not starting new therapy (drop down: PCT Algorithm + clinical status, improving clinical status, worsening signs and symptoms, clinical assessment did not match PCT algorithm, other (free text)).
- **Presence of pre-defined overruling criteria** (indicated according to Appendix A, 11.2)
- **Reason if recommendation from stewardship team is overruled** (Clinician gave antibiotics before recommendation was available; Clinician believes bacterial infection present; Clinician unfamiliar/uncomfortable/disagrees with PCT value; Attending physician overruled; Patient ' s clinical condition is worsening/severely ill; Borderline PCT result; Patient expectations/satisfaction required antibiotics; COPD exacerbation/flare for anti-inflammatory properties (particularly for azithromycin); Meets guideline criteria for ABX in COPD flare; Other, free text))
- **Antibiograms –** antibiotic susceptibility will be collected to determine evolution of multi-drug resistant flora.
- **Secondary infections –** microbiological evidence of secondary infection will be captured to monitor patients throughout the patient's hospitalization
- **Concomitant Therapy -** (list of current medications)
- **Azithromycin** (query at time of randomization and on study day 5 if used for non-antibiotic purposes according to Appendix G)
- **Survival status** (at ICU discharge, hospital discharge, 30-days after discharge if available)
- **CDI status** occurs during hospitalization or is identified upon rehospitalization within 30 days after enrollment
- **Disposition** (date last follow up and disposition: dead, alive, unknown)
- **Complications until Day30** (Septic shock, mechanical ventilation, renal failure, lung abscess/empyema, development of pneumonia in non-pneumonia LRTI: date and time at start and stop)

7.2 Healthcare Resource Utilization Data

- **Cost of Antibiotics** (total cost of antibiotics per patient inclusive of antibiotic, tubing, IV bag, discharge antibiotic prescription)
- **Total per patient cost** (including blood cultures and mechanical ventilation days)
- **Antibiotic ADRs (e.g. CDI)**
- **AB days difference plus prescriptions avoided, and infection adverse event incidence modeling**[29]
- **Cost of readmissions**
- **Cost of Procalcitonin**

8 STATISTICS

For more detailed information regarding the statistics portion, please refer to the Statistical Analysis Plan (SAP).

8.1 Study Design

8.1.1 Study type

Prospective randomized controlled two-arm multi-center trial, see Section 4.

8.1.2 Study goal

The study goal is to validate that a specified PCT algorithm applied to non-COVID-19 patients hospitalized with suspected pneumonia

1. reduces antibiotic exposure specified as an increase of *short* antibiotic pneumonia treatments lasting less than 4 days,
2. is not inferior concerning safety according to composite adverse events until day 30, and
3. reduces antibiotic exposure specified as a decrease of antibiotics prescribed at discharge for pneumonia treatment.

8.1.3 Randomization

Patients will be randomized with equal 50% probability to the two treatment arms “PCT arm” and “control arm”, see Section 6. Block randomization per study site will be applied, with random block length in order to prevent the possibility of predicting study arm assignments.

8.2 Mathematical Definitions

8.2.1 Short antibiotic treatments (“shortABx”, primary endpoint)
will be encoded as the proportion of patients per study arm (PCT arm, control arm) with less than 4 days of antibiotic duration

“antibiotic duration” (third secondary endpoint) is defined as the number of days per patient with antibiotic treatment for pneumonia comprising the number of days of antibiotic treatment during hospitalization (“ABx-days$_{hospital}$”, starting with the first day of PCT measurement which is one day

before enrollment into the study, counting all days with antibiotics not marked "not used for pneumonia") and the number of prescribed days of antibiotic treatment at hospital discharge ("ABx-days$_{\text{prescribed at discharge}}$", counting all days with antibiotics marked "to treat pneumonia"). The resulting sum will be bounded up to a maximum follow-up time of 30 days:

Antibiotic duration = min(30, ABx-days$_{\text{hospital}}$ + ABx-days$_{\text{prescribed at discharge}}$)

8.2.2 The first secondary endpoint **"composite adverse events until day 30"** ("CAE30") will be encoded as the patient level Boolean inclusive disjunction ("OR") of the following eight binary (true/false) single adverse event endpoints (1a) all-cause in-hospital mortality, (1b) all-cause mortality after discharge (as available), (2) septic shock (vasopressor use for > 1 h), (3) mechanical ventilation (via endotracheal tube), (4) needed dialysis, (5) lung abscess/empyema or (6) hospital readmission.

The variable CAE30 mirrors the safety endpoint for pneumonia used in the study ProACT[8]. And, also as in ProACT, the endpoint will be analyzed in the form of study-arm-specific proportions, see Section 8.6.

8.2.3 The second secondary endpoint "**antibiotic exposure at discharge"** ("prescribedABx") will be encoded as the proportion of patients per study arm (PCT arm, control arm) with antibiotic prescription for pneumonia treatment at discharge from index hospitalization.

8.2.4 The third secondary endpoint **"antibiotic duration"** will be computed per patient as described in Subsection 8.2.2.

8.2.5 The fourth secondary endpoint "**days of therapy per 1000 patient days**" will be computed per patient i as follows (i: index distinguishing different study patients):

DoT(patient i) = antibiotic duration(patient i) / los30(patient i) x 1000

with length of stay of patient i

los30(patient i) = min(30, number of hospital days of patient i).

Note that DoT(patient i) is not capped by 1000 because antibiotic duration also includes antibiotics days prescribed at discharge while los30 only counts the number of in-hospital days.

8.2.6 The fifth secondary endpoint **"antibiotic days prescribed at discharge**" will be computed per patient as the number of prescribed days of antibiotic treatment at hospital discharge counting all days with antibiotics marked "to treat pneumonia".

8.2.7 The sixth secondary endpoint **"treatment or readmission for CDI until day 30 after enrollment"** will be encoded in binary Boolean form ("true": patient treated or re-hospitalized for CDI until day 30 after enrollment, otherwise "false").

8.2.8 The seventh secondary endpoint **"length of stay in hospital until day 30**" ("los30") will be computed per patient as described in the previous subsection.

8.2.9 The eighth secondary endpoint "**length of stay in ICU**" ("losICU30") will be computed analogously to los30 but will only count days on ICU:

losICU30 = min(30, number of ICU days of patient i).

8.2.10 The ninth secondary endpoint "**ICU admission until day 30**" will be encoded per patient in binary form ("true": patient admitted to ICU within study follow-up time of 30 days, otherwise "false").

8.2.11 Exploratory Endpoints

All the individual variables constituting the composite safety endpoint "composite adverse events until day 30" will be considered as exploratory endpoints and be encoded in Boolean-binary form (true/false).

8.3 Primary Study Hypothesis

For the primary study endpoint "**short antibiotic treatments**" ("shortABx"; proportion of patients with short antibiotic treatments of pneumonia less than 4 days) the study hypotheses for statistical inference are as follows:

H0: The probability of patients with short antibiotic treatment of pneumonia is smaller or equal in the PCT arm versus the control arm.

H1: The probability of patients with short antibiotic treatment of pneumonia is greater in the PCT arm than in the control arm.

*Note that t*he study goal is one-sided: to validate a shortABx probability in the PCT arm that is higher than the shortABx probability in the control arm (see Section 8.6 and 8.9; one-sided statistical testing at 2.5% significance level controlled for multiple testing / interim analyses. Bayesian statistics with uninformative priors will be applied for analysis (see Section 8.6.2).

8.4 Analysis Populations

The intention-to-treat ("**ITT**") patient population will comprise all randomized non-COVID-19 patients.
The per-protocol ("**PP**") patient population will comprise all ITT patients
(a) fulfilling study inclusion criteria,
(b) not meeting study exclusion criteria at enrollment,
(c) even if meeting study exclusion criterion after enrollment or meeting a pre-defined overruling criterion,

(d) with PCT measurements performed daily in the first week and thereafter at least every 48 hours during hospitalization and antibiotic treatment,
(e) if assigned to PCT group, antibiotic steward ship team recommendation given to the treating physician on enrollment day and for each PCT measurement taken Monday-Friday described under d) and antibiotics stopped according to the PCT algorithm. An exception will be made if the stewardship team decides the patient will be given the same recommendation throughout their hospitalization.

Consequently, it should be noted that stewardship team recommendations should also be provided for patients meeting pre-defined overruling criteria (e.g., need for ICU care) since such patients may still qualify for the per-protocol population.

Patients of the PCT arm who are discharged before that day's PCT has resulted will be excluded from the per protocol population. Patients in the PCT arm who were continued on antibiotics despite a weekend/holiday/no stewardship team member available PCT value that would have resulted in an stewardship team recommendation to stop antibiotics will also be excluded from the per protocol population. Patients in the PCT arm whose antibiotics were discontinued despite weekend/holiday/no stewardship team member available PCT value that would have resulted in continuation of antibiotics will also be excluded.

(f) if assigned to control group, no PCT measurements to treating physician during index hospitalization.

Primary analysis of the superiority endpoint "antibiotic exposure" will be conducted on the basis of the ITT patient population. Analysis of the non-inferiority endpoint "composite adverse events until day 30" will be conducted on the basis of PP and ITT patient population. PP-results will be compared and discussed with corresponding results obtained for ITT patient population.

8.5 Handling of Missing Data

Complete case analysis will be conducted as long as the fraction of missing values for "composite adverse events until day 30" and "antibiotic exposure" ("short antibiotic treatments" and "antibiotic exposure at discharge") remain in the range of up to 5%. If the number of missing values turns out to be above 5%, an additional analysis will be conducted using **multiple or Bayesian imputation**. In any case, the possible impact of missing values on study results will be assessed by **sensitivity analysis** using worst-case and best-case imputations.

8.6 Statistical Analysis

8.6.1 Descriptive Statistics

The first step of statistical data analysis will comprise the application of conventional data cleaning and checking procedures including assessment of missing data and outliers, and uni- and bivariate plausibility checks. Data verifications and if applicable corrections will be requested.

Next, a thorough description of the overall study sample and of the two randomized study arms will be conducted for the two analysis populations ITT and PP. Frequency counts will be used for nominal variables and means with standard deviations or medians with inter-quartile ranges will be used for numerical variables as appropriate. Statistical hypothesis tests will be used to check the success of

randomization, e.g. chi-square test, Wilcoxon signed-rank test or t-test.

8.6.2 Primary Analysis of Antibiotic Exposure

The primary endpoint "short antibiotic treatments" will be analyzed for superiority. We will assess the differences in proportions by Bayesian analysis assuming binomially distributed events (beta-distributed study-arm specific probabilities) and uninformative uniform priors.

More specifically, the following generative model will be used:

$N^{s}_{PCT} \sim$ Binomial(N_{PCT}, p_{PCT})
$N^{s}_{Ctrl} \sim$ Binomial(N_{Ctrl}, p_{Ctrl})
p_{PCT}, $p_{Ctrl} \sim$ Uniform(0, 1)
with
N^{s}_{PCT}, N^{s}_{Ctrl} : number of patients with shortABx of the PCT arm and control arm, respectively
N_{PCT}, N_{Ctrl} : number of patients randomized to the PCT arm and control arm, respectively
p_{PCT}, p_{Ctrl} : shortABx probability for patients of the PCT arm and control arm, respectively

Differences between study-arm specific probabilities will be computed by Monte Carlo simulation with sampling from study-arm specific posterior probabilities. Success of the analysis of antibiotic exposure is specified by more than 98.5% [1] posterior probability for more frequent short antibiotic treatments in the PCT arm than in the control arm, i.e.,

Probability[prob(short-ABx | PCT arm) > prob(short-Abx | control arm)] > 98.5%
with
prob(short-ABx | PCT arm) : probability of short antibiotic treatment for patients randomized to the PCT arm,
prob(short-ABx | control arm) : probability of short antibiotic treatment for patients randomized to the control arm.

The primary analysis will be conducted based on the ITT population. The analysis will also be conducted based on the PP patient populations and ITT- and PP-results will be compared and discussed.

8.6.3 Secondary Analysis of CAE30

The first secondary endpoint "composite adverse events until day 30" (CAE30) will be analyzed for safety non-inferiority of the PCT arm vs. the control arm on the basis of the PP patient population. The analysis will also be conducted on the basis of the ITT patient populations and ITT- and PP-results will be compared and discussed. Differences in proportions of CAE30 between PCT arm and control arm will be assessed by Bayesian analysis assuming binomially distributed events (beta-distributed study-arm specific CAE30 probabilities) and uninformative uniform priors. More specifically, the following generative model will be used:

$NE_{PCT} \sim$ Binomial(N_{PCT}, p_{PCT})
$NE_{Ctrl} \sim$ Binomial(N_{Ctrl}, p_{Ctrl})

p_{PCT}, p_{Ctrl} ~ Uniform(0, 1)

with

NE_{PCT}, NE_{Ctrl} : number of patients with CAE30 of the PCT arm and control arm, respectively
N_{PCT}, N_{Ctrl} : number of patients randomized to the PCT arm and control arm, respectively
p_{PCT}, p_{Ctrl} : CAE30 probability for patients of the PCT arm and control arm, respectively

Differences between study-arm specific CAE30 probabilities will be computed by Monte Carlo simulation sampling CAE30 probabilities p_{PCT}, p_{Ctrl} from their analytically computed study-arm specific posterior probabilities. Study success is specified by more than 98.5%[1] posterior probability for a CAE30 probability of patients of the PCT arm smaller than the CAE30 probability of patients of the control arm plus 10% (NI margin):

Probability(CAE30 probability of PCT arm < CAE30 probability of control arm + 10%) > 98.5% [1],

or with the above introduced notation

Probability($p_{PCT} < p_{Ctrl} + 0.1$) > 98.5% [1] .

8.6.4 Secondary Analysis of Antibiotic Exposure

The second secondary endpoint "antibiotic exposure at discharge" will be analyzed for superiority. We will assess the differences in proportions by Bayesian analysis assuming binomially distributed events (beta-distributed study-arm specific probabilities) and uninformative uniform priors. More specifically, the same generative model will be used as the one for short antibiotic treatments (see Section 8.6.2). Differences between study-arm specific probabilities will be computed by Monte Carlo simulation with sampling from study-arm specific posterior probabilities. Success of the analysis of antibiotic exposure at discharge is specified by more than 98.5% [1] posterior probability for less antibiotic exposure of the PCT arm than of the control arm, i.e.

Probability[prob(discharge-ABx | PCT arm) < prob(discharge-ABx | control arm)] > 98.5%

with

prob(discharge-ABx | PCT arm) : probability of prescribed antibiotics at hospital discharge for patients randomized to the PCT arm
prob(discharge-ABx | control arm) : probability of prescribed antibiotics at hospital discharge for patients randomized to the control arm

The analysis will be conducted first based on the ITT population. The analysis will also be conducted based on the PP patient populations and ITT- and PP-results will be compared and discussed.

8.6.5 Further Secondary and Exploratory Analysis

[1] Simulation of the selected adaptive Bayesian design with specified interim analyses based on 200, 350, 550, and 650 patients showed that the one-sided type-I error was controlled to be below 2.5% by choosing the value 98.5% as the threshold for study success. See [SAP4.0] for more information.

Secondary and exploratory endpoints will be analyzed according to variable type:

Numerical endpoints:
Distributions of numerical variables will be visualized for all patients and separately for PCT and control arm. Study arm-specific distributions will be compared with each other by statistical tests (e.g. Wilcoxon rank-sum tests), and by comparing descriptive summary measures (e.g. group medians and means).

Binary endpoints:
2 x 2 contingency tables will be reported for counts stratified according to study arm (PCT, control) and endpoint level (true/false). Associations between study arms and endpoints will be analyzed by statistical tests (e.g. chi-square test or Fisher's exact test). Proportions and two-sided 95% confidence intervals or Bayesian credible intervals will be computed for all patients and separately for PCT and control arm.

8.7 Sensitivity Analysis

Sensitivity analysis will be conducted to assess the robustness of primary and secondary analysis results.

- The results obtained for ITT and PP patient population will be compared and discussed.
- Safety analysis (as described in Section 4.4) will also be conducted for the alternative safety endpoint definition CAE30' only counting safety adverse events that occur at least 24 hours after patient randomization. The results will be compared and discussed with the results for counting all safety adverse events after patient randomization.
- For endpoints CAE30, shortABx, and prescribedABx the study-arm specific proportions will be compared and discussed with the corresponding proportions that were obtained for the two run-in studies that were performed for accurate calculation of sample size and required power; these first two ProSAVE pilot-level study batches were named "ProSAVE-1 & -2" (comprising 95 (ITT) and 60 (PP) non-COVID patients not transferred to ICU within 24 hours, patients enrolled from 2020-05-28 to 2021-02-24).
- The safety endpoint CAE30 will be analyzed and discussed regarding its individual constituent adverse event variables.

8.8 Sample Size

We plan to enroll an adequate number of patients for the study by a Bayesian adaptive design with a maximum number of 700 patients and interim analyses after the enrollment of 200 patients, 350 patients, 550 patients and 650 patients.

Sample size estimation was based on the observed results of the first two ProSAVE pilot-level study batches, see Table 8.1 (analysis population and endpoint specific results; "ProSAVE-1 & -2" comprising 95 (ITT) and 60 (PP) non-COVID patients not transferred to ICU within 24 hours, patients enrolled from 2020-05-28 to 2021-02-24). 5000 clinical trials were simulated per analysis setting (study endpoint, analysis population and assumed fixed sample size from 200 to 700 patients) with the distribution of events according to predictive posterior distributions (computed for the assumed sample sizes from pilot posterior probability distributions derived with uninformative conjugate priors). The corresponding statistical power estimates were determined as the proportions of study successes when applying the analyses and success criteria specified in Section 8.6.

We considered a sample size of about 500 patients to be adequate for the study because a statistical power of 90% was reached with 500 patients for the safety endpoint CAE30 assuming pilot ITT results.

In order to account for additional sources of variation and missing data, e.g. due to seasonal changes during the year, possible influences of a potential fourth wave of COVID-19 and the inclusion of additional study sites, we specifed the study design in an adaptive way with planned interim analyses after 200, 350, 550 and 650 patients and a maximum number of 700 enrolled patients.

Table 8.1: Pilot study results for the safety endpoint "CAE30" and for the antibiotic exposure endpoints "shortABx" and "prescribedABx" for ITT and PP patient populations.

Simulation scenario			Pilot study results			
n	Endpoint	Data	PCT		Control	
			n	n_{pos}	n	n_{pos}
1	CAE30	pilot, ITT	48	3	47	10
2		pilot, PP	30	1	30	7
3	shortABx	pilot, ITT	48	14	47	5
4		pilot, PP	30	12	30	3
5	prescribedABx	pilot, ITT	47	15	46	24
6		pilot, PP	30	7	29	19

Table 8.2: Estimation of statistical power (i.e. proportion of simulated trials reaching study success) for the three study endpoints "CAE30", "shortABx" and "prescribedABx" with fixed sample sizes from 200 to 700 patients (total; 100 to 350 patients per study arm) assuming effect sizes (estimate and uncertainty) of the "ProSAVE-1 & -2" pilot data results.

Data	# Patients		Statistical Power		
	Total	Per arm	CAE30	shortABx	prescribedABx
pilot, ITT	200	100	79%	82%	76%
	300	150	84%	86%	81%
	400	200	87%	90%	86%
	500	250	90%	92%	87%
	600	300	91%	93%	88%
	700	350	92%	94%	90%
pilot, PP	200	100	88%	94%	98%
	300	150	91%	96%	99%
	400	200	93%	97%	99%
	500	250	93%	98%	100%
	600	300	95%	98%	99%
	700	350	95%	98%	100%

The adequacy of the study design was re-assessed for the following changes: (a) exchange of primary endpoint and (first) secondary endpoint (new primary endpoint: shortABx, new first secondary endpoint: CAE30), (b) change of CAE30 inference from superiority to non-inferiority, and (c) change of

the times of interim analyses from 500 and 600 patients to 550 and 650 patients, respectively. The evaluation of the study design was done analogously to the initially applied method described in Section 2.3.2 of [SAP3.0] (clinical trial Monte Carlo simulations based on pilot study results). The new simulations (including some improved approximations of protocol and data generation) for the implemented changes resulted in an increase of the analysis parameter γ from 0.9785 to 0.985 in order to keep type-I error control at 2.5%. We valued the new design adequate with statistical powers of 99%, 75% and 48% to show shortABx superiority, CAE30 non-inferiority and prescribedABx superiority, respectively, assuming half of the effects observed in the pilot study concerning antibiotic exposure ($RR_{shortABx}$ = 1.9 and $RR_{prescribedABx}$ = 0.8) and considerably smaller CAE30 effects than observed in the pilot study (RR_{CAE30} = 0.9 for one tenth of the effect observed in the pilot study).

8.9 Interim Analyses

Interim analyses will be conducted after the enrollment of 200 patients, 350 patients, 550 patients and 650 patients.

After the enrollment of 200 and 350 patients an interim analysis will be conducted applying a criterion for potentially *stopping for futility*. A non-binding recommendation to stop patient enrollment for futility will be given if interim results are not in a "promising zone" to reach the CAE30 success criterion. More specifically, the stopping recommendation will be given if the posterior predictive probability of CAE30 success (i.e., proving non-inferiority) with the maximum number of 700 patients is below a specific futility cut-off Θ^F_N = 0.1 with N = 200 or 350 representing the respective enrollment status:

Probability(CAE30 success with 700 patients | interim data) < Θ^F_N , i.e.
Probability(Posterior predictive probability($p_{PCT} < p_{Ctrl} + 0.1$, 700 patients | interim data) > 98.5% [1]) < 0.1

After the enrollment of 550 and 650 patients an interim analysis will be conducted applying criteria to stop potentially (a) for futility or (b) for study success:

a. ***Stopping for futility:***

A non-binding recommendation to stop patient enrollment for futility will be given if interim results are not in a "promising zone" to reach the CAE30 success criterion. More specifically, enrollment will be stopped if the posterior predictive probability of CAE30 success with the maximum number of 700 enrolled patients is below a specific futility cut-off Θ^F_N = 0.1 with N = 550 or 650 representing the respective enrollment status:

Probability(CAE30 success with 700 patients | interim data) < Θ^F_N, i.e.
Probability(Posterior predictive probability($p_{PCT} < p_{Ctrl} + 0.1$, 700 patients | interim data) > 98.5% [1]) < 0.1

b. ***Stopping for success:***

Enrollment will be stopped for success if interim results reveal a sufficiently high probability that success criteria are reached for the endpoints CAE30, shortABx and prescribedABx. More specifically, enrollment will be stopped if the posterior predictive probabilities of the three endpoints CAE30, shortABx and prescribedABx for the respective number

of enrolled patients are above the cut-off $\Theta^{s}_{N} = 0.9$:

Probability(CAE30 success with enrolled patients | interim data) > Θ^{s}_{N} AND
Probability(shortABx success with enrolled patients | interim data) > Θ^{s}_{N} AND
Probability(prescribedABx success with enrolled patients | interim data) > Θ^{s}_{N}

Note: Use of the posterior predictive probability will allow to conduct the interim analysis in a timely manner without the need to wait for the completion of the 30 days follow-up times of all patients. Thereby, missing or incomplete endpoint data of enrolled patients will be imputed by predicted endpoint data including its respective level of uncertainty.
The cut-off parameters of the stopping criteria Θ^{F}_{200}, Θ^{F}_{350}, Θ^{F}_{550}, Θ^{F}_{650}, Θ^{s}_{550} and Θ^{s}_{650} were specified by numerical simulations as $\Theta^{F}_{200} = \Theta^{F}_{350} = \Theta^{F}_{550} = \Theta^{F}_{650} = 0.1$ and $\Theta^{s}_{550} = \Theta^{s}_{650} = 0.9$ to assure a sufficiently controlled one-sided type-I error < 2.5% and a sufficiently high statistical power (study success probability) assuming pilot study results, see [SAP3.0].

8.10 Safety Analyses for DMC (See DMC Charter for detailed information)

Safety analyses will be conducted at least twice when 350 and 550 patients are enrolled. The DMC will receive corresponding safety datasets and safety relevant interim analysis results:

a. Safety datasets will be on patient level and comprise at least the following information: study arm assignment, CAE30, and all single binary CAE30 endpoint components. The DMC may request additional data at its discretion.
b. As safety relevant interim analysis results the DMC will receive:
    a. A contingency table of study arm (PCT, control) vs. safety endpoint CAE30 (event occurred yes/no/NA; NA for patients with incomplete follow-up and no event yet)
    b. 95% credible intervals of study-arm specific CAE30 probabilities and of the difference in CAE30 probability between study arms (complete case analysis)
    c. Posterior probability distributions on the basis of all patients with CAE30 data (complete case analysis) of
        a. study-arm specific posterior probability distributions of CAE30
        b. the difference in CAE30 probability between study arms
    d. Predictive posterior distributions on the basis of all enrolled patients (including patients with missing or incomplete CAE30 data) of
        a. study-arm specific posterior probability distributions of CAE30
        b. difference in CAE30 probability between study arms

8.11 Health Economic Evaluation

The clinical outcomes of the study will be analyzed from a health economic hospital perspective, extrapolation to third party payer remains optional. Clinical data and local cost data will be processed in the previously published/under publication Health Economic Model (Janne C Mewes et. al., The cost impact of PCT-guided antibiotic stewardship versus usual care for hospitalized patients with suspected sepsis or lower respiratory tract infections in the US: a health economic model analysis).[28] All available information will be used in the model. Missing/confidential cost data will be substituted with publicly available data and highlighted accordingly.

These clinical parameters will be multiplied with the respective cost per unit, e.g. 1 day of mechanical ventilation, and its differences will be calculated, to understand the changes in cost when using PCT. All cost results per clinical parameter will be aggregated to average cost of 1 patient of each group, finally the cost of each study group will be modelled.

All findings will be discussed in the local hospital context as well as how these compare to the overall situation in the United States.

9 REGULATORY & COMPLIANCE

9.1 IDE-status & Adverse Device Effect Reporting

The proposed IVD study is exempt from most provisions of the IDE regulation as it fulfills all of the following criteria. The IVD:

- is properly labeled in accordance with 21 CFR 809.10(c);
- is noninvasive;
- does not require an invasive sampling procedure that presents significant risk;
- does not by design or intention introduce energy into a subject; and
- is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

Elecsys B·R·A·H·M·S PCT™ immunoassay or Abbott Alinity will be used according to the Indications for Use outlined in the package insert and cleared by the FDA as safe and efficacious for the intended population. Events such as death or worsening of a medical condition will be considered study endpoints and not device related or study related adverse events.

Adverse device effects are reportable if they include deaths and serious injuries that the medical device under investigation may have caused or contributed to, i.e., the device may have directly caused the events or played a role in the events.

The IVD test will be used in a laboratory with trained lab personnel following the manufacturer's instructions for use in the package insert and analyzer manual. Therefore, there is no risk of serious device related adverse events to the patient. Laboratory staff will follow the instruction for use of the device including information on limitations, warnings and precautions. Therefore, there is no risk of serious device related adverse events to the laboratory staff.

9.2 Informed Consent

Procalcitonin will be measured and interpreted within the context of its intended use as cleared by the FDA. Additionally, Procalcitonin will use leftover serum from routine blood draws and results will be interpreted in conjunction with other clinical and laboratory parameters by an Antibiotic Stewardship Team. As such, Informed Consent will be waived for this study.

9.3 Ethics Approval

It is the investigator's responsibility to ensure that this Study Protocol is reviewed and approved by the appropriate Institutional Review Board ("IRB")/Ethics Committee ("EC") (21 CFR 50). If applicable, the IRB/EC must also review and approve the site's Informed Consent form ("IC form") form and any other written information provided to the patient prior to any enrollment of patients and any advertisement that will be used for patient recruitment. The investigator must forward to the B·R·A·H·M·S GmbH copies of the IRB/EC approval or letter indicating the trial is waived from obtaining informed consent which must be received and approved by the B·R·A·H·M·S GmbH prior to the start of the trial.

If, during the trial, it is necessary to amend either the Study Protocol or the Informed Consent form (if applicable), the Principal Investigator will be responsible for ensuring the IRB/EC reviews and approves these amended documents. If applicable, the IRB/EC approval of the amended IC form must be obtained before new patient consent to take part in the trial using this version of the form. Copies of the IRB/EC approval, and as applicable, of the amended IC form, must be forwarded to the B·R·A·H·M·S GmbH as soon as available.

9.4 Case Report Form (CRF)

The data of this study will be obtained by using a web-based electronic case report form ("CRF"). Access to the CRF will be provided via sign on link to a web accessible secured database using role based authenticated user accounts. Users have data entry access for all subjects from their site but data from different sites is segregated by application. At each site, only unblinded research staff will have access to all PCT results of patients (both arms). At predefined points for interim analysis and at the end of the study, the Principal Investigator or study team members will transfer all eCRF data to B·R·A·H·M·S GmbH for analysis.

9.5 Data Management and Confidentiality

Protocol deviations will be monitored and, if evaluable, included in the ITT analysis.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the B·R·A·H·M·S GmbH and their agents. This confidentiality is extended to cover testing of biological specimens and clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

B·R·A·H·M·S GmbH and other authorized representatives, and representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records, pharmacy records, and imaging results for the participants in this study. The clinical study sites will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be stored in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be coded by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected.

9.6 Safety Monitoring

Safety oversight will be under the direction of a Data Monitoring Committee (DMC) composed of individuals with the appropriate expertise, including infectious diseases. The DMC will meet approximately every six months to assess safety data by querying safety outcomes in a proportion of study subjects in each arm.

9.7 Responsibility and Compliance

Quality Assurance ("QA") is maintained to meet practice standards required by the IRB, regulatory agencies. The principal investigator and site investigators will ensure regulatory and clinical study requirements. The internal requirements for the institution are maintained by the institution.

9.7.1 Trial Monitoring

In accordance with applicable regulations, Good Clinical Practice ("GCP"), the investigator will ensure quality oversight and adherence to this protocol.

In particular, the investigator or his delegate will:

- Check and assess the progress of the trial
- Review trial data collected
- Conduct Source Document Verification
- Identify any issues and address their resolution

This will be done in order to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of patients are being protected
- Trial is conducted in accordance with the currently approved protocol (and any amendments), and all applicable regulatory requirements

The investigators agree to allow BRAHMS direct access to all relevant documents including electronic medical records or provide copies of all relevant medical records during a trial audit.

The investigator will also allocate his/her time and the time of his/her staff to the sponsor to discuss findings and any relevant issues.

In addition to contacts during the trial, BRAHMS will also contact the site prior to the start of the trial to discuss the protocol and data collection procedures with site personnel.

9.8 Trial and Site Closure

Upon completion of the trial, the following activities, when applicable, must be conducted by the research staff, principal investigator and B·R·A·H·M·S GmbH as appropriate:

- Data clarifications and/or resolutions
- Review of site trial records for completeness

In addition, B·R·A·H·M·S GmbH reserves the right to temporarily suspend or prematurely discontinue this trial either at a single site or at all sites at any time and for any reason. The principal investigator will inform all trial investigators if the trial is suspended or terminated. The investigators will inform their local /national regulatory authorities (as appropriate) of the suspension or termination of the trial and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB/EC promptly and provide the reason for the suspension or termination.

9.9 Records Retention

In accordance with applicable regulatory requirements, following closure of the trial, the investigator will maintain a copy of all site trial records in a safe and secure location. All records, documents, and supporting material related to the study are required to be retained for a minimum of two years after the latter of either the termination or completion of the study or the date the records are no longer required for supporting a premarket approval application in compliance with 21 CFR 812.140(d) or a premarket notification.

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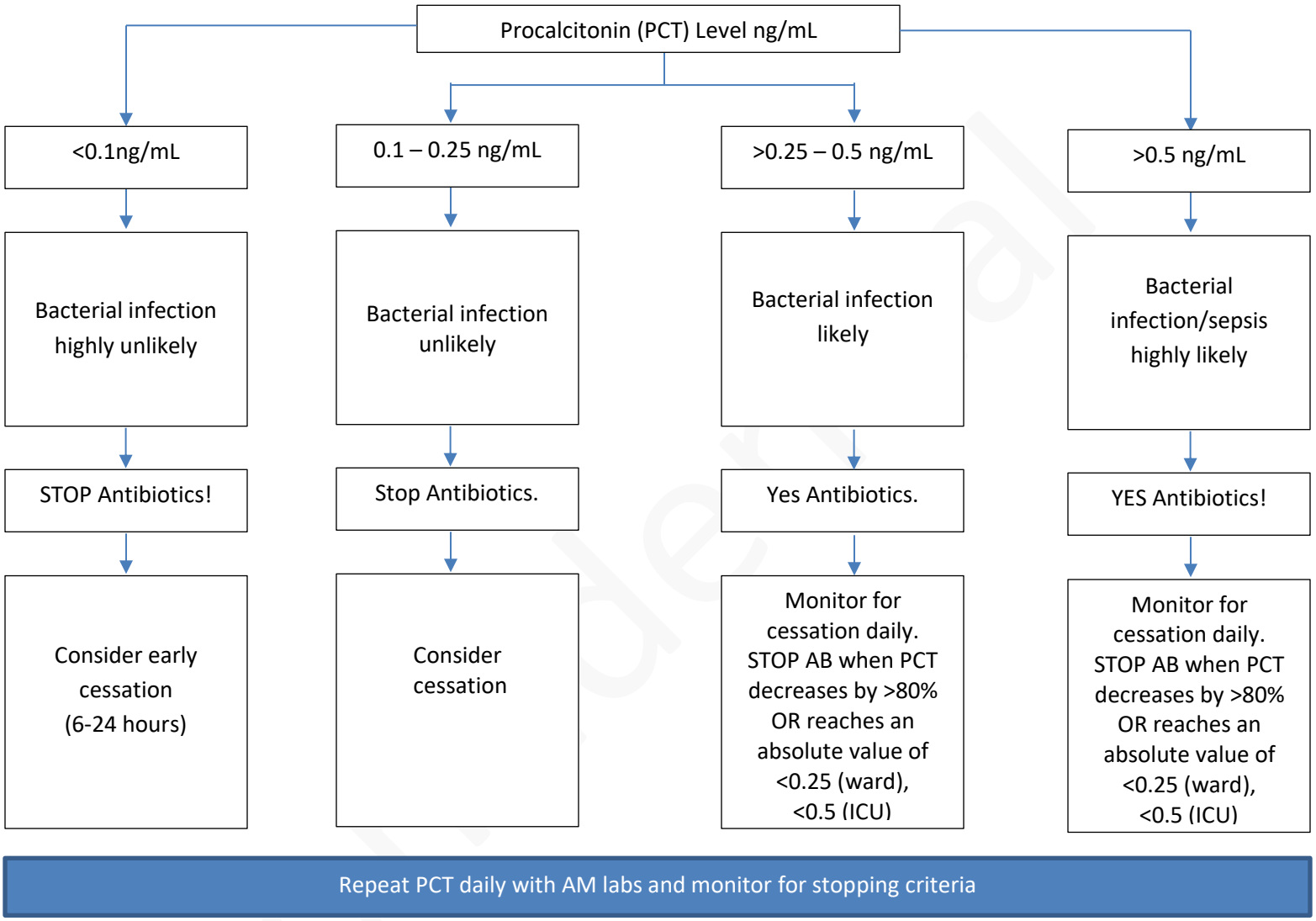
11 APPENDIX A

11.1 PCT Algorithm (Intervention)



11.2 PCT overruling criteria (Intervention)

Antibiotics can be continued in the following situations despite reaching stopping criteria:

- Respiratory instability (taken at rest)
  - RR > 30 breaths per min
- Oxygen saturation <90% on 6 liters of oxygen/minute
  - RR>18 with sustained need (1 hour) for oxygen >4L
- Hemodynamic instability (systolic <90 for more than 1 hour) or vasopressor use >1 hour
- Life-threatening co-morbidity
- Need for ICU care
- PCT < 0.1 PSI V (>130) or CURB-65 >3
- PCT >0.1 and < 0.25 PSI >= IV (91-130) or CURB-65 >2
- Severe immunosuppression

12 APPENDIX B

12.1.1 Elecsys B·R·A·H·M·S PCT™ package insert V3

https://usdiagnostics.roche.com/download/en/document/technical/ms/07301715501v3.pdf

13 APPENDIX C

13.1 CURB-65 Score[9]

(https://www.mdcalc.com/curb-65-score-pneumonia-severity)

Confusion	**No** 0	Yes +1
BUN > 19 mg/dL (> 7 mmol/L)	**No** 0	Yes +1
Respiratory Rate ≥ 30	**No** 0	Yes +1
Systolic BP < 90 mmHg or Diastolic BP ≤ 60 mmHg	**No** 0	Yes +1
Age ≥ 65	**No** 0	Yes +1

14 APPENDIX D

14.1 PSI Score[10]

(https://www.mdcalc.com/psi-port-score-pneumonia-severity-index-cap#evidence)

Patient Characteristics	Points
Demographics	
Age(years): Male: age	—
Female: age	—
Nursing home resident	+10
Co-morbidities	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Examination findings	
Altered mental status	+20
Respiratory rate ≥30/minute	+20
Systolic blood pressure <90 mmHg	+20
Temperature <35°C or ≥40°C	+15
Pulse ≥125/minute	+10
Laboratory findings	
pH <7.35 (do ABG only if hypoxic or COPD)	+30
BUN ≥10.7 mmol/ L	+20
Sodium <130 mEq/L	+20
Glucose ≥13.9 mmol/L	+10
Hematocrit <0.30	+10
PaO_2 <60mmHg or oxygen saturation <90%	+10
Pleural effusion	+30

Risk	Class	Score
Low	I	<51
Low	II	51 - 70
Low	III	71 - 90
Medium	IV	90 - 130
High	V	>130

15 APPENDIX E

15.1 Approved Use of PCT

Used in conjunction with other laboratory findings and clinical assessments, procalcitonin (PCT) is intended for use as follows:

- to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock,
- to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission,
- to aid in decision making on antibiotic therapy, for inpatients or patients in the emergency department with suspected or confirmed lower respiratory tract infections (LRTI) – defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD),
- to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

Two systematic literature reviews were performed to produce both study and patient-level meta-analyses, which are studies that combine and contrast data from multiple sources to identify patterns among study results (FDA public docket FDA-2016-N-2880). The study-level meta-analysis used aggregate descriptive information extracted from publications, and the patient-level meta-analysis used aggregate patient-level data from the raw dataset of each study. Each meta-analysis used random-effects models and calculated point estimates, differences, odds ratios (OR), interquartile ranges (IQRs) and 95% confidence intervals as appropriate. The endpoints evaluated were: proportion of subjects initiating antibiotics, duration of antibiotic therapy, exposure to antibiotics, length of hospital stay, mortality, and complications (patient level only).

The study-level meta-analysis encompassed 11 randomized control trials (RCTs) [12,14,15-20,,24-27] which were published between 2004-2016, and included 4090 patients.

The patient-level meta-analysis encompassed 13 RCTs [12-23, 27] which were published between 2004-2011, and included 3142 patients as listed below.

Publication	N patients	PCT device
Bouadma, 2010	630	B·R·A·H·M·S PCT sensitive KRYPTOR®
Briel, 2008	300	B·R·A·H·M·S PCT sensitive KRYPTOR®
Burkhardt, 2010	550	B·R·A·H·M·S PCT sensitive KRYPTOR®
Christ-Crain, 2004	243	B·R·A·H·M·S PCT sensitive KRYPTOR®
Christ-Crain, 2006	302	B·R·A·H·M·S PCT sensitive KRYPTOR®
Hochreiter, 2009	110	B·R·A·H·M·S PCT LIA®
Kristoffersen, 2009	223	B·R·A·H·M·S PCT sensitive KRYPTOR®
Long, 2011	172	B·R·A·H·M·S PCT sensitive KRYPTOR®

Long, 2009	127	B·R·A·H·M·S PCT LIA®
Nobre, 2008	79	B·R·A·H·M·S PCT sensitive KRYPTOR®
Schroeder, 2009	27	B·R·A·H·M·S PCT LIA®
Schuetz, 2009	1381	B·R·A·H·M·S PCT sensitive KRYPTOR®
Stolz, 2007	226	B·R·A·H·M·S PCT sensitive KRYPTOR®

These meta-analyses concluded that PCT guided antibiotic therapy resulted in:

- 19.2% reduction in relative antibiotic initiation for all patients
- 38% reduction in overall antibiotic exposure (i.e. total days of antibiotic therapy) for inpatients
- 51% reduction in overall antibiotic exposure (i.e. total days of antibiotic therapy) for patients who presented to the Emergency Department and other associated clinics, but were not admitted
- 2.9 day reduction in antibiotic duration [1.25 day reduction in study-level]
- 3.6 day reduction in total antibiotic exposure [2.79 day reduction in study-level]
- No negative effects in regards to mortality, complications, or length of stay

Overview of the patient-level meta-analysis:

Parameter	Standard Care Therapy		PCT Guided Therapy	
	N included	N (%) or Days, median (IQR)	N included	N (%) or Days, median (IQR)
Initiation of antibiotics	1606	1420 (88.4%)	1536	1096 (71,4%)
Duration of antibiotics	1420	10 (7, 12)	1096	7 (4, 10)
Total exposure of antibiotics	1606	9 (8, 12)	1536	5 (0, 8)
30 day mortality	1606	119 (7.4%)	1536	103 (6.7%)
Complications	1606	339 (21.1%)	1536	276 (18.0%)
Hospital length of stay	1583	6 (0, 13)	1508	7 (0, 12)

16 APPENDIX F

Stewardship Team Discordance Survey:

Reason(s) for discordance:

1- Respiratory Rate > 30 breaths per min
2- Patient has significant oxygen desaturation
3- Patient is hemodynamically unstable (e.g. hypotensive or use of vasopressors)
4- Patient has life-threatening co-morbidity or need for intensive care
5- Patient has worsening symptoms
6- Patient has PSI of IV or CURB-65 > 3 or Gold>or=3
7- Patient was started on immunosuppressants
8- Concomitant or localized infection or confirmed pathogen present requiring antibiotics (e.g. abscess, empyema, parapneumonic effusion)
9- You believe bacterial infection is present
10- You disagree with the PCT algorithm
11- Antibiotics are given for non-infectious or anti-inflammatory properties
12- Antibiotics are given for non-pulmonary infection
13- Other (please specify):

17 APPENDIX G

Medical Team discordance Survey:

Reason(s) for discordance:

1- Respiratory Rate > 30 breaths per min
2- Patient has significant oxygen desaturation
3- Patient is hemodynamically unstable (e.g. hypotensive or use of vasopressors)
4- Patient has life-threatening co-morbidity or need for intensive care
5- Antibiotics are given for non-infectious or anti-inflammatory purposes
6- Patient has worsening symptoms
7- patient has PSI of IV or CURB-65 > 3 or GOLD criteria >or= 3
8- Patient was started on immunosuppressants
9- Concomitant or localized infection or confirmed pathogen present requiring antibiotics (e.g. abscess, empyema, parapneumonic effusion)
10- You believe bacterial infection is present while microbiological evidence is lacking

11- You are unfamiliar/uncomfortable/disagree with PCT-guided antibiotic decision making
12- Patient expectations/satisfaction required antibiotics
13- Antibiotics given for non-pulmonary infection
14- Other (please specify):