

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

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STATISTICAL ANALYSIS PLAN OF THE PROCALCITONIN ANTIBIOTIC CONSENSUS TRIAL (PROACT)

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ABSTRACT

Background: The Procalcitonin Antibiotic Consensus Trial (ProACT) is a multicenter randomized trial designed to determine the impact of a procalcitonin antibiotic prescribing guideline, implemented with basic reproducible strategies, in US emergency department (ED) patients with lower respiratory tract infection.

Objective: To provide the a priori trial statistical analysis plan.

Methods: The ProACT trial is a patient-level randomized, multicenter, prospective, parallel-arm clinical trial. A total of 1,664 patients were randomly allocated 1:1 to either the procalcitonin guided arm or usual care. The primary outcome measures are total antibiotic days and a composite adverse outcome endpoint by Day 30. Secondary outcomes and other measured data are declared. Key trial design components are highlighted. Methods for statistical analysis are described, including the primary analysis method, secondary and sensitivity analyses, plan for handling missing data, and accounting for non-compliance. Intervention effect will be evaluated in pre-specified subgroups.

Discussion: Our analysis plan set in advance limits bias in data analyses and reporting of results.

Trial registration: This study was registered at ClinicalTrials.gov, NCT02130986, on May 1, 2014.

I. OVERVIEW

BACKGROUND AND GOALS

Antibiotic prescribing is a common medical decision-making problem. Clinicians over prescribe antibiotics for fear of untreated bacterial illness, contributing to antibiotic overuse [1, 2] and resistance [3, 4]. This pattern is common in suspected lower tract respiratory infection (LRTI), where distinguishing bacterial from viral etiologies is challenging. As a marker for bacterial infection [5-7], several European trials found that procalcitonin-guided care may safely reduce antibiotic use in LRTI [8-11]. However, applicability to United States (US) practice is unclear[12]. Current recommendations for procalcitonin guided LRTI care vary from strong support to discouraging routine adoption [13-15].

The Procalcitonin Antibiotic Consensus Trial (ProACT) is a patient-level randomized, multicenter, prospective, parallel-arm trial to assess the effects of a procalcitonin guideline (implemented with basic reproducible strategies) on antibiotic exposure and adverse outcomes in patients managed for a clinically diagnosed LRTI in a U.S. emergency department. The University of Pittsburgh institutional review board (IRB) approved the design. The trial is registered with ClinicalTrials.gov (NCT02130986). Further details about the study rationale, design, and implementation are reported elsewhere [16].

The aim of this paper is to present the statistical analysis plan for the ProACT trial. We finalized the plan before treatment assignment was unblinded.

PATIENT POPULATION

From 14 EDs in the US, we enrolled adults with a primary clinical diagnosis of acute LRTI. Detailed inclusion and exclusion criteria were previously reported [16] and are summarized below.

Inclusion criteria

Enrolled patients were at least 18 years of age, with a primary clinical diagnosis of acute LRTI (as per the treating clinician), and treated by a clinician willing to consider procalcitonin in antibiotic decision-making.

Exclusion criteria

Patients with conditions where (1) physicians are unlikely to withhold antibiotics (e.g., endotracheal ventilation), (2) procalcitonin can be elevated without bacterial infection (e.g., recent surgery), or (3) follow-up would be difficult (e.g., prisoners, homeless) were excluded.

STUDY HYPOTHESES

We will sequentially test the following null hypotheses:

- H1o: Procalcitonin guideline implementation does not reduce antibiotic exposure by Day 30.
- H2o: Procalcitonin guideline implementation increases the proportion of subjects who experience a composite endpoint of adverse outcomes by Day 30, by $\geq 4.5\%$. (noninferiority)

In the final analyses, we will also test a more conservative null hypothesis:

- H1o: Procalcitonin guideline implementation does not reduce or increase antibiotic exposure by Day 30.

II. MEASURES

PRIMARY OUTCOMES

Our primary outcome (Aim 1) is total antibiotic exposure, defined as the total number of antibiotic-days by Day 30. An antibiotic-day occurs when a patient receives any oral or intravenous antibiotics, excluding antibiotics given for non-infectious indications (e.g. rifaximin for hepatic encephalopathy) and antivirals. We will determine the total number of antibiotic-days by Day 30 by combining the number of antibiotic-days from ED or hospital admission to discharge, with the number of antibiotic-days from discharge to Day 30 (obtained by phone calls at Day 15 and Day 30, and from any rehospitalization up to Day 30). Our primary safety outcome (Aim 2) is a combined endpoint of adverse outcomes that could result from withholding antibiotics in LRTI. The composite endpoint consists of death, septic shock (vasopressor use), mechanical ventilation via endotracheal tube, renal failure (Kidney Disease: Improving Global Outcomes stage 3 – new renal replacement therapy, tripling of baseline creatinine, or serum creatinine ≥ 4.0 mg/dL [17]), lung abscess/empyema, development of pneumonia in non-pneumonia LRTI, and hospital readmission. The primary safety outcome is reached if at least one of these outcomes occur by Day 30. We will also examine each adverse outcome individually. We will determine if these outcomes have been reached by Day 30 by combining outcome occurrences from ED or hospital admission to discharge, with outcome occurrences from discharge to Day 30 (obtained by phone calls at Day 15 and Day 30, and from any rehospitalization up to Day 30).

SECONDARY OUTCOMES

Secondary outcomes include antibiotic initiation by the initial ED clinician (reached if the patient received antibiotic during ED visit), hospital length of stay (number of days from ED admission to hospital discharge), 90-day and 1-year mortality (determined through a National Death Index [NDI] search or by direct contact with the patient or their listed contacts), ICU admission and subsequent ED visits by Day 30, and quality of life using AQ-20.

ADVERSE EVENTS

We captured the major potential adverse events related to antibiotic withholding in our combined safety endpoint, and examine each adverse event using standard reporting methodology. We used the standard definitions of adverse events (AE) and serious adverse events (SAE) that met the definition of an Immediately Reportable Event (serious, unexpected AND related) within 48 hours of recognition; the coordinating center then notified the data and safety monitoring board (DSMB) and University of Pittsburgh IRB within 48 hours. All other AEs and SAEs were reviewed quarterly by the DSMB. When an AE/SAE occurred, it was the site PI's responsibility to review the pertinent records, and assess causality between the event and the study protocol using best clinical judgment. AEs were reviewed by the DSMB, which recommended follow-up or protocol modification, as deemed appropriate.

III. DESIGN

DATA COLLECTION AND FOLLOW-UP

Site study coordinators collected data by direct observation, chart review, and subject or family member interview, and entered data into a Web-based form. This form was linked to a comprehensive server, provided built-in logic checks and queries, and had comprehensive training and instruction documentation to minimize site burden.

The stages of data collection and follow-up are randomization, baseline, ED, hospital follow-up, 30-day follow-up, and post-discharge survival. **Table 1** describes data that were collected at each stage. To further minimize site burden, all data except 30-day follow-up could be collected retrospectively.

TREATMENT ALLOCATION

We randomized subjects equally to either the procalcitonin guideline arm or usual care arm under a permuted block design, stratified by center, race, and age. The allocation list was computer generated and concealed within an automated centralized Web-based randomization system. This system ensures that treatment assignment is free from human influence. Only patients who met eligibility criteria and consented for participation were enrolled. The system assigned patients to a study arm only after enrollment. Coordinators entered participant information into the web-based data collection form then received a study ID number and treatment assignment from the randomization system.

BLINDING

The treating clinician and study staff could not be blinded to allocation due to the nature of the intervention, but post-discharge outcome assessors and statistical summaries for trial monitoring were unaware of group allocation. We restricted unblinded data evaluation during the trial and before setting this plan to a designated study statistician and the DSMB. We will unblind investigators and begin analyses only after all data collection forms are completed, data queries resolved, and data are locked for analysis.

POWER AND SAMPLE SIZE

The sample size was driven by the safety aim (H2o) due to the non-inferiority hypothesis and the binary nature of the outcome. The original sample size of 1,514 participants (757 per arm) was based on the differences in proportions in the composite adverse outcomes endpoint between the two arms. Our power calculations accounted for two interim analyses at approximately 1/3 and 2/3 enrollment with stopping boundaries calculated using the O'Brien and Fleming method, $\geq 80\%$ power to reject H2o, and a predefined 4.5% noninferiority margin. The noninferiority margin was chosen based on clinical meaningfulness and feasibility within funding constraints. It is approximately half that of the Infectious Diseases Society of America's recommendation and of two large trials of procalcitonin antibiotic guidance [10, 18].

We assumed 11% adverse outcomes by Day 30 in the usual care arm [19, 20] and a 10% loss to follow up for the original sample size estimate. We prospectively monitored both frequencies based on the overall blinded sample with intent to recalculate and adjust the sample size as necessary. The use of blinded data for the recalculation ensures that the overall significance level is 0.05. After approval by the DSMB in April 2017, the sample size was increased to 1,664 participants.

IV. STATISTICAL ANALYSIS

TRIAL PROFILE

We summarize participant flow using the Consolidated Standards of Reporting Trials diagram (CONSORT) [21-23]. The report will include number of patients screened, eligible, consented, enrolled, completed follow-up, and included in the analyses.

ANALYSIS PRINCIPLES

- We will do all primary analyses using the intention-to-treat (ITT) principle, and analyze subjects with protocol violations based on the assigned study arm, excluding only patients who withdrew consent. We will report exclusions reasons and counts by arm. For missing data, we will use multiple imputation [24] to allow standard implementation of the ITT principle [25] and to reduce bias and increase efficiency relative to a complete-case analysis [23, 26].

- Per CONSORT recommendations [22], we will also conduct per-protocol analyses in which non-protocol compliant subjects are excluded. This is deemed important because ITT may lead to false rejection of H2o, which uses a noninferiority design. Per-protocol analysis may not be the best alternative to ITT, as it may be biased when inherent differences between compliers and non-compliers exist[27]. Therefore, we will conduct sensitivity analyses by using instrumental variable [29-33] approaches to determine the complier average causal effect (CACE) [31].
- For H1o, we initially chose and conducted interim analyses based on one-sided significance levels, because we believed procaltitonin would not increase antibiotic use over an already high baseline. However, in the final analysis, we will also conduct a two-sided test to be more conservative and not rule out a potential increase in antibiotic exposure. For H2o, noninferiority testing is inherently one-sided.
- We plan pre-defined subgroups analyses irrespective of treatment effect in the overall cohort.

BASELINE COMPARISONS AND ASSESSMENT OF RANDOMIZATION

We will compare the distribution of baseline variables between study arms to assess randomization success. To summarize continuous variables, we will use means and standard deviations or medians and interquartile range, and will deploy frequencies and percentages for categorical variables.

INTERIM ANALYSES

The ProACT Coordinating Center planned to conduct two interim analyses and a final analysis using the O'Brien and Fleming stopping rules defined *a priori* controlling for an overall Type I error rate of 0.05. The first and second interim analyses occurred by plan at approximately 1/3 and 2/3 enrollment and completed in September 2016 and April 2017, respectively. The independent DSMB reviewed the results from each of the two interim analyses. Before trial completion, only the DSMB and a designated study statistician had access to unblinded data. During the interim looks, the DSMB could have recommended early trial termination due to one or more of the following reasons:

1. Efficacy - a significant difference is found for H1o and significant noninferiority for H2o, indicating decreased antibiotic exposure in the intervention arm and not worse in a combined adverse outcome point based on a predetermined noninferiority margin, resulting in a decision to stop the trial for efficacy.
2. Futility (H1o) - no difference is found for H1o based on defined futility bounds, resulting in a decision to stop the trial.
3. Futility (H2o) - a significant difference is found for H1o (i.e., decreased antibiotic exposure in the intervention arm) and a futility bound is crossed for H2o because of excess adverse outcomes in the intervention arm.
4. Failure to obtain success in the implementation of the trial either through failure to accrue subjects at the necessary rate, improper data handling, or inability to implement study protocols.

Figure 1 provides a schematic overview of these scenarios. The stopping boundaries are shown in **Table 2**. In addition to the findings of formal hypothesis testing, the DSMB could have recommended trial stoppage due to safety concerns.

MISSING DATA

Despite best efforts to obtain follow-up data, we anticipated some loss-to-follow-up. Optimal ITT includes analysis of data from all subjects randomized and cannot be directly adopted in the presence of missing data [25]. A complete-case analysis may lead to loss of power, and bias may be introduced when missing is not completely at random [23]. To resolve, we chose multiple imputations [24] to conduct the ITT analyses.

We will describe the extent and reasons that data are missing, summarizing the proportion of patients with missing data for each outcome and by study arm and by site. We will compare baseline patient characteristics between those who have complete outcome data and those that do not.

Multiply-imputed datasets will be generated using multivariate imputation by chained equations, an approach designed for multivariate data that can accommodate mixed data types [34]. We will use predictive mean matching and logistic regression to impute continuous and binary outcomes, respectively. We will generate 100 imputed datasets to maintain power, although 3-5 imputed datasets are usually sufficient to obtain excellent results [35].

We assume that missing outcome data are missing-at-random (MAR) in that they can be imputed reasonably well from the observed study data. We will perform imputation based on the study arm the patient was assigned to. Auxiliary variables for the imputation model will include patient baseline variables (e.g, age, sex, race, comorbidity, and condition), key ED clinician type (i.e., attending, fellow/resident, physician assistant/nurse practitioner) and study site. We will also include available intermediate outcomes, such as 15-day data to impute 30-day missing data.

ANALYSIS OF PRIMARY OUTCOMES

For H1o, we will test the hypothesis that procalcitonin guideline implementation does not change antibiotic exposure by comparing the mean number of 30-day total antibiotic-days between the procalcitonin and usual care arms using a two-sample t-test, or a Wilcoxon rank sum test if data are non-normal.

For H2o, we will compare the difference in proportions of the composite adverse outcomes endpoint, relative to a 4.5% noninferiority margin, and construct a two-sided 95% confidence interval for the difference in proportions. We will declare noninferiority if the upper limit of the confidence interval is below 4.5%.

ACCOUNTING FOR NON-COMPLIANCE

The study protocol intervention reports the procalcitonin results and guideline to the treating clinician. The first and primary measure of protocol compliance is intervention delivery. We define procalcitonin reporting compliance to have been achieved in those subjects whose key clinician received procalcitonin information at $\geq 80\%$ of the protocol-specified timepoints (in the ED, and if hospitalized, 6-24h after the ED measurement, and on Days 3, 5, and 7 if still in hospital and on antibiotics). As the protocol intervention involves multiple time points, we defined compliance based on satisfactory rather than full adherence [36].

The study protocol stipulates clinicians have decision-making autonomy, and thus clinicians who act discordantly with the procalcitonin guideline are not in violation of the protocol. We do however aim to understand cases where clinicians choose actions congruent with the procalcitonin guideline, and term this scenario procalcitonin guideline care congruence. We define procalcitonin guideline care congruence to have been achieved in those subjects whose key clinician followed the procalcitonin guideline $\geq 80\%$ of the time in the procalcitonin guideline arm. These criteria imply that congruence status is only observable in the intervention arm. If the clinician never received procalcitonin information at any of the time points, we exclude the subject from the congruence analysis since congruence status is unevaluable.

We will report frequency and rates of each compliance type. For procalcitonin guideline care congruence (or lack of congruence), we will also consider magnitude (e.g., antibiotic prescription despite a strong versus a simple guideline recommendation to withhold) and direction (e.g., antibiotic prescription despite guideline recommendation to withhold, versus antibiotic withholding despite recommendation to prescribe).

Under imperfect compliance in the procalcitonin guideline arm, an ITT analysis evaluates the effect of random assignment (effectiveness), not necessarily the effect of the intervention itself if received as intended (efficacy) [27, 37]. It can bias towards no difference, which may lead to a false rejection of H_0 , which uses a noninferiority design. Hence, we will also perform a per-protocol analysis in the final look following CONSORT guidelines, focusing on compliance of procalcitonin reporting.

SECONDARY OUTCOMES ANALYSIS

We will follow the analysis strategies used for the primary outcomes to compare the secondary outcomes between study arms. Both ITT and per-protocol analyses will be conducted. Differences in proportions for secondary binary endpoints (antibiotic initiation by initial ED physician, ICU admission, subsequent ED visits by Day 30) will be estimated along with 95% confidence intervals. Continuous secondary endpoints (hospital length of stay, quality of life) will be compared using two-sample t-test or Wilcoxon rank sum test. Mortality at 90-days and 1 year will be estimated using Kaplan-Meier. All analyses of the secondary outcomes are considered descriptive and no formal inferences will be drawn from the secondary outcome analyses.

SUBGROUP ANALYSES

We will conduct prespecified subgroup analyses to understand the treatment effect, and to identify subgroups of patients for whom the treatment was particularly beneficial and/or harmful. These analyses will allow future hypothesis generation. The subgroups are predefined to limit bias. We will include subgroup analyses on lower respiratory tract infection subtype; ethnicity – Hispanic/Latino, race – African-American, White, other; gender – female, male; and age – below 65 years, 65 years and older.

SENSITIVITY ANALYSES

The MAR assumption in imputing missing data is unlikely to bias findings for H2o, which uses a noninferiority design [38]. Sensitivity analyses will assess the robustness of study findings to missing data. We will conduct a complete-case analysis, which assumes that data are missing-completely-at-random (MCAR). We will also conduct a missing-not-at-random (MNAR) sensitivity analysis using control-based imputation in which all data are imputed based on the usual care arm. This assumes that the unobserved outcome in the procalcitonin arm would have been similar to what was observed in the control arm. It imputes an outcome almost certainly worse than that assumed by MAR [38], and is unlikely to positively bias the efficacy aim H1o.

Per-protocol analyses may suffer from selection bias [27]. As an alternative, we will use an instrumental variable approach to estimate the CACE. The CACE measures the impact of the intervention in the subgroup of the population that complies with the assigned intervention [29, 31]. It is a widely used complementary parameter of interest for treatment efficacy in randomized experiments [31]. The intervention assignment will be used as the instrument since

due to randomization, its impact on outcome is expected to be entirely mediated through the receipt of the intervention [33].

EXPLORATORY ANALYSES

The instrumental variable approach could correct the selection bias in the per-protocol analysis if the bias stems from unmeasured confounders. However, if the bias was due to measured variables, propensity scores can be used to balance background characteristics facilitating a fair comparison between groups. We will also conduct a propensity score approach to estimate the CACE. To build the propensity score model for compliance, we will consider all available baseline variables of patients, key clinician characteristics, and site. We will then adopt the principal causal effect estimation method [28] to estimate CACE .

If antibiotic use differs between the two study arms, we will also explore ways to determine integrated measures of overall gains in decision-making accuracy due to the procalcitonin guideline. We will leverage the randomized design, which allows an assumption that the underlying rate of a given condition, even when not directly measured, is balanced at baseline between study arms.

V. CONCLUSION

We described our approach to analyzing the data from ProACT prior to unblinding. This will enhance the utility of the reported results and allow readers to better judge the quality and credibility of the findings.

TABLES

TABLE 1 – DATA COLLECTED AT EACH TRIAL STAGE

| Stage | Data collected |
|-------------------|---|
| Pre-randomization | <ul style="list-style-type: none"> • Patient demographics and inclusion/exclusion criteria |
| Baseline | <ul style="list-style-type: none"> • Sociodemographics - age, sex, race, ethnicity, residence, employment status, baseline physical function • Comorbidities and medications - Charlson comorbidity index, and medications related to respiratory care • Respiratory history - onset of symptoms, respiratory symptoms, tobacco, chronic respiratory diseases • Severity of illness and laboratories: PSI, CURB-65; clinically obtained labs, pulse oximetry • LRTI categories <ul style="list-style-type: none"> i. CAP - new radiologic pulmonary infiltrate, and one or more of the following criteria: cough, > 38.0 or $< 36.0^{\circ}\text{C}$, sputum production, dyspnea, tachypnea, rhonchi, wheezing, chills, chest discomfort, white blood cell count $> 10^{10}$ or $< 4 \times 10^9$ cells/L [10, 39, 40] ii. COPD exacerbation - past medical history of or consistent with COPD, and acute worsening dyspnea, cough, or sputum production [41] |

| | |
|----|---|
| | <p>iii. Asthma exacerbation - past medical history of or consistent with asthma, and acute worsening dyspnea, cough, wheezing, or chest discomfort [42-44]</p> <p>iv. Acute bronchitis - acute onset of cough, lasting less than 3 weeks in the absence of underlying lung disease (no past medical history of or consistent with COPD or asthma) or new infiltrate on chest x-ray [8, 45]</p> <p>v. Other</p> <p>a. Other, LRTI - > 1 respiratory symptom (cough, sputum, dyspnea, tachypnea, chest discomfort), and > 1 auscultation abnormality (wheezing or rhonchi) or > 1 infection sign (> 38.0 or < 36.0°C, chills, or white blood cell count > 10^{10} or < 4×10^9 cells/L), that does not meet (i)-(iv) criteria [10, 40]</p> <p>b. Other, non-LRTI - those that do not meet (i.) - (v.a.) criteria</p> |
| ED | <ul style="list-style-type: none"> • Antibiotics prescribed – name, dose, route, time • Therapeutics and diagnostics – mechanical ventilation, steroids, bronchodilators, diuretics, CT scans, and chest x-rays • Disposition – home, observation unit, hospital admission (floor, stepdown, ICU) |

| | |
|-------------------------|---|
| Hospital follow-up | <ul style="list-style-type: none"> • Antibiotics prescribed – name, dose, route, days • Therapeutics and diagnostics – mechanical ventilation, steroids, bronchodilators, diuretics, radiologic tests • Adverse outcomes – vasopressors/mechanical ventilation/new renal replacement therapy ever used, highest recorded creatinine, lung abscess/empyema, pneumonia diagnosed after enrollment (for non-CAP LRTI), date of discharge (length of stay), ICU admission • Clinically obtained microbiology results • Disposition – home, nursing home, rehabilitation facility, etc. • 15-day and 30-day follow-up • We used a structured interview process for vital status, antibiotic days, repeat ED visits/hospital admissions and reason, and quality of life. |
| Post-discharge survival | <ul style="list-style-type: none"> • We are collecting 90-day and 1-year mortality data through a National Death Index (NDI) search or, for more recently enrolled subjects, by direct contact with the patient or their listed contacts. For NDI, there is a 2-year time lag before these data are available, so for patients enrolled near the end of the trial, we will perform primary analyses before their 1-year follow-up data are available, and a shorter follow-up will be handled with censoring. |

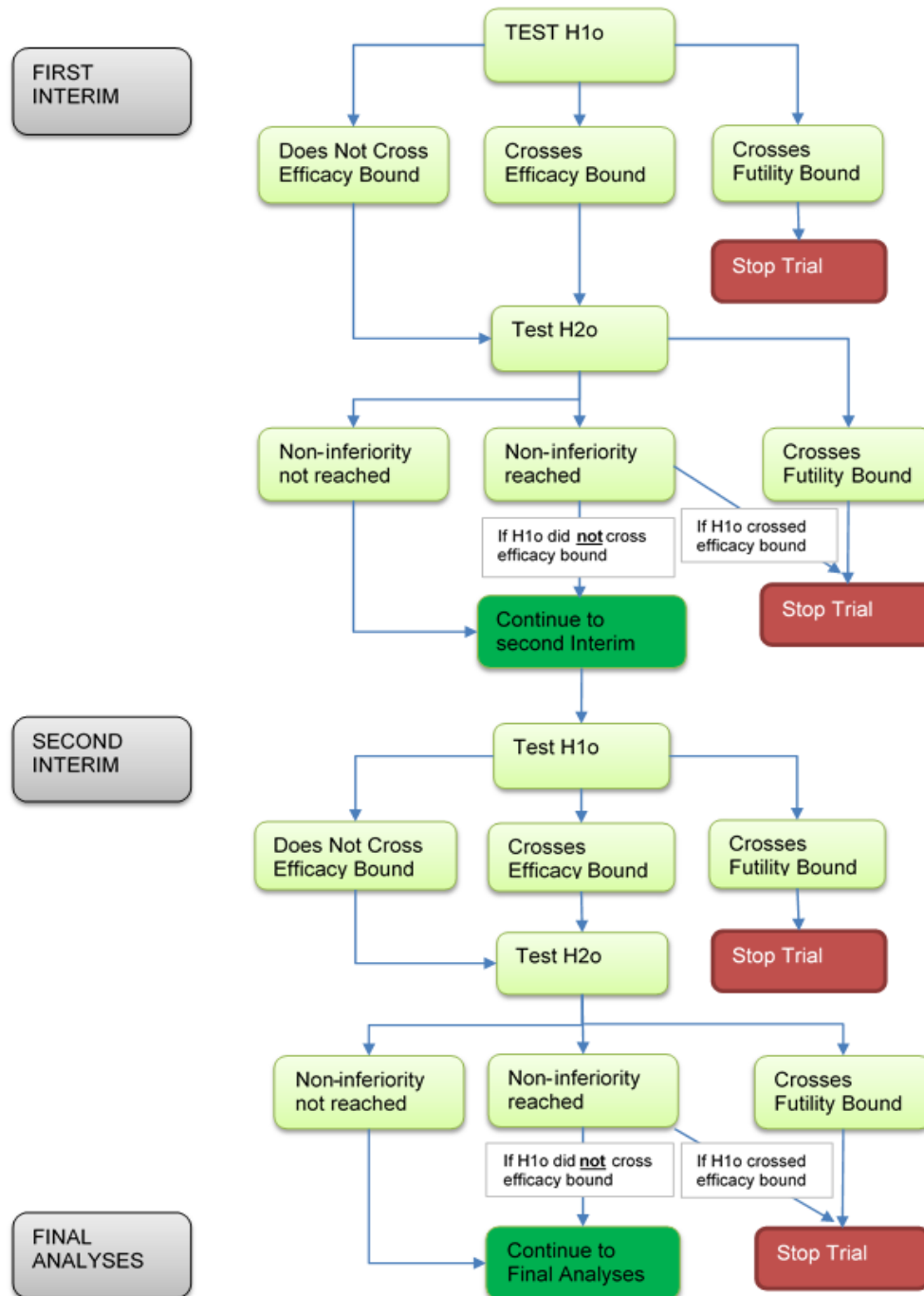
TABLE 2 – INTERIM ANALYSES T-VALUE STOPPING BOUNDARIES

| Interim | H1o | | H2o | | α – spending* |
|---------|----------|----------|----------|----------|----------------------|
| | Efficacy | Futility | Efficacy | Futility | |
| 1 | < -3.21 | > 1.64 | < -3.26 | > 0.55 | 0.001 |
| 2 | < -2.15 | > -0.49 | < -2.16 | > -0.87 | 0.016 |
| Final | < -1.70 | > -1.70 | < -1.71 | > -1.71 | 0.034 |

* Overall $\alpha = 0.05$; Stopping boundaries represent one-sided tests for significance. Two-sided tests will also be conducted in the final analysis.

FIGURES

FIGURE 1 – TRIAL OUTCOME SCENARIOS ON INTERIM LOOKS



ABBREVIATIONS

AE: Adverse event

CACE: Complier average causal effect

CONSORT: Consolidated standards of reporting trials

DSMB: Data and safety monitoring board

ED: Emergency department

IRB: Institutional review board

ITT: intent-to-treat

LRTI: Lower respiratory tract infection

MAR: Missing-at-random

MCAR: Missing-completely-at-random

MNAR: Missing-not-at-random

NDI: National death index

ProACT: Procalcitonin antibiotic consensus trial

SAE: Serious adverse event

US: United States

DECLARATIONS

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AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHORS' CONTRIBUTIONS

JGY, CHC, FP, LAW conceived and designed the statistical analysis plans. DTH and DCA provided clinical expertise to refine the plans. EG and LYM provided database management expertise. DMY, MJF and YD provided consultative guidance for the manuscript. MJF and YD provided consultative guidance for the protocol. JAK and OMP provided laboratory expertise.

All authors contributed to the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The University of Pittsburgh Institutional Review Board approved the ProACT trial.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

David T. Huang receives grant funding from ThermoFisher for a study examining the microbiome in lower respiratory tract infection.

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