TITLE: Procalcitonin Antibiotic Consensus Trial **(ProACT)**

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ProACT

(Procalcitonin Antibiotic Consensus Trial)

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ProACT Trial Registration Data

Primary registry and trial identifying number:	ClinicalTrials.gov
Date of registration in primary registry:	May 1, 2014
Primary sponsor:	National Institutes of General Medical Sciences (NIGMS) (1R01GM101197 and 1R34GM102696)
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Public title:	Procalcitonin Antibiotic Consensus Trial (ProACT)
Countries of recruitment:	United States
Health condition(s) or problem(s) studied:	Procalcitonin-guided antibiotic use in lower respiratory tract infection (LRTI)
Intervention(s):	*Experimental:* Reporting of serial procalcitonin results and antibiotic guideline to treating clinicians. Clinicians retain complete decision-making autonomy. *Control:* Usual care; no procalcitonin results will be reported to treating clinicians.
Key inclusion and exclusion criteria:	*Inclusion* - ≥ 18 years old; a primary clinical diagnosis in the ED (emergency department) of acute LRTI (< 28 days duration); clinician willing to consider procalcitonin in antibiotic decision-making. *Exclusion* – systemic antibiotics before ED presentation; current vasopressor use; mechanical ventilation (via endotracheal tube); known severe immunosuppression; accompanying non-respiratory infection; known lung abscess/empyema; chronic dialysis; metastatic cancer; surgery in the past 7 days (excluding minor surgery); incarcerated or homeless; enrolled in ProACT in the past 30 days.

Study type:	Patient-level, multi-center, randomized, combined superiority (primary outcome) and non-inferiority (primary safety outcome) trial
Date of first enrollment:	November 2014
Target sample size:	1674
Recruitment status:	Enrollment phase
Primary outcome(s):	Total antibiotic exposure, defined as the total number of antibiotic-days by Day 30
Primary safety outcome(s):	Combined endpoint of adverse outcomes that could be attributable to withholding antibiotics in LRTI, by Day 30
Key secondary outcome(s):	Rate of antibiotic initiation by the initial ED clinician
Protocol Version:	Version 1.4; March 8, 2017
Source(s) of monetary or material support:	NIGMS, BioMerieux
Purpose:	To test the effect of implementation of a novel procalcitonin guideline on antibiotic and adverse outcomes in ED patients with LRTI

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Glossary of Terms

AE	Adverse events
ANC	Absolute neutrophil count
CAP	Community acquire pneumonia
CD4	cluster of differentiation 4 (glycoprotein)
COPD	Chronic obstructive pulmonary disease
CRISMA	Clinical Research, Investigation and Systems Modeling of Acute Illness
DCF	Data collection form
DSMB	Data Safety and Monitoring Board
eDCF	Electronic data collection form
ED	Emergency Department
FDA	Food and Drug Administration
GenIMS	Genetic and Inflammatory Markers of Sepsis (GenIMS) Study
HIPAA	Health Insurance Portability and Accountability Act
ICU	Intensive care unit
IRB	Institutional Review Board
KDIGO	Kidney Disease: Improving Global Outcomes
LAR	Legally authorized representative
LRTI	Lower respiratory tract infection
NDI	National Death Index
NIH	National Institutes of Health
NIGMS	National Institute of General Medical Sciences
PHI	Protected Health Information
PI	Principal Investigator
ProACT	Procalcitonin Antibiotic Consensus Trial
ProHOSP	Procalcitonin-Guided Antibiotic Therapy and Hospitalization in Patients with Lower Respiratory Tract Infections (ProHOSP) Study
PSI	Pneumonia severity index
SAE	Serious adverse event
SAS	Statistical analysis software
Site SC	Site study coordinator
UAP	Unanticipated problem
WBC	White blood cells

1 INTRODUCTION

A. OBJECTIVE AND SPECIFIC AIMS

The study objective is to target emergency department (ED) patients with clinically diagnosed lower respiratory tract infection (LRTI) and test the effects of implementation of a procalcitonin antibiotic guideline for LRTI.

Aim #1: To determine the effect of implementation of a procalcitonin guideline on antibiotic exposure in clinically diagnosed LRTI.

Aim #2: To determine the effect of implementation of a procalcitonin guideline on a 30-day combined adverse outcome.

The primary study outcome (Aim 1) is total antibiotic exposure (defined as the total number of antibiotic days by Day 30). The primary safety outcome (Aim 2) is a combined endpoint of adverse outcomes that could be attributable to withholding antibiotics in LRTI.

B. BACKGROUND AND RATIONALE

There is a need for improved decision-making for antibiotic prescription in acute suspected infection. Infections, particularly in the early stages, can have protean manifestations, often do not manifest with "classic" signs, and clinically overlap with non-infectious conditions. However, the imperative to quickly give antibiotics for bacterial infection has led to antibiotic overuse and resistance.

Strategies that combine novel diagnostics with therapeutics have improved decision-making in oncology, cardiology, and other fields. These strategies aim to identify those patients most likely to be helped or harmed by the therapeutic intervention and allow more individualized care. This approach takes diagnostics to the next level, by demanding a test not only measure well, but also that clinical care be improved by tying the test to a treatment strategy.

Procalcitonin, a novel biomarker of bacterial infection, may help physicians make more appropriate antibiotic decisions. Of the many proposed biomarkers of infection and sepsis, procalcitonin is currently the most studied, feasible, and clinically promising.[1] Procalcitonin is a calcitonin precursor measurable in serum and elevated in bacterial infections, yet low in viral infections.[2] Distinct from traditional endocrine pathways, bacterial infection induces a ubiquitous increase of calcitonin-I gene expression and subsequent constitutive release of procalcitonin from multiple tissue and cell types.[3] Importantly, in 2008, the FDA cleared for marketing a new, rapid (< 1 hour), high-sensitivity procalcitonin assay. The difference in functional assay sensitivity between the new and older assays contributed to initial conflicting studies on utility.[4-6]

Procalcitonin outperforms traditional means of detecting bacterial infection. Recent observational studies using the high-sensitivity assay show procalcitonin has superior discrimination for bacterial infections over other markers and correlates well with outcome.[7-13] A study of 545 LRTI patients found procalcitonin, but not high-sensitivity C-reactive protein or leukocyte count, increased with higher CAP severity, and had superior performance for differentiation of CAP from non-CAP LRTI and prediction of bacteremia.[14] A recent meta-analysis found procalcitonin had superior performance for detection of bacterial infection versus C-reactive protein, with 92% sensitivity for differentiating bacterial from viral infection.[7] A 2011 study of severe influenza pneumonia found procalcitonin levels in isolated viral pneumonia were 60-fold lower than cases with bacterial co-infection.[15] Our group recently demonstrated in a large CAP

cohort that low procalcitonin not only correlated well with low subsequent positive cultures, but also portended low morbidity and mortality, even in high-risk subjects.[13] All observational studies of infection are challenged by lack of a "gold standard." Cultures are often negative and cannot distinguish between colonization and infection, and physician adjudication panels are subjective. Biomarker-guided trials offer a novel solution to this well-known methodological problem by using patient outcome as the primary measure of biomarker performance.

Lower respiratory tract infection (LRTI) is an ideal trial population. LRTI accounts for a large proportion of antibiotic prescription, and exemplifies the imprecise clinical phenotype of infection. Respiratory infection is the most common reason for ambulatory care visits, and accounts for >12 million annual ED visits.[16] Determining which patients require antibiotics is difficult due to overlapping clinical presentations between LRTI subtypes and non-infectious conditions, and insensitivity of clinical exam and standard diagnostics for distinguishing bacterial from viral infection.

Important "proof of concept" trials using procalcitonin have been conducted. In 2004, a single center trial of 243 LRTI patients presenting to the ED of a Swiss academic hospital randomized patients to standard care or procalcitonin-guided care.[17] In the procalcitonin arm, physicians were advised to withhold antibiotics if procalcitonin was low, and to administer antibiotics if procalcitonin was high. Procalcitonin-guided care halved antibiotic initiation with no apparent harm. The same research group achieved similar results in a 2007 single center trial of 208 COPD patients[18] and a 2009 six center trial of 1359 LRTI patients powered for safety (ProHOSP).[19] A recent single-center Shanghai study had similar findings.[20] However, key questions remain.

Questions of generalizability and safety preclude widespread application. In these trials, a senior investigator potentially influenced ED staff by directly providing procalcitonin guideline advice. In ProHOSP, "enforcement" was accomplished by requiring physicians to follow Web-based instructions before registering their patient in the study. Physicians could only overrule the guideline after consulting the coordinating center. In routine US practice, neither method is ideal nor practical. Senior investigator influence threatens generalizability and direct interference with physician decision-making is counter to practice norms. US physician and patient expectations also likely differ from their Swiss counterparts and will require contemporaneous, individual data to alter. Further, only ProHOSP was powered to test safety. ProHOSP found no difference between groups in a composite adverse outcome endpoint, but used a relatively large non-inferiority margin. Their combined endpoint included an adverse outcome already potentially present at enrollment and subject to non-physiologic factors such as bed availability (ICU admission). The authors also observed in the procalcitonin arm a slightly higher mortality rate and did not report outcomes past 30 days.

C. TRIAL DESIGN

We propose a patient-level randomized trial to test an evidenced-based implementation strategy of a novel procalcitonin antibiotic guideline for LRTI. We will test the impact of serial procalcitonin measurement on total antibiotic exposure by Day 30. ProACT is powered to demonstrate safety with a 4.5% non-inferiority margin for a combined adverse event endpoint of the primary concerns of withholding antibiotics, and to detect a reduction of $\geq$ 1 antibiotic-day. We will enroll all LRTI as initial clinical presentations, embracing the clinical overlap that exists in practice and to optimize enrollment.

2 METHODS

A. PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

i. STUDY SETTING

Screening and enrollment will occur in the EDs from approximately 14 sites across the US, with the University of Pittsburgh serving as the Coordinating Center. Sites were chosen based on the following considerations: sample size and projected recruitment rates; site willingness and ability to institute all required study interventions successfully and appropriately; and generalizability of findings.

ii. ELIGIBILITY CRITERIA

a. PARTICIPANT INCLUSION CRITERIA

1. ≥ 18 years old
2. A primary clinical diagnosis in the ED of acute LRTI (< 28 days duration)
3. Clinician willing to consider procalcitonin in antibiotic decision-making

LRTI will be classified after enrollment into the following categories:

(i) Community acquired pneumonia (CAP) [21]

(ii) COPD exacerbation

(iii) acute asthma exacerbation

(iv) acute bronchitis

(v) other LRTI

b. PARTICIPATION EXCLUSION CRITERIA

<u>Conditions where physicians are unlikely to withhold antibiotics</u>

1. Systemic antibiotics before ED presentation
    a. All prophylactic antibiotic regimens, OR
    b. Received >1 dose within 72 hours prior to ED presentation
2. Current vasopressor use
3. Mechanical ventilation (via endotracheal tube)
4. Known severe immunosuppression
5. Accompanying non-respiratory infections
6. Known lung abscess or empyema

<u>Conditions where PCT can be > 0.25 ug/L without infection</u>

7. Chronic dialysis
8. Metastatic cancer
9. Surgery in the past 7 days (excluding minor surgery such as skin biopsy)

<u>Conditions rendering follow-up difficult</u>:

10. Incarcerated or homeless
11. Enrolled in ProACT in the past 30 days

iii. STUDY INTERVENTIONS AND PROCEDURES

After written informed consent is obtained, participants will be randomized and enrolled into one of two different study groups: the procalcitonin group or the usual care (UC) group.

Study procedures specific to the procalcitonin group:

In the procalcitonin group, the intervention consists of reporting procalcitonin results and the procalcitonin antibiotic guideline to clinicians, while embracing clinician autonomy. Study staff will be trained to inform clinicians that the procalcitonin information is available, and not to otherwise influence care. At all times, the clinician retains complete decision-making authority. **The final decision to give antibiotics is at the discretion of the treating clinician.**

Participants in the procalcitonin group will have one teaspoon of blood drawn for a procalcitonin level (≤ one hour after randomization goal) in the ED, and if hospitalized, 6-24 hours after the initial ED blood draw, and on Days 3, 5, and 7. Days 3, 5, and 7 blood draws for procalcitonin will only occur in hospitalized patients on antibiotics and/or at the treating clinician's discretion. For the purpose of this study, time zero is at randomization and Day 1 is defined as time of enrollment through 11:59PM of the same day.

In the ED, we will quickly (<1 hour goal) provide clinicians the procalcitonin result, accompanied by the procalcitonin antibiotic guideline (provided below). For participants who have not yet received antibiotics, we will ask the clinician to consider waiting for the procalcitonin result.

For patients admitted to hospital (or to an observation unit), we will inform the hospital clinician of the ED procalcitonin result, and that serial procalcitonin levels will be obtained, including a second one in 6 - 24 hours after the initial ED blood draw. During the hospital stay, study staff will inform clinicians when new serial procalcitonin results are available. The same procalcitonin guideline will be provided with both the initial and serial procalcitonin measurements - withhold or cease antibiotics if low, administer or continue if high.

Procalcitonin antibiotic guideline

Procalcitonin level (μg/L)	Bacterial etiology	Recommendation
< 0.1	Very unlikely	Antibiotics strongly discouraged[1]
0.1 - 0.25	Unlikely	Antibiotics discouraged[1]
> 0.25 - 0.5	Likely	Antibiotics recommended[2]
> 0.5	Very likely	Antibiotics strongly recommended[2]

1. Initial antibiotics can be considered for critical illness, Legionella pneumophilia. Procalcitonin should be evaluated in context with all findings and the total clinical status; clinical judgment always necessary.
2. For outpatients, antibiotic duration based on level (> 0.25-0.5 ug/L:3 days; > 0.5-1.0 ug/L:5 days; >1.0 ug/L:7 days). Physician follow-up is recommended.

Upon discharge (from ED or hospital) in the procalcitonin group, participants will receive a ProACT study information packet which includes a letter for their primary care clinician which provides an explanation of the study and the study guideline (Appendix 5), an instructional letter (Appendix 6), and a 30 day antibiotic use calendar (Appendix 7). This information packet will be provided to the participant as a tool to boost study awareness

and a reminder of the two subsequent phone visits described below. The 30 day antibiotic use calendar is an optional tool for the participant to aid in antibiotic use recall.

Study procedures specific to the usual care group:
After randomization, study staff will inform the treating clinician that the patient was assigned to the usual care group, and that procalcitonin will not be provided. At all times, all patient care is at the discretion of the treating clinician.

Upon discharge (from ED or hospital), usual care participants will receive a ProACT study information packet which includes an instructional letter (Appendix 6) and a 30 day antibiotic use calendar (Appendix 7). As stated above, this information packet will be provided to the participant as a tool to boost study awareness and a reminder of the two subsequent phone visits described below. The 30 day antibiotic use calendar is an optional tool for the participant to aid in antibiotic use recall.

Study procedures common to both groups:
1. All participants will have approximately four teaspoons of blood drawn in the ED after randomization. This blood sample will be sent to the CRISMA Molecular Core Laboratory at the University of Pittsburgh for research purposes related to procalcitonin, infection, and outcome.

2. All participants will have the following data collected during their ED visit:
    - Sociodemographic information
    - Comorbidities and current medications
    - Vital signs
    - Respiratory history
    - Test results and therapeutics relevant to current illness, including medications, significant lab values and imaging results
    - Antibiotics prescribed and received
    - Patient disposition upon ED discharge and ED final diagnosis

3. If admitted to hospital, both groups will have the following information collected from the medical record:
    - Antibiotics prescribed and received
    - Therapeutics and diagnostics (steroids, bronchodilators, radiologic test results)
    - Clinically obtained microbiology results
    - Disposition upon discharge

4. Safety outcomes will be collected from the medical record on both groups and include:
    - death, vasopressor use for ≥1h, mechanical ventilation, new renal replacement therapy, all creatinine results, diagnosis of lung abscess/empyema, new diagnosis and/or treatment of pneumonia for non-CAP LRTI, length of hospital stay which includes any ICU admissions.

5. All participants will participate in 2 telephone visits, lasting approximately 10 minutes each. These visits will be conducted by the ProACT Coordinating Center Long-Term Follow-Up Core, located at the University of Pittsburgh. These visits will occur on Day 15 (+/- 5 days) and Day 30 (+ 10 days). Data collected from these calls will primarily include: antibiotic use, the AQ-20 questionnaire (Appendix 8), and post discharge resource use (Appendix 4). If the participant is hospitalized at either time point, the site SC will be responsible for collecting medical record data only, listed above in items 3 & 4, and the telephone visit will not be conducted at that time point.

During data collection in the ED, the participant's Protected Health Information (PHI) (e.g. SSN, name, DOB, address, phone number, etc.) will be collected and sent directly from the local study site to the ProACT Coordinating Center Honest Broker. This information will be maintained in strict confidentiality according to the Honest Broker's standard operating procedure (Appendix 9). The PHI will be used for Day 15 and Day 30 telephone visits as well as obtaining long-term survival information. Long-term survival status (Day 90 and 1 year post study enrollment date) will be obtained through the NCHC/NDI (National Center for Health Statistics/National Death Index). The following data is needed for the NDI search: name, father's surname, SSN, DOB, race, sex, marital status, state of residence, and state of birth. Contact information (name, address, telephone number) will also be obtained for 2 relatives or close friends. This will be used to minimize "lost to follow-up" in cases where the ProACT Coordinating Center Long-Term Follow-Up Core is unable to contact the participant for Day 15 and Day 30 visit data collection. The Long-Term Follow-Up Core will also utilize text messaging for reminders, setting up appointments for interviews, and in some instances questionnaire responses in an attempt to minimize "lost to follow-up" cases. Texting will only be utilized for subjects that agree to receive study text messages.

For subjects that we have been unable to reach to complete 30 day interviews via phone call, we will send a letter informing the subject that we have attempted to reach them without success. This letter will include a toll-free number that subjects may call in order to schedule or complete their interview. Alternatively, we will also provide a paper version of the interview questions for those subjects that prefer to complete via paper. Subjects will be provided with a prepaid envelope to send back completed paper interviews. Subjects may receive an email message reminder for the interview that will include a link to a Qualtrics version of the survey that is identical to the paper version. Subjects who have agreed to receive text messages may also be prompted to complete the survey via text messaging.
In the event that the participant is hospitalized between ProACT study enrollment and Day 30 at a facility different from the enrolling site, a medical release will be requested for feasibility of long-term follow-up to ascertain clinical events related to the study (Appendix 10).

iv. OUTCOMES

Our **primary outcome** is total antibiotic exposure, defined as the total number of antibiotic-days by Day 30. We define an antibiotic-day as each day a participant receives any oral or intravenous antibiotics, excluding antibiotics given for non-infectious indications (e.g. neomycin for hepatic encephalopathy) and antivirals. Secondary outcomes include the rate of antibiotic initiation by the initial ED clinician.

Our **primary safety outcome** is a combined endpoint of adverse outcomes that could be attributable to withholding antibiotics in LRTI, that occur by study Day 30, as below. Our combined endpoint captures the components of the treatment failure endpoint used in a recent study of 80,000 COPD patients (death, mechanical ventilation, readmission).[22] We assume no patient discharged from ED has met primary safety outcome endpoint at time of discharge (death, organ failure, empyema); post-discharge events are captured in follow-up. Secondary outcomes include vital status at Day 90 and 1 Year, as determined by National Death Index (NDI) query.

Measurable adverse events for primary safety outcome:

i. death
ii. septic shock (vasopressor use for > 1h)

iii. mechanical ventilation (via endotracheal tube)
iv. renal failure (KDIGO-3)
v. lung abscess/empyema
vi. development of pneumonia in non-pneumonia LRTI
vii. subsequent hospitalization (for both those discharged from ED and those admitted to hospital)

v. SAMPLE SIZE

We desire at least 80% power to conduct our primary hypothesis tests using a one-sided significance level of 0.05. As shown below, determination of sample size was dependent on the hypothesis test for the primary safety outcome, as this required a larger sample size than the tests for antibiotic exposure. Analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC). **Allocation of 757 subjects in each arm (total trial sample size of 1514) meets our goal of at least 80% power.**

Testing H1: Procalcitonin guideline implementation reduces the total number of antibiotic-days by Day 30.

For H1, ProHOSP reduced antibiotic exposure from 8.7 to 5.7 days (35% relative risk reduction). We chose a 20% relative reduction as an appropriate minimum threshold and to detect a lower effect size than ProHOSP.

We assumed control arm antibiotic exposure of 8 days, and calculated sample size based on a two-sided two-sample test at 0.05 significance. Under these assumptions, the sample size of 1514 required for H2 provides >99% power to detect a 20% relative reduction, and 80% power to detect a reduction of as low as one antibiotic-day (12% relative reduction). Power is preserved under a wide range of assumptions. Thus, we are exceptionally well-powered for H1.

Testing H2: Procalcitonin guideline implementation does not increase the proportion of subjects who experience a composite endpoint of adverse outcomes by Day 30.

ProHOSP estimated a maximum combined adverse outcome rate of 20% (actual – 17%) and set their non-inferiority margin as an absolute difference of 7.5%. In addition, a multicenter study of CAP (GenIMS), ~11% experienced our combined endpoint (6% death by Day 30, 5% septic shock, 7% mechanical ventilation, 10% renal failure). Similarly, a recent 80,000 COPD patient study reported 10.6% met a combined endpoint of death, mechanical ventilation, and readmission.[22] We have therefore chosen an estimated combined adverse outcome rate of 11%. We also have set a narrower non-inferiority margin of 4.5%, approximately half that of ProHOSP's, to provide a higher degree of safety evaluation. **A sample size of 1514 patients provides at least 80% power to demonstrate that procalcitonin guideline implementation does not increase overall adverse outcomes by more than 4.5%, if the true difference between arms is zero.** This sample size also accounts for an approximately 10% lost to follow-up rate. Thus, we are well-powered to test safety.

vi. RECRUITMENT AND CONSENT

Each site will follow their IRB's guidelines regarding HIPAA authorization and informed consent (including those guiding the use of genetic material).

Patients will be screened for in the ED by the ProACT site study team. The ED clinical team will obtain potential participant or legally authorized representative (LAR)/proxy agreement verbally to be approached by the ProACT study representative to participate.

This will avoid “cold calling” coercion that could occur if direct contact by research team members was the initial method of assessing willingness to enroll.

Trained ProACT study team members will then discuss the trial with the patient or LAR/proxy, and explain the goals, procedures, and risks associated with the study. If patient or LAR/proxy agrees to participate, written authorization and consent will be obtained.

Some potential participants will lack capacity for informed consent and therefore LAR/proxy consent may be necessary. Individuals legally authorized to provide consent are defined in the Code of Federal Regulations as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant’s participation in the procedure(s) involved in the research" (45 CFR 46.102(c)). Each site will follow their state law guiding LAR/proxy consent for participation of a decisionally-impaired participant. The LAR/proxy will be informed of the risks, benefits and alternatives to the research study and will be asked to make a decision considering the view of the potential participant while decisionally-capable and to act in the best interest of the potential participant.

If consent is refused, a limited set of demographic data (to the extent allowed by each site’s IRB) will be collected to compare patients who did and did not enroll in the study. This minimal data set will gather participation rates and variables (sex, age and race), permitting analysis of potential selection biases and determination of the generalizability of the study results.

vii. POTENTIAL RISKS AND BENEFITS

Participation in this study involves minimal risk only. According to 45 CRF 46.102(i), minimal risk is defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Risks of the procalcitonin guideline: Clinicians may be influenced by the guideline, but they are not required to follow it. Best clinical judgment in determining each case will be used, just as it would without the procalcitonin guideline.

Risks of blood sampling: The risks of drawing blood include bleeding, bruising, and pain at the blood draw site. These risks will be reduced by making every attempt to use blood that has already been drawn, or to collect this sample when the participant is having other blood drawn.

Risk of release of information: We will minimize this potential breach of confidentiality risk by coding study information with a number instead of a name and storing it in a secure location.

There may not be a direct benefit from taking part in this research study. For participants in the procalcitonin group, clinicians may use the procalcitonin levels to make more informed decisions about current treatment planning. It is possible that study findings will help future patients with lower respiratory tract infections.

B. ASSIGNMENT OF INTERVENTIONS

i. ALLOCATION

a. SEQUENCE GENERATION

Participants will be randomly assigned to control or intervention group with a 1:1 allocation as per a computer generated randomization schedule stratified by site, race, and age using permuted blocks of random sizes for each enrolling site. The block sizes will not be disclosed to ensure concealment.

b. ALLOCATION CONCEALMENT MECHANISM

Allocation concealment will be ensured, as the ProACT coordinating center data management team will not release the randomization group until the participant has been recruited into the trial, which takes place after all required pre-randomization data have been completed and entered into the study eDCF.

c. IMPLEMENTATION

All participants who give consent for participation, fulfill inclusion criteria, and do not meet exclusion criteria will be randomized. Randomization will be conducted without any influence of the principal investigator, site study team, or ProACT coordinating center study team. Following participant recruitment, the site study team member will enter participant information into the eDCF and receive from the randomization system a study ID # and treatment assignment. In the rare case of eDCF malfunction, manual randomization will occur. Random assignment will be determined by a coin-flip method performed by the ProACT medical monitor and treatment assignment and subject ID# will be communicated to the ProACT coordinating center data team and site study team. All pre-randomization data will then be sent to the ProACT coordinating center study team to be entered into the eDCF.

d. BLINDING

Due to the nature of the intervention, neither the treating clinician nor the study staff can be blinded to allocation in the ED. ProACT coordinating center research staff conducting post-discharge follow up will be blinded to allocation.

ii. DATA COLLECTION, MANAGEMENT, AND ANALYSIS

a. DATA COLLECTION METHODS

Information will be obtained by direct observation, from chart review, and from participant and/or family interview by the site study team member. In the ProACT trial, all data collected will subsequently be entered electronically into the eDCF. Original study forms (source documents) will be kept on file at the local study site. A subset may be requested later for data monitoring and quality control. When this occurs, the participating site staff will pull the requested source documents, copy and send securely to the ProACT Coordinating Center for review. All data will be kept for a minimum of five years following the close of the study.

Once a participant is enrolled, the study site and ProACT coordinating center long term follow up team will make every reasonable effort to follow the participant for the entire study period. It is projected that the rate of lost-to follow-up on an annual basis will be approximately 10%. The ProACT coordinating center has developed and will implement local standard operating procedures to achieve this level of follow-up.

b. DATA MANAGEMENT

Data management will be coordinated by the CRISMA Center at the University of Pittsburgh. The data management system will be based on a PC platform, using a relational database server (SQL Server software) and Microsoft .NET framework. Enrollment and randomization data will be handled by a web-based system that uses Microsoft's .NET web application. A complete backup of the server data is performed every day. SSL certification ensures encryption of data between site and the web server. All participant data will by entered by the site ProACT study staff into the secure web-based data entry system and uploaded to the study database server via secure internet connection. Laboratory data will be maintained in a separate, secure location within the CRISMA Center at the University of Pittsburgh, with access limited only to laboratory personnel. Any identifying data will be maintained separately from clinical, laboratory and follow-up data for added security and confidentiality.

c. STATISTICAL METHODS

Primary analysis

The primary analysis is an intent-to-treat (ITT) analysis that includes two interim analyses at 1/3 and 2/3 enrollment, and a final analysis using Lan-DeMets stopping rules. ITT generally biases towards no difference. We therefore will also perform per-protocol analyses where the guideline was followed.[65] The primary test for H1o tests the null hypothesis of no difference between intervention and control for antibiotic exposure (superiority). The primary test for H2o tests the null hypothesis of a significant difference between intervention and control for a combined endpoint of adverse events (non-inferiority).

As we have two primary outcomes, our overall approach during the interim monitoring of the trial is to test H1 at the first interim. Should the null hypothesis for H1 be rejected at the first interim, then H2 will be tested and the decision to continue the trial would be based on this result. Should a second interim analysis be needed, then H2 would be assessed at this interim and decisions for continuation would be based on H2. In the event that H1 is not rejected at the first interim analysis, the study will proceed with no test of H2. At the second interim analysis, H1 will again be tested and if rejected, then H2 will be tested and the continuation decision will be based on this results. If H1 is not rejected at the second interim, then H2 will not be tested until the final analysis. We believe the most likely scenario is H1 testing will cross the pre-specified boundary at 1st or 2nd interim analysis, but that H2 testing will not meet non-inferiority until the full sample size is enrolled.

Each individual adverse event of the combined endpoint will also be reported to the DSMB, which can stop the trial for a priori statistical tests for efficacy, futility, harm, and as per their judgment. The final analysis will consist of: i.) descriptive analyses, ii.) the primary tests of the study hypotheses, and iii.) modeling to examine whether confounding factors impact estimates of treatment effect and safety. Assessment of randomization quality will consist of an examination of potential differences between arms for baseline variables. Chi-square tests will be used for categorical measures (race, employment status) and t-tests and/or Wilcoxon tests for continuous measures (Charlson score, PSI).

We will explore main effects models and interaction terms by stepwise fitting a series of models. We will retain model(s) with best fit to generate an estimate of treatment effect. Fit will be determined by model parsimony and goodness-of-fit tests, such as the Hosmer-Lemeshow test for logistic regression and the R2 measure for linear regression. We will also examine regression diagnostics for influential observations and as a second assessment of model fit. For subgroup analyses we will use the same methods used for the primary hypotheses, including descriptive analyses, regression, and modeling. We anticipate sufficient female, African-American, and Hispanic/Latino enrollment to be able to perform meaningful a priori analyses in these subgroups. Other a priori subgroup analyses include analysis of each LRTI sub-type. We will also fit mixed models with center as a random effect to explore potential center effects.

Handling threats to the accuracy of estimated treatment effects

While many of the proposed analyses are standard for trials, potential threats include missing data, handling of participant's data for individuals who withdraw from study, and incorrect randomization. We expect incorrect randomization to be very rare. Missing data, from either incomplete data entry or participant withdrawal, present a greater challenge. We will minimize missingness by creating a concise Web-based data collection form, incorporating extensive logic checks to prevent erroneous entry, auto-prompts for missingness, and close site coordination. We will apply methods for missingness analyses based on weighted estimating equations[66], multiple imputation using methods proposed by Rubin and Schneker, and/or pattern mixture models.[67] We have expertise in this area[68], including development of the necessary software.

Potential outcomes of proposed approach

We anticipate demonstrating an evidence-based implementation strategy of a procalcitonin guideline will reduce antibiotic exposure (accept H1), without compromising safety (accept H2). These findings should prompt hospitals nationwide to incorporate procalcitonin, and we would make available the implementation techniques we found most effective. Notably, the patent on the Kryptor procalcitonin assay expires in 2014, which should lead to reduction in cost (~$15 in Switzerland). We also have considered other outcomes:

Antibiotic exposure is not reduced. Taking this finding in isolation, we would not recommend procalcitonin guideline implementation. However, if this finding is due to lower control arm antibiotic use relative to common clinical practice, we would conclude hospitals could choose either procalcitonin guideline implementation or compliance with current guidelines to reduce antibiotic use.

Antibiotic exposure is reduced, but safety worsens. Under this situation, we would not recommend widespread procalcitonin guideline implementation, but would analyze our composite adverse outcome results to determine if select adverse outcomes drive the overall finding, and if these outcomes occur predominantly in certain patient subgroups (e.g., elderly patients or those presenting with high PSI scores).

iii. MONITORING

a. DATA MONITORING

The ProACT Data Safety and Monitoring Board (DSMB), chosen by the funding source, the National Institute of General Medical Sciences (NIGMS), will provide a multidisciplinary, independent review of the study design, ethical and scientific conduct of the study, monitor interim results and make recommendations with respect to continuation, modification, and termination of the study. Each individual is an experienced academician and together will provide clinical, research, and statistical expertise. The DSMB will meet at two planned interim analyses for safety, at completion, and at any other needed interval.

b. HARMS

Event reporting

We will capture the major potential adverse events related to antibiotic withholding in our combined primary safety outcome. With this in mind, **the adverse outcomes that comprise the primary safety outcome will be included in outcome reporting, and will not be reported a second time as AEs or SAEs.**

However, as with any experimental procedure, there may be adverse events that are currently unknown and certain of these unknown risks could be permanent, severe, or life threatening.

Monitoring of adverse events (AEs) is critical to the participant's safety and data integrity. An adverse event will be defined as any untoward medical occurrence (unfavorable and unintended sign, symptoms, or disease) in a participant temporarily associated with the study intervention or other aspects of study participation, but not necessarily considered related to the participant's participation in the research study. An untoward medical occurrence that: (1) results in death, (2) is life-threatening, (3) requires hospitalization or prolongation of existing hospitalization, or (4) results in disability/incapability will be defined as a serious adverse event (SAE).

All adverse events (AEs and SAEs) occurring after study enrollment until the study day 30 follow-up visit will be recorded.

AEs and SAEs will be recorded when reported by the participant, attending physician or site SC or PI, or when documented in the medical record. When a reportable SAE occurs, it will be the site PI's responsibility to review the pertinent records, notes, laboratory and radiographic data. This information will be recorded on the eDCF along with the site PI's impression of the diagnosis. The site PI will assess causality between the event and the study interventions using their best clinical judgment. **Notification of coordinating center regarding any AE that is serious, unexpected and related (possibly, probably or definitely related) to the study intervention will take place within 48 h of recognition (expedited reporting**); in addition, a copy of all documents submitted to the site IRB will be sent to the coordinating center.

A reportable AE or SAE that also meets **ALL** of the following criteria is also required to be reported as an Unanticipated Problem (UAP) Involving Risk to Human Subjects or Others as per local site IRB reporting procedures:

1. unexpected in terms of nature, severity, or frequency;
2. related, or possibly related, to a participant's participation in the research;
3. places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) that was previously known or recognized.

"Other" Unanticipated Problems (UAPs) Involving Risk to Subjects or Others

As per local study site IRB reporting procedures, this category includes all other incidents not previously included in the above AE reporting section and can include protocol deviations, non-compliance, or other unanticipated problems **that place subjects at risk of harm**.

This includes any accident, experience, or outcome that meets ALL of the following criteria:

1. Unexpected in terms of nature, severity, or frequency;
2. Related, or possibly related, to a participant's participation in research;
3. Places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Incidents falling into this category that require reporting to the ProACT Coordinating Center include:

- Enrollment of a participant that did NOT meet inclusion or met exclusion criteria
- Incomplete or lack of participant written consent
- Breach of confidentiality
- Incomplete data collection

Non-Compliance

Protocol deviations and incidents of non-compliance, which do **NOT** involve risk to participants or others must be reported as "Non-compliance" as per local site IRB reporting procedures.

Protocol deviations that require reporting to ProACT Coordinating Center by the local study site via eDCF documentation:

- Deviating from the protocol without risk to the participant
- Obtaining consent using an outdated consent form with no other substantive difference other than the date

Please Note:

- Incidents of non-compliance on the part of the research participant which do not involve risk do NOT need to be reported to the ProACT coordinating center.

Notification of DSMB

The ProACT coordinating center will be responsible for notifying the DSMB regarding all event reporting. The ProACT coordinating center will notify the DSMB and the University of Pittsburgh IRB within 48 hours of their knowledge of all AEs that are categorized as serious, unexpected and related.

All other reportable events and will be recorded on the DCF, entered into the database and reported to the DSMB in routine reports. The DSMB will request any follow-up information they feel is necessary and will recommend modifications to the study protocol or consent as necessary.

c. INTERVENTION ADHERENCE

To improve intervention adherence, we will focus site start-up and education efforts on the key logistics steps required to accomplish the intervention. We will regularly monitor time to procalcitonin reporting (e.g., time to blood draw, lab receipt, assay time, assay completion to reporting) and receipt by clinicians (coordinators will document information receipt).

We will also conduct basic in-servicing to raise clinician awareness of the study and the procalcitonin algorithm. Our primary in-servicing message will be “Please look at the procalcitonin value and algorithm recommendation – the final antibiotic decision is entirely yours.”

d. AUDITING

We will conduct ProACT in compliance with all federal regulatory requirements, ensuring compliance. Site monitoring will consist of internal monitoring of the research database and external/on-site monitoring of source documents. Internal monitoring will consist of missingness checks for completeness and chronology, logic checks for accuracy, and trend analysis to identify problem areas. External monitoring will consist of site visits to evaluate human subject protections and source documents. Monitoring will be done by the ProACT project management team. The first site visit will occur after initial enrollment to verify consent procedures, participant eligibility, reported data, and IRB compliance. If a problem is identified during the visit (i.e. poor communication with the ProACT coordinating center, inadequate or insufficient staff to conduct the study, missing study documents) the monitor will assist the site in resolving the issues. Data verification for primary outcomes will be a priority during monitoring visits. A follow-up site visit will be conducted if a site is found to have continued and/or excessive issues. We will conduct regular site audits to determine reasons for study intervention non-adherence and procalcitonin algorithm non-adherence (e.g., patient condition worsening).

3. ETHICS AND DISSEMINATION

A. RESEARCH ETHICS APPROVAL

This protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents – and any subsequent modifications – will be reviewed

and approved by the study site ethical review bodies with respect to scientific content and compliance with applicable research and human subjects regulation. Subsequent to initial review and approval, the responsible local IRB will review the protocol at least annually. The site investigator will be responsible to make local safety and progress reports to the IRB at least annually. The ProACT Coordinating Center will provide each site with summaries of all ProACT data safety and monitoring board (DSMB) reports as well as annual ProACT study progress reports.

B. PROTOCOL AMENDMENTS

Any modifications to the protocol which may impact the conduct of the study, potential benefit of the patient or may affect patient safety, including changes to study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects, will require a formal amendment to the protocol. Such amendments will be agreed upon by the ProACT Coordinating Center research team and will require approval by local site IRB prior to implementation.

C. CONFIDENTIALITY

All study-related information, including regulatory and source documents, will be stored securely at the study site after data is entered electronically into the eDCF. All participant information will be stored in locked areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms at the local study site will be identified by a coded identification number only to maintain confidentiality. Participant data will be entered by the site study team member into a secure web-based data entry system and uploaded to the study database server via secure internet connection. PHI (including contact information for participant and primary/secondary contact persons) will be collected directly from the research sites via the study's web interface by the ProACT coordinating center's certified honest broker. This information will be encrypted during transmission and once transmitted it will no longer be accessible through the web interface. The encrypted data will be stored at the ProACT Coordinating Center within the project database, which resides on the secure, password protected network drive, behind an enterprise firewall. Permission to access this database is restricted to the honest broker. The honest broker will provide necessary PHI and/or related contact information to the ProACT Coordinating Center Long Term Follow-Up Core for required follow up calls and NDI searches, blinded to study intervention. All PHI and related contact information will be destroyed once long-term follow up survival data is obtained. No investigator or representative/agent of the study sponsor will have access to this protected information.

D. DECLARATION OF INTERESTS

The PI (DTH) consulted for BRAHMS Diagnostica in 2006 and 2007, and received one speaking honorarium and travel expenses for presentation at a satellite symposium of the September 2006 European Respiratory Society meeting in Munich, Germany.

E. ACCESS TO DATA

In compliance with NIH policy, resources developed through this project will be made readily available to investigators and data will be released completely and in a timely manner to facilitate use within the broader community. We will work collaboratively after award with the other funded sites to prepare a joint dissemination plan. It is our plan to freely allow access to the study data as soon as the study is completed and the main manuscripts published.

Our final study dataset will include de-identified demographic and clinical information, outcome data, and procalcitonin values. Protected health information or patient identifiers will not be part of any dataset. The recommended data documentation elements will be provided in accordance with NIH policy on sharing and releasing data. We will employ methods and procedures for sharing data that have been developed and utilized successfully with previous projects within our

research group. For example, we create a Data Use and Publications Request Form for our large federally funded projects. This form will be posted on the project website and, once a request is approved, data will be shared with the requestor. Once the data are scrutinized for errors and validated, the data team will generate appropriate datasets in response to the specific needs of the proposed analysis. Documentation elements necessary to utilize the study data (e.g., data dictionary, study operating procedures) will also be shared via the project website. The website will be password-protected with access provided only to those who have received approval of their data request.

F. ANCILLARY AND POST-TRIAL CARE

Emergency medical treatment for injuries solely and directly related to the participation in the ProACT trial will be provided by the local study site. Costs associated with this care will be directed and managed as outlined by each the local study site regulations. If research-related injury requires medical care beyond this emergency treatment, the participant will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation.

G. DISSEMINATION POLICY

We will publish study results in a PubMed referenced journal, regardless of study findings (i.e., whether a "positive" or "negative" trial), and will not use professional writers.

All core, currently planned manuscripts will be drafted and submitted by the ProACT Publication Committee, led by the Principal Investigator from the University of Pittsburgh ProACT Coordinating Center. The Publication Committee will invite ProACT site collaborators with satisfactory enrollment, protocol adherence, and data quality to participate on the writing committee for each planned manuscript. The preferred authorship of core manuscripts is "The ProACT Investigators," with the Publication Committee noted and available from electronic searches.

We will post the protocol outline on ClinicalTrials.gov and plan to publish a trial methodology, manuscript and our statistical analysis plan. We will provide public access to data as noted above under the above section "Access to Data."

H. COSTS AND PAYMENTS

There will be no additional costs to participants as part of this study. The study sponsor, the National Institute of General Medical Sciences (NIGMS) is providing core funding for the trial. BioMerieux will be providing clinical lab procalcitonin equipment and training. Participants and their insurers or third party payers will not be billed for research related services. All research related services (central laboratory supplies/services) will be paid for by the study sponsor.

Participants and their insurers and third party payers will be billed for routine care services, or services not connected with the study. These routine care services include services provided during this hospitalization and any ongoing services or medications required after leaving the hospital. Participants will be responsible for any applicable copays, coinsurances, and deductibles.

Research participants will receive a $50 debit card after completing both phone visits (Day 15 and Day 30).

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Appendix 1: ProACT Informed Consent Form Template

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

Title: Procalcitonin Antibiotic Consensus Trial (ProACT)

PRINCIPAL INVESTIGATOR:

Sub-Investigator:

Study Sponsor: National Institutes of Health

INTRODUCTION

You are being asked to consider participating in this research study because you have been diagnosed with a lung infection.

There are two main types of germs that cause infections: bacteria and viruses. Most lung infections are caused by viruses. Antibiotics kill bacteria, but not viruses. Taking antibiotics for virus infections is harmful; patients can experience side effects, and unnecessary antibiotics make bacteria harder to kill in the long run.

A new FDA (Food and Drug Administration) approved blood test called "procalcitonin" can help determine if your lung infection is caused by a bacteria or a virus. Procalcitonin levels are typically high with bacterial infection, and low with viral infection.

In this consent form, "you" always refers to the subject. If you are a Legally Authorized Representative (LAR), please remember that "you" refers to the study subject.

PURPOSE OF THE STUDY

This research study will test if a guideline using this new blood test can help doctors make better antibiotic decisions. The guideline recommends taking antibiotics if your procalcitonin level is high and no antibiotics if your procalcitonin level is low. **Because this is just a guideline, the final decision on antibiotic use is entirely up to your treating doctors**.

DESCRIPTION OF THE RESEARCH

A total of 1674 men and women 18 years old and older will be enrolled at approximately 14 different study sites across the US. You will be expected to participate in the study for 30 days. At SITE, 150 subjects will be enrolled in this research study.

STUDY PROCEDURES

If you decide to take part in this study, the following will occur in addition to your standard medical care:

- You will be assigned by 50:50 chance (like a coin flip) to the "procalcitonin" group or the "usual care" group.

For the procalcitonin group – to check your procalcitonin level, you will have 1 teaspoon (5mL) of blood drawn, and this lab result and the procalcitonin guideline will be provided to your doctors, who will take into account this information when deciding your plan of care. Your procalcitonin level will be checked once in the Emergency Department (ED), and if you are hospitalized, we will withdraw 1 additional teaspoon of blood at 4 timepoints (6-24 hours later, on Days 3, 5 and 7) to check procalcitonin level again during your hospital stay. Additionally, we will collect and store a 20mL blood sample (4 teaspoons) in the Emergency Department for storage and future analysis.
Upon discharge from the ED or hospital, you will receive a ProACT information packet, which includes a letter to your primary care physician explaining your participation in this research study, a study instructional letter for your reference and a 30 day antibiotic use calendar. The completion of this calendar is not mandatory, but will assist you in tracking your antibiotic use.

For the usual care group – doctors will treat you according to their standard treatment plan and without any influence from the study team. We will collect and store a 20mL blood sample (4 teaspoons) in the Emergency Department for storage and future analysis. Upon discharge from the ED or hospital, you will receive a ProACT information packet, which includes a study instructional letter for your reference and a 30 day antibiotic use calendar. The completion of this calendar is not mandatory, but will assist you in tracking your antibiotic use.

- In both groups, the blood sample obtained in ED for future analysis (20 mL) will be stored in the CRISMA Molecular Core Lab at the University of Pittsburgh for potential inclusion in future research studies. As part of the study, your blood sample will be stored indefinitely. The sample may be tested for molecules related to procalcitonin, infection and outcome, differences in genes, and/or other types of research purposes. Personal identifiers such as name, address, Medical Record Number, etc. will be removed before they are sent to be stored.

- In both groups, we will check your progress by reviewing your hospital records until you are discharged from the hospital or hospital day 30, whichever comes first. We will also obtain your hospital records for any re-hospitalization you may have during the first 30 days after enrolling in this study; this includes obtaining hospital records from a hospitalization not occurring at SITE.

- In both groups, we will contact you approximately 2 and 4 weeks from now for a brief interview (5-10 minutes) to find out about your antibiotic use, medical care you have received since your ED visit, and ask you questions specific to your current respiratory status. If you are hospitalized at either time point, the telephone interview will not occur. The telephone interview will not occur if you are still in the hospital. Contact information will also be collected for you and 2 family members and/or friends (name, address and telephone number). We will reach your contact member in case we are unable to locate you after your discharge from hospital for the telephone interview. We may also send you a letter with a toll free number that you can use to call us to complete your interviews.

- Your direct participation in the study is complete after the interview at 4 weeks, but after that we will collect survival status information at Day 90 and 1 year post study enrollment on you through the NCHC/NDI (National Center for Health Statistics/National Death Index).

POTENTIAL RISKS AND DISCOMFORTS

Procalcitonin Guideline: The risks are minimal. Your doctors may be influenced by the guideline, but they are not required to follow it. Your doctors will use their best clinical judgment in determining your care, just as they would without the guideline.

Blood Sampling: You may experience some temporary discomfort, bruising and pain at the blood draw site. These risks will be reduced by making every attempt to use blood that has already been drawn, or to collect this sample when you are having other blood drawn.

Breach of Confidentiality: It is possible that someone could find out you were in this study and could find out information about you. Every effort will be made to prevent this from happening. To protect your confidentiality, we will remove your name and other personal identifiers from the samples and from the medical record information we obtain. This information will be identified by a code and sent to a research laboratory at the University of Pittsburgh, where it will be stored indefinitely.

Genetic information from your stored blood samples may be used for research in the future. Any information gathered will be stripped of personal identifiers (such as name, address, Medical Record Number, etc.). It is possible that someone could figure out who you are from this information, even without the personal identifiers. This re-identified genetic information could potentially be used against you, your family, or other groups. We will safeguard this information using multiple widely accepted standard practices. You may withdraw consent for research use of genetic information at any time without penalty or loss of benefit. However, please be advised that any information already distributed for research use will not be retrieved

ANTICIPATED BENEFITS TO SUBJECTS

You may receive no direct benefit from taking part in this research study. If you are in the procalcitonin group, your doctors may use your procalcitonin results to avoid prescribing an antibiotic when your lung infection is likely caused by a virus. It is also possible that study findings will help future patients with lung infections.

COSTS AND PAYMENTS

After both interviews are completed (at 2 weeks and 4 weeks), you will be sent a $50 debit card to compensate you for your time.

You and your insurer will not be billed for research-related services; services related solely to the research will be paid for by the sponsor. You or your insurer will be billed for all other usual care services and/or services not connected with the study, just as you would if not in the study.

If you decide to not participate in this study, your doctors will continue to treat you according to their usual treatment plan.

USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

As part of this study, we are also requesting your authorization or permission to review your medical records to obtain past, current, and future medical information from hospital and other

medical facilities. We will obtain information concerning your diagnosis, age, past medical history, diagnostic procedures, and results of any blood tests, including results of genetic tests that were already done as part of your standard medical or psychiatric evaluations a SITE.

This identifiable information will be made available to members of the research team for an indefinite period of time. That medical information, as well as information obtained during this research study, may be shared with other groups, possibly including authorized officials from the Food and Drug Administration and from the National Institutes of Health (the agency that is paying for this study) and the SITE Research Conduct and Compliance Office, for the purpose of monitoring the study. You should also be aware that as part of this research study, some information that we obtain from you may be placed into your medical records held at SITE, including the results of medical tests. Any information that is entered into your medical records will be available to you, in accordance with SITE Privacy Practices. A description of this clinical trial will be available on www.clinicaltrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results from this study, but not your individual results. You can search this website at any time.

MEDICAL CARE FOR RESEARCH RELATED INJURY

If you think that injury or illness has happened to you from being in the study, contact the Principal Investigator listed on the first page of this consent. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of SITE. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Participation is completely voluntary and a decision to participate, or to later withdraw from the study, will not affect either your current or future medical care at SITE. If you decide you no longer wish to continue to participate after you have signed the consent form, contact the principal investigator listed on the first page of this consent document. You have the right to request that all information and/or blood samples be destroyed.

VOLUNTARY CONSENT

The study has been described to me and all of my questions have been answered. Any additional questions or concerns about any aspect of this study will be answered by the researchers if questions, concerns or complaints arise. Questions I might have about my rights as a research participant will be answered by the Human Subject Protection Advocate at 1-XXX-XXX-XXXX. By signing this form I consent to participate in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

_____	_____	_____
Participant's Signature	Printed Name of Participant	Date and Time

SURROGATE CONSENT

_____ is unable to provide direct consent for study participation
Participant's Name (Print)

because:_____

Therefore, by signing this form, I give my consent for his/her participation in this research study.

_____	_____
Representative's Name (Print)	Relationship to Participant
_____	_____
Representative's Signature	Date and Time

INVESTIGATOR'S CERTIFICATION

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this research study have been explained to the subject or his/her authorized representative and any questions about this information have been answered.

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study
_____	_____
Signature of Person Obtaining Consent	Date and Time

CONSENT FOR CONTINUED RESEARCH PARTICIPATION

I understand I am currently participating in a research study. Permission for my participation in this study was obtained initially from my authorized representative (proxy) because of my inability to provide consent when initial permission was requested.

I have now recovered to the point where I feel that I can provide direct consent for continued participation in this research study.

The study has been described to me and all of my questions have been answered. I understand that I have the right to request that all information collected to date and/or my blood samples be destroyed.

Any additional questions or concerns about any aspect of this study will be answered by the researchers. Questions I might have about my rights as a research participant will be answered by the Human Subject Protection Advocate at 1-XXX-XXX-XXXX.

By signing below, I agree to continue my participation in this research study. A copy of this consent form will be given to me.

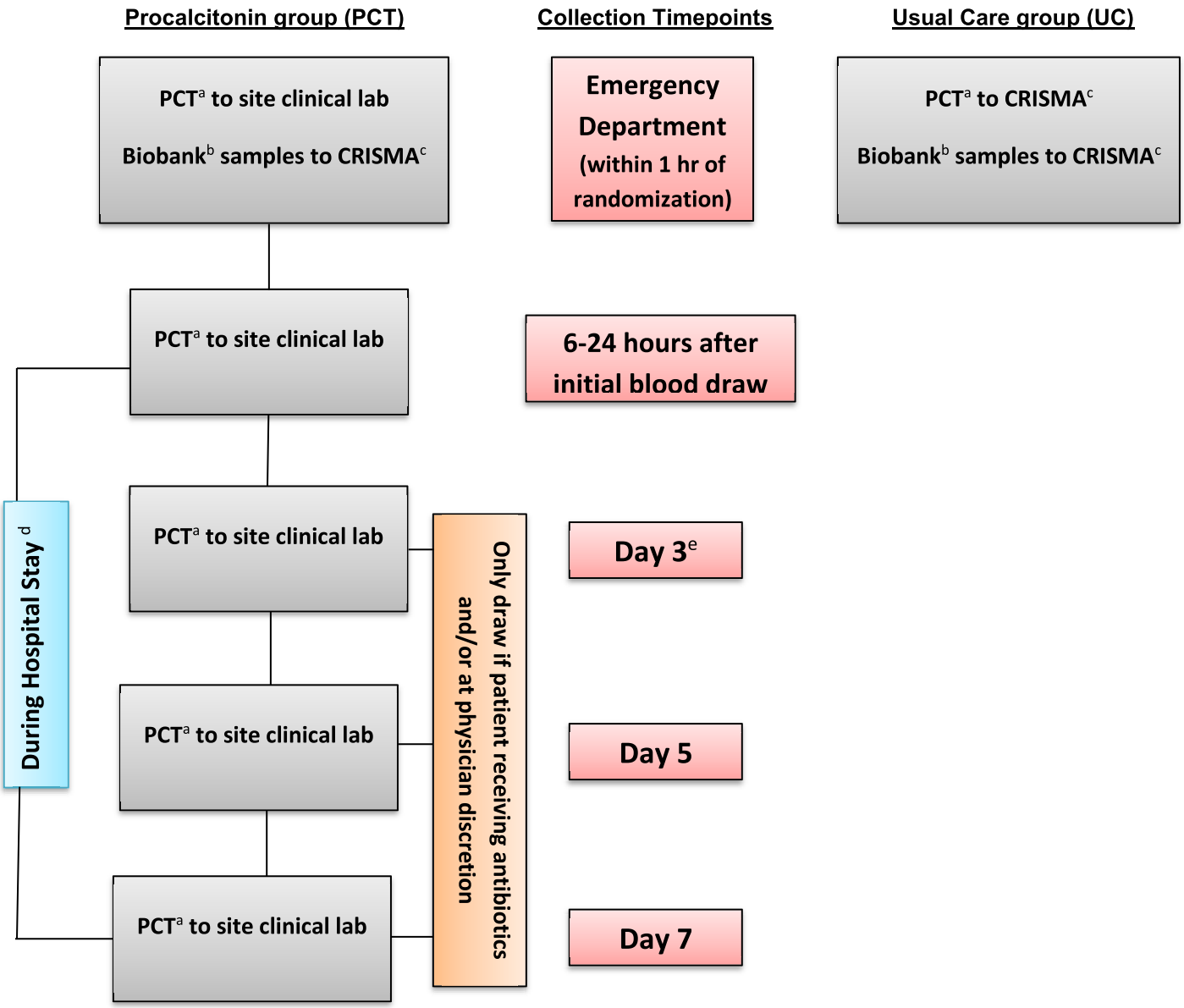
_____	_____
Participant's Signature	Date and Time

INVESTIGATOR'S CERTIFICATION

I certify that the nature and purpose, the potential benefits, and possible risks associated with continued participation in this research study have been explained to the subject or his/her authorized representative and any questions about this information have been answered.

Printed Name of Person Obtaining Consent	Role in Research Study
Signature of Person Obtaining Consent	Date and Time

Appendix 2: Biological Specimen Flowchart



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a. Procalcitonin level – drawn in lithium heparin collection tube (green top tube)
b. Includes: Citrate (blue top tube), lithium heparin (green top tube), EDTA (purple top tube), and PAXgene™ DNA + RNA tubes. Usual care group will use leftover sample from PCT draw and will not require an additional lithium heparin tube.
c. CRISMA Center– Clinical Research, Investigation, and Systems Modeling of Acute Illness, located at the University of Pittsburgh, Department of Critical Care Medicine
d. These levels are only drawn if the patient is in the hospital at the designated collection timepoint.
e. Day 1 is defined as time of randomization in the ED through 11:59PM of that same day.

Appendix 3: Participant Timeline

	Pre-randomization	Randomization /Allocation	In ED/Hospital					Post Discharge[1]	
			Post-Randomization (within 1 hour)	6-24h after 1st PCT draw	Days 3, 5 & 7 while in ED/Hospital	Days while in ED/Hospital[2]	D/C from the ED/Hospital	Day 15[3]	Day 30 [4]
ENROLLMENT									
Eligibility screen	X								
Informed Consent	X								
LRTI Source Document	X								
Allocation/Randomization		X							
INTERVENTIONS									
Procalcitonin test			X[5]	X[6]	X[7]				
Reporting of Procalcitonin			X[8]	X[8]	X[8]				
Biobank samples			X[9]						
ASSESSMENTS									
PHI			X						
Sociodemographic information			X						
Baseline variables & medical history			X						
Diagnostics/Therapeutics/Microbiology/labs			X			X			
Safety outcomes						X			
Antibiotic use			X			X			
Outcome/Disposition							X		
D/C packet							X[10]		
TELEPHONE VISITS									
AQ-20 Questionnaire[11]								X	X
Antibiotic Use								X	X
Post D/C information								X	X
Debit card sent to patient									X

[1] A telephone call will be conducted by the ProACT Coordinating Center Long-term Follow-Up Core for Days 15 & 30. If the participant is still in the hospital for this visit or has been re-admitted to the same hospital, the SC will be responsible for collecting medical record data only.
[2] Day 1 is defined as time of enrollment through 11:59p of the same day. Data collected at this timepoint also includes any rehospitalizations.
[3]; Day 15 will be defined as Day 15 (+/- 5 days)
[4] Day 30 will be defined as Day 30 (+7 days)
[5] Participants randomized to the PCT arm only
[6] PCT arm only; attempt to draw 2nd PCT 6-24 hours after initial ED draw
[7] While in hospital for PCT arm only; if on antibiotics and/or at treating physician's discretion (days 3, 5 & 7)
[8] In the ED, the clinician will be given the PCT result within < 1 hour (goal) – for PCT arm only
[9] All participants will have samples sent to CRISMA at the University of Pittsburgh for research purposes
[10] The discharge packet will consist of an instructional letter and a 30 day antibiotic use calendar.
[11] The AQ-20 questionnaire is not completed if participant still hospitalized at Day15 or Day 30.

Appendix 4: ProACT Telephone Interview Script

Subject Study ID Number								
		-					-	

ProACT Telephone Interview Script

Interviewer: Please complete before start of the interview. Enter ID number on top of every page.									
Date of ED/Hospital Discharge					2	0			
Date of last Interview (if applicable)					2	0			
Date of current interview (MMDDYYYY)					2	0			
Time Point ☐ Day 15 ☐ Day 30									

Start time: _____ _____ : _____ _____

Interviewer (After you have filled the information in the box above and have the proper consent in hand, start timing and begin.):

My name is …from the University of Pittsburgh. I want to thank you for agreeing to participate in this interview as a part of the ProACT Study. As a reminder, you were enrolled into this study when you went to the Emergency Department at [ENROLLING SITE NAME]. This study is being done to learn if a new lab test can help doctors make better decisions about prescribing antibiotics.

The interview will take about 10 minutes to complete and is only for research purposes, does not affect your medical care and will not go into your medical record. When you were discharged you were given a ProACT Study folder containing an Antibiotic Biotic Use Calendar. If you have used the calendar it may be helpful for you to refer to it during this interview. First, I would like to know how you would like to be addressed and verify your contact information.

Respondent
Subject ☐
Proxy ☐ Specify Relationship to Subject _____
Reason for proxy response: Subject too sick/physically unable to speak on phone ☐ Subject has died ☐ Date of Death(mm/dd/yy):_____ Other _____ ☐

Confirm current subject contact information

Is the following information up to date?

Refer to Contact Form to confirm street address, email address, and phone numbers.

☐ **NO CHANGE**

Street Address: ***(Only If Changed)***											
City:											
State:			Zip code:								
Telephone number ***(Only if Changed)***				--				--			
Other number ***(If given another #)***				--				--			
Email address ***(Only if Changed)***											

SECTION 1: Antibiotic Use

Interviewer: I am now going to ask you some questions about your use of antibiotic medications since leaving the Emergency Department/ hospital/our last interview on _____ [date]. Please refer to the antibiotic use calendar you were given when you left the hospital if you have been using it to keep track of the days you have used antibiotics since leaving the hospital. As with everything else in the study, all of the information is confidential.

1. Since being discharged from the Emergency Department/Hospital/our last interview on [DATE] have you taken or are you taking any ANTIBIOTIC Medications?

Yes ☐
No ☐
Unknown ☐
Refused ☐

Interviewer: If "no" or "unknown" skip to Section 2

2. Since being discharged from the Emergency Department/Hospital/our last interview on [DATE] how many total days have you taken ANY antibiotic medication?

Number _____
Unknown ☐
Refused ☐

3. [If antibiotics have been used] What is/are the name(s) of the antibiotic medications you have taken?

Name of Medication

1. _____
2. _____
3. _____
4. _____
5. _____

SECTION 2: Post-Discharge Resource Use

4. Since being discharged from the Emergency Department/Hospital/our last interview on [DATE] have you had any return visits to any Emergency Department or Urgent Care Center?

Yes ☐

Type of Return Visit:	
Emergency Department	☐
Urgent Care Center Visit	☐

No ☐
Unknown ☐
Refused ☐

5.	Since being discharged from the Emergency Department/Hospital/our last interview on [DATE] have you been admitted to any hospital overnight (do not include overnight stays in the ED) Yes ☐ No ☐ Unknown ☐ Refused ☐
6.	[If Yes to question 6]: What is the name of the hospital to which you were readmitted? Enrollment Hospital ☐ Name of Hospital if other: _____ Date of Readmission (mm/dd/yy) :_____

SECTION 3: AQ-20 Questionnaire

Interviewer: The following are some questions about how any breathing or chest issues have been affecting you since leaving the Emergency Department/hospital/since our last Interview

1.	Do you suffer from coughing attacks during the day?	Yes ☐ No ☐ Not Applicable ☐
2.	Because of your chest trouble do you often feel restless?	Yes ☐ No ☐ Not Applicable ☐
3.	Because of your chest trouble do you feel breathless maintaining the garden?	Yes ☐ No ☐ Not Applicable ☐
4.	Do you worry when going to a friend's house that there might be something there that will set off an attack of chest trouble?	Yes ☐ No ☐ Not Applicable ☐
5.	Do you suffer from chest symptoms as a result of exposure to strong smells, cigarette smoke or perfume?	Yes ☐ No ☐ Not Applicable ☐
6.	Is your partner bothered by your chest trouble?	Yes ☐ No ☐ Not Applicable ☐
7.	Do you feel breathless while trying to sleep?	Yes ☐ No ☐ Not Applicable ☐

8.	Do you worry about the long term effects on your health of the drugs that you have to take because of your chest trouble?	Yes ☐ No ☐ Not Applicable ☐
9.	Does getting emotionally upset make your chest trouble worse?	Yes ☐ No ☐ Not Applicable ☐
10.	Because of your chest trouble are there times when you have difficulty getting around the house?	Yes ☐ No ☐ Not Applicable ☐
11.	Because of your chest trouble do you suffer from breathlessness carrying out activities at work?	Yes ☐ No ☐ Not Applicable ☐
12.	Do you feel breathless walking upstairs because of your chest trouble?	Yes ☐ No ☐ Not Applicable ☐
13.	Because of your chest trouble do you suffer from breathlessness doing housework?	Yes ☐ No ☐ Not Applicable ☐
14.	Because of your chest trouble do you go home sooner than others after a night out?	Yes ☐ No ☐ Not Applicable ☐ Unknown ☐ Refused ☐
15.	Because of your chest trouble do you suffer from breathlessness when you laugh?	Yes ☐ No ☐ Not Applicable ☐
16.	Because of your chest trouble do you often feel impatient?	Yes ☐ No ☐ Not Applicable ☐
17.	Because of your chest trouble do you feel that you cannot enjoy a full life?	Yes ☐ No ☐ Not Applicable ☐
18.	Do you feel drained after a cold because of your chest trouble?	Yes ☐ No ☐ Not Applicable ☐
19.	Do you have a feeling of chest heaviness?	Yes ☐ No ☐ Not Applicable ☐
20.	Do you bother much about your chest trouble?	Yes ☐

		No ☐ Not Applicable ☐

Section 4: Interview Burden
I have one final question for you. We would like to know whether this interview was difficult, inconvenient, or was a problem for people to complete.

1. BURDEN OF INTERVIEW. Would you say that this interview was…?	
No problem	☐ 1
A small problem	☐ 2
A moderate problem	☐ 3
A major problem	☐ 4

INTERVIEWER: [For subjects who will have a subsequent Interview]: That completes the interview for today. In order to complete this study, we would like to speak with you one more time and repeat the same questions as were asked today. We would like to schedule this interview with you in approximately 2 weeks, any day

After [DAY 30 date]. What day and time would you like to set up our next phone appointment to complete this interview? [**Interviewer**: Attempt to schedule M-F 8:00 am to 4:00 pm Eastern time]. As a reminder, you will receive $50 as compensation for your time after the second interview is completed.

Next Interview Date/Time; _____
Thank you very much for your participation today and I look forward to speaking with you again on [next interview date/time]. If you have any questions or would like to change your interview time, please call me toll-free at 888-238-0365.
[If second interview completed]Thank you very much for your participation today. To compensate you for your time, we'd like to send you out a MasterCard brand debit card loaded with the amount of $50. [. In order to activate the card, I just need to collect some information from you. **[Interviewer: fill out WePay Information Form]**. Thank you again for your participation, and please feel free to give me a call if you have any questions. My toll-free phone number is 1-888-238-0365.

INTERVIEWER ***(do this AFTER THE END of the interview; this is not part of the script)***: Please describe your impressions of the attitude and cooperation of the respondent as well as any unusual circumstances that might have occurred during the interview.

END TIME:

Appendix 5: Sample Discharge Letter to PCP

Primary care physician letter for ProACT participants randomized to the intervention arm

Dear Site Coordinators,

Please complete the yellow highlighted areas and provide this text on your site's letterhead to the patient when discharged.

(Print on Site hospital / university letterhead) Insert Date

Dear Colleague,

Your patient, _____, agreed to become a participant in a NIH funded randomized trial designed to determine the effectiveness and safety of implementing a procalcitonin-guided guideline on antibiotic use in lower respiratory tract infection (ProACT – Procalcitonin Antibiotic Consensus Trial).

Your patient was enrolled in the intervention arm, which allowed the hospital clinicians to know serum procalcitonin results and view recommendations encapsulated in the below guideline. The treating clinicians could choose any treatment they saw fit after receiving this information.

Procalcitonin level (μg/L)	Bacterial etiology	Recommendation
< 0.1	Very unlikely	Antibiotics strongly discouraged[1]
0.1 - 0.25	Unlikely	Antibiotics discouraged[1]
> 0.25 - 0.5	Likely	Antibiotics recommended[2]
> 0.5	Very likely	Antibiotics strongly recommended[2]

1. Initial antibiotics can be considered for critical illness, Legionella pneumophilia. Procalcitonin should be evaluated in context with all findings and the total clinical status; clinical judgment always necessary.

2. For outpatients, antibiotic duration based on level (> 0.25-0.5 ug/L:3 days; > 0.5-1.0 ug/L:5 days; >1.0 ug/L:7 days). Physician follow-up is recommended.

Your patient's last procalcitonin result, on ____DATE_____, was _____ ug/mL.

Sincerely,

INSERT SITE PI NAME + CONTACT INFO

Procalcitonin Antibiotic Consensus Trial

ProACT Team

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Tel: 412-864-5507

Dear Study Participant,

Thank you for giving your consent to take part in this research study for the University of Pittsburgh. The title of this study is ProACT-Procalcitonin Antibiotic Consensus Trial. The goal of the study is to examine the decisions that doctors are making regarding prescribing antibiotics. A member of the follow up team will be calling you up to two times within 30 days of your visit to the hospital. During these phone calls we will be asking you about your antibiotic use and your health. The calendar that we have included in your discharge folder will be a helpful tool for you to keep track of the days you took an antibiotic. After you have completed both of your follow up phone calls we will be sending you a debit MasterCard in the amount of $50.00 to compensate you for your participation. Please feel free to contact me should you have any questions.

Sincerely,
Kourtney Wofford
Project Coordinator
(412) 647-2584

Email: rymanam@upmc.edu **Project Coordinator** **Kourtney Wofford** CRISMA Center University of Pittsburgh Department of Critical Care Medicine 609 Scaife Hall 3550 Terrace St. Pittsburgh, PA 15261 Tel: 412-647-2584 Email: woffordka@upmc.edu	

Appendix 7: 30 Day Antibiotic Use Calendar

ProACT Telephone Interview Appointment date: **Mm/dd/yyyy**

Preferred time of day: **Morning/Afternoon** (circle one)

Preferred Contact Phone Number: **Home/Cell/Work** (circle one)

ProACT Study Antibiotic Use Tracker

Instructions: For each day on your Antibiotic Use Tracker, please record if you have taken any antibiotics on this day by marking "yes" or "no". You will be asked about the number of days you have taken antibiotics since leaving the hospital at the time of your scheduled telephone interview appointment. Begin marking your antibiotic use on the day that you leave the hospital.

Date/Study Day _____/___	Date/Study Day _____/___	Date/Study Day _____/___	Date/Study Day _____/___	Date/Study Day _____/___	Date/Study Day _____/___	Date/Study Day _____/___
Any Antibiotics? ***___yes ___no***	***Any Antibiotics?*** *___yes ___no*	***Any Antibiotics?*** *___yes ___no*	***Any Antibiotics?*** *___yes __no*	***Any Antibiotics?*** *___yes __no*	***Any Antibiotics?*** *___yes __no*	***Any Antibiotics?*** *___yes ___no*
Date/Study Day _____/___	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**
Any Antibiotics? ***___yes ___no***	***Any Antibiotics?*** *___yes ___no*	***Any Antibiotics?*** *___yes ___no*	***Any Antibiotics?*** *___yes __no*	***Any Antibiotics?*** *___yes __no*	***Any Antibiotics?*** *___yes __no*	***Any Antibiotics?*** *___yes ___no*
Date/Study Day _____/___	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**
Any Antibiotics? ***___yes ___no***	***Any Antibiotics?*** *___yes ___no*	***Any Antibiotics?*** *___yes ___no*	***Any Antibiotics?*** *___yes __no*	***Any Antibiotics?*** *___yes ___no*	***Any Antibiotics?*** *___yes __no*	***Any Antibiotics?*** *___yes ___no*
Date/Study Day _____/___	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**	**Date/Study Day _____/___**
Any Antibiotics? ***___yes ___no***	***Any Antibiotics?*** *___yes ___no*	***Any Antibiotics?*** *___yes ___no*	***Any Antibiotics?*** *___yes __no*	***Any Antibiotics?*** *___yes __no*	***Any Antibiotics?*** *___yes ___no*	***Any Antibiotics?*** *___yes ___no*
Date/Study Day _____/___	**Date/Study Day _____/___**					
Any Antibiotics? ***___yes ___no***	***Any Antibiotics?*** *___yes ___no*					

Appendix 8: Airway questionnaire 20 (AQ-20)

AIRWAY QUESTIONNAIRE 20 (AQ20)

	Yes	No	Not Applicable
1. Do you suffer from coughing attacks during the day?			
2. Because of your chest trouble do you often feel restless?			
3. Because of your chest trouble do you feel breathless maintaining the garden?			
4. Do you worry when going to a friend's house that there might be something there that will set off an attack of chest trouble?			
5. Do you suffer from chest symptoms as a result of exposure to strong smells, cigarette smoke or perfume?			
6. Is your partner bothered by your chest trouble?			
7. Do you feel breathless while trying to sleep?			
8. Do you worry about the long term effects on your health of the drugs that you have to take because of your chest trouble?			
9. Does getting emotionally upset make your chest trouble worse?			
10. Because of your chest trouble are there times when you have difficulty getting around the house?			
11. Because of your chest trouble do you suffer from breathlessness carrying out activities at work?			
12. Do you feel breathless walking upstairs because of your chest trouble?			
13. Because of your chest trouble do you suffer from breathlessness doing housework?			
14. Because of your chest trouble do you go home sooner than others after a night out?			
15. Because of your chest trouble do you suffer from breathlessness when you laugh?			
16. Because of your chest trouble do you often feel impatient?			
17. Because of your chest trouble do you feel that you cannot enjoy a full life?			
18. Do you feel drained after a cold because of your chest trouble?			
19. Do you have a feeling of chest heaviness?			
20. Do you bother much about your chest trouble?			

University of Pittsburgh Department of Critical Care Medicine

CRISMA Center
Data Management Core
Standard Operating Procedures

Honest Broker Services

Purpose	This document describes the CRISMA Center's policies for Honest Broker services for ensuring compliance with the Health Insurance Portability and Accountability Act (HIPAA) and US Department of Health and Human Services Office for Human Research Protections (OHRP) regulations regarding human subject data.
Scope	This document applies to all personnel employed by or using any computer owned and operated by CRISMA; all computers owned or operated by CRISMA; and all human subject data managed by CRISMA and determined by regulatory agencies to require Honest Broker services.
Definitions	**Protected Health Information (PHI).** Any information about health status, provision of health care or payment of health care that can be linked to a specific individual. **HIPAA Privacy Rule.** The portion of the Health Insurance Portability and Accountability Act of 1996 that governs use and disclosure of PHI. Under the privacy rule, PHI can be used for research purposes with either patient approval or waiver by an authorized regulatory agency. **Common Rule.** US Federal regulations for protection of human subjects in research, described by the Department of Health and Human Services in the Code of Federal Regulations Title 45 Part 46. **Unique identifiers.** Variables defined by HIPAA as uniquely identifying individuals, including names; geographical subdivisions smaller than a state except the initial three digits of a ZIP code as long as that ZIP code contains more than 20,000 people; all elements of dates except year and all ages over 89; phone numbers; fax numbers; e-mail address; social security numbers; medical record numbers; health plan numbers; account numbers; certificate/license numbers; vehicle numbers; web URLs; IP addresses; biometric identifiers; full face photos; and any other unique identifying numbers. **De-identified data.** Health data that does not contain unique identifiers as defined by HIPAA. **Limited data set.** A de-identified data set that contains either (a) geographic subdivisions not smaller than a town, city, state and ZIP code; (b) dates, or (c) ages over 89 **Safe harbor data set.** A de-identified data set that does not contain any of the unique identifiers as defined by HIPAA. **Researcher.** As defined by the Common Rule, any individual conducting or a assisting in the conduct of a systematic investigation designed to develop or contribute generalizable knowledge.

	Honest Broker. An individual serving as a disinterested intermediary between the researcher and PHI, ensuring that the researcher does not have access to identifiable information.
Responsibilities	**Research team responsibilities** *Regulatory approval.* All CRIMSA research projects involving PHI must be reviewed and approved by the University of Pittsburgh Institutional Review Board (IRB). CRISMA researchers are responsible for adhering to IRB-approved data storage and analysis policies at all times, including seeking the services of an Honest Broker when required. *Data security.* CRISMA researchers or agents working with CRISMA data must maintain appropriate electronic and physical data security procedures at all times. Electronic security procedures include developing secure passwords, disabling automatic logons, locking computers when unattended, and reporting all suspicious electronic events. Physical security procedures include keeping all hard-copy PHI in locked filing cabinets in locked offices, shredding all paper records when finished, and securely delivering all hard-copy PHI to an Honest Broker as required by IRB policies. **Honest Broker responsibilities** *Honest Broker agreement.* The Honest Broker must execute and maintain an up-to-date Business Associate Agreement with UPMC and/or the University of Pittsburgh, the terms of which will specify the continuing confidentiality requirements, duties and other expectations of an Honest Broker service. *Data security.* The Honest Broker must maintain all data containing PHI according to the data security procedures set out in the CRISMA Standard Operating Procedures for Data Management. *Confirmation of IRB approval.* The Honest Broker must ensure IRB approval for the research study for which Honest Broker services are requested. *Adherence to IRB terms.* The Honest Broker must adhere to all of the terms and conditions specified by the IRB of record for any research study for which Honest Broker services are requested, including the type of data requested (Limited Data Set or Safe Harbor Data Set) and the identity of the researchers granted access to the data. *Ensure proper de-identification.* The Honest Broker will produce the requested dataset (either Limited Data Set or Safe Harbor Data Set) from the PHI as required by the investigator and approved by the IRB. Maintain documentation. The Honest Broker will maintain documentation of the processes and/or systems used to develop de-identified datasets from PHI.

Procedures	**Receipt of data** • When the Honest Broker receives PHI, the Honest Broker will upload it onto a secure data storage system as described in the CRISMA Data Management Standard Operating Procedure. Access to the PHI shall be restricted to only the Honest Broker. • If the PHI is received via e-mail or network, the Honest Broker will ensure that the original and all copies of the file are deleted after uploading. • If the PHI is received via paper or electronic media, the Honest Broker will lock the media in a secure file cabinet in a secure office after uploading it the appropriate secure data storage system. **De-identification of data** • The Honest Broker will confirm IRB approval for the individual requesting data and the type of dataset requested. • If a limited data set is requested, the Honest Broker will create a new data set containing all the data present in the original data set except for the appropriate unique identifiers. The Honest Broker will create a new study identifier and retain a crosswalk between this identifier and unique identifiers in the PHI, storing this crosswalk in a secure location. • If a safe-harbor data set is requested, the Honest Broker will create a dataset containing all the data present in the original data except for any unique identifiers. **Re-identification** • If re-identification of data is necessary for research and approved by the IRB, the Honest Broker will use study identifiers in the retained crosswalk to link datasets to PHI. This process will be performed in a secure computing environment as described in the CRISMA Data Management SOPs. **Documentation** • The Honest Broker will keep a record of each data transaction, including the transaction date and time; the identity of the researcher; the name of the study; the nature of the data set; the name and location of the crosswalk file; and the corresponding IRB approval numbers. This record will kept in a secure data file as described in the CRISMA Data Management SOPs.
Approval	This CRISMA Standard Operating Procedure was approved by the CRISMA Executive Committee on 3.4.2013.

Appendix 10: ProACT Medical Records Release Form

Authorization to Release Protected Health Information for Research

Participant Name _____ Date of Birth _____

Social Security/Medical Record Number: _____

I authorize _____ to release information from the record _____
Hospital/Provider Participant Name
to the **ProACT** study team located within the Department of Critical Care Medicine at the University of Pittsburgh. The reason for this request is that I am a participant in this research study. These records are for **research purposes only**, and are not being used for patient care. I authorize a photocopy or facsimile of this authorization to be acceptable and valid. I understand that I may revoke this authorization in writing at any time by providing a request to the study investigators. I understand that once this information is disclosed, it may be re-disclosed by the recipient and the information may not be protected by federal privacy laws or regulations. My request to release these records will have no impact on the releasing facility's provision of care to me.

The records to be released are for the treatment dates: __ __/__ __/__ __to __ __/__ __/__ __ for a diagnosis of

_____.

_X_ Face Sheet/Attestation with ICD codes _X_ Discharge/Death Summary

_X_ Admitting History & Physical Exam

_X_ Medication Administration Records

_X_ Radiology Reports

_____ _____
Participant/ Representative Signature Date Witness Date

_____
Relationship to participant, if representative

Health Information Department:
Records may be faxed to Jonathan Holton, Honest Broker, at 412.864.5901. Please call Elizabeth Gimbel at 412-647-7776 or Ashley Ryman at 412-864-5507 with any questions about this request.