Randomized Trial of Endotracheal Tubes to Prevent Ventilator-Associated Pneumonia – Prevent 2 Study

Protocol Number: 001

National Clinical Trial (NCT) Identified Number: NCT03705286

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Funder: NHLBI

Sponsor: Miriam Treggiari, MD, PhD, MPH

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9 June 2021

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1 STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the NIH Institute Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All study personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

2 PROTOCOL SUMMARY

2.1 SYNOPSIS

Title:	Randomized Trial of Endotracheal Tubes to Prevent Ventilator-Associated Pneumonia – Prevent 2 Study
Study Description:	The study will be a Phase II randomized, controlled trial that will equally randomize 1,074 patients requiring emergency endotracheal intubation to receive either a polyurethane-cuffed endotracheal tube equipped with continuous aspiration of subglottic secretions designed to prevent ventilator-associated pneumonia (EVAC-PU-ETT) or a conventional, polyvinylchloride-cuffed endotracheal tube (PVC-ETT). Using a pragmatic approach, we will determine if, by reducing the incidence of ventilator-associated pneumonia, the modified endotracheal tube (ETT) improves long-term quality of life and cognitive function, and if it is as safe as the conventional endotracheal tube, thus providing much needed evidence supporting decision-making.
Objectives:	The primary objectives of the proposed trial are to compare the safety and effectiveness of EVAC-PU-ETT and PVC-ETT, initiated at the time of first emergency intubation in the ER or in-hospital. The specific aims are

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as follows:

Primary Specific Aim: We will determine if long-term patient quality of life and cognitive function are better using EVAC-PU-ETT compared with PVC-ETT.

For the primary effectiveness endpoint, we will determine if the effect of EVAC-PU-ETT on quality of life (physical and mental component summary), as measured by the 36-item Short-Form General Health Survey, is better compared with PVC-ETT, at 6 months after randomization. An additional patient-centered endpoint will be the proportion of patients cognitively impaired, assessed by the National Alzheimer Coordinating Center's Uniform Data Set.

Secondary Specific Aims: We will determine if EVAC-PU-ETT is as safe as PVC-ETT. We will also determine if EVAC-PU-ETT reduces Infection Related Ventilator-Associated Complications (IVACs) and is more cost effective than PVC-ETT.

Aim 2. For our safety endpoint, we will evaluate the safety profile of EVAC-PU-ETT based on airway-related complications, compared with the PVC-ETT, at 6 months after randomization.

Aim 3. To determine if the EVAC-PU-ETT is effective in reducing the incidence of Center for Disease Control (CDC)-defined IVACs and Ventilator-Associated Events (VAEs) compared with PVC-ETT.

Aim 4. To perform economic evaluation (cost-consequence approach) of quality of life of patient and the healthcare resource utilization and cost for hospitals of EVAC-PU-ETT compared with PVC-ETT.

Endpoints:

Primary Endpoint: The study primary endpoints will be measures of quality of life, and cognitive function at 6 months after randomization. Additional endpoints include safety and ventilator associated events.

Quality of life. The patient interview will also include the evaluation of quality of life using the RAND version 1.0 of the Medical Outcomes Study 36-item Short-Form (SF- 36) General Health Survey. This instrument includes eight sub-indices of the following types: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. It also includes a single item that provides an indication of perceived change in health.

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Cognitive function. At the six-month follow up, we will also assess cognitive function using a battery of tests assessing domains previously demonstrated to be potentially affected by periods of respiratory distress and validated in both normal aging and cognitively impaired populations. The core battery will consist of measures from the National Alzheimer Coordinating Center's Uniform Data Set (UDS): 1) Montreal cognitive assessment (MoCA), a global cognitive screen which has been shown to be much more sensitive than the Mini Mental Status Examination; 2) Craft Story Recall (an analogue to the Logical Memory subtest of the Wechsler Memory Scale), measuring immediate and delayed verbal contextual recall; 3) Benton Complex Figure test, which measures executive function and visuospatial ability, as well as visuospatial recall; 4) Digit Span, a test of attention and working memory; 5) Trail Making, Parts A and B, measures of attention and divided attention/working memory; and 6) semantic and phonemic verbal fluency test. Advantages of using the UDS are that it contains tests sensitive to cognitive impairment following respiratory illness that have been validated in older impaired and unimpaired populations, is freely available via the National Alzheimer Coordinating Center website, provides normative data and a normative calculator that are easily accessible online, and permits comparison with a nationwide database of older adults. Additional tests will be included to ensure specific impairments in patients with respiratory illness are adequately assessed: 1) Hopkins Verbal Learning Test-Revised – (HVLT-R), a measure of declarative verbal list learning and memory, which allows evaluation of the participant's ability to use semantic clustering strategies during recall, which may be disrupted following acute or prolonged respiratory illness; 2) Coding (previously termed "Digit symbol", from the Wechlser Adult Intelligence Scale-4th ed [WAIS-IV], 2008, PsychCorp), a measure of speed of information processing /working memory. Participants will be considered cognitively impaired if any test is 2 standard deviations or greater below the age, sex, education adjusted mean, or if two tests are 1.5 standard deviations or greater below the mean, consistent with previous studies in this area. As we will not have access to neuropsychological tests prior to illness, we will include a measure of premorbid ability, the Test of Premorbid Functioning (TOPF, 2009, PsychCorp), in order to gauge whether current performance on cognitive measures may represent a change from previous levels of function.

Safety. Safety endpoints include clinical measures intended to evaluate the direct effect of the device at the site of placement. To evaluate the effect of the ETT at the local level we will be assessing subjective and

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objective measures of laryngeal anatomy and function, in addition to any device-related adverse events. We will record: 1) airway complications at the time of ETT insertion; 2) the presence of cuff leak test prior to study ETT removal; 3) stridor immediately after extubation; 4) requirement for stridor treatment (racemic epinephrine, helium-oxygen gas mixture); or 5) reintubation within 24 hours due to upper airway complications such as stridor or obstruction. Long-term safety will be assessed by ascertaining the persistence of airway sequelae six months after randomization using a standardized questionnaire via in-person interview. Data collected include the presence of persistent throat discomfort or pain, residual hoarseness, change in voice, and dyspnea.

VAE: The trial will use CDC-defined Ventilator-Associated Events (VAEs). The tiered CDC approach includes the identification of ventilator associated conditions (VACs) in the first step, the presence of fever or increased white blood count and the initiation of new antimicrobial in the second step (IVAC), and documentation of a respiratory source of infection in the third step (possible ventilator associated pneumonia - VAP).

Study Population:

An estimated 1,074 patients will be enrolled in the study. Those eligible to participate in the trial are adult patients (older than 18 years of age) requiring emergency endotracheal intubation in the ED or in the hospital for acute respiratory distress or failure resulting in the requirement for Intensive Care Unit (ICU) admission and mechanical ventilation.

Inclusion criteria

Subjects eligible to participate in the trial are adult patients (18 years of age or older) requiring emergency endotracheal intubation in the ED or in-hospital for acute respiratory distress or failure resulting in ICU admission and mechanical ventilation. For a patient to be enrolled in the trial, a study intubation kit containing the study ID number must have been used for the emergency intubation.

Exclusion criteria

1) Patients electively intubated in the operating room whether or not they require subsequent ICU admission; 2) Use of a non-study intubation kit (such as nasal intubation, tracheotomy, intubation occurring at a location not supplied with the study intubation kits); 3) Patients with permanent tracheostomy; 4) Protected populations including children (age <18 years), pregnant women, prisoners; and 5) Evidence of unwillingness to participate in a research study as documented in the patient's electronic health record, or at the time of intubation if there is opportunity to read the opt-out script.

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Phase:	2
Site/Facility:	The study will be conducted at a single site. The first 90 patients were enrolled at Oregon Health & Science University (OHSU), the subsequent 984 subjects will be enrolled at Yale New Haven Hospital (YNHH), a non-profit 1,541-bed hospital and tertiary referral center for critically ill patients in the region with four intensive care units and emergency department. YNHH is a nationally recognized biomedical research institution with adequate administrative core resources to enable start-up processes of post-award facilitation and ethics board review as well as smooth facilitation of study processes.
Description of Study Intervention:	The study ETTs (EVAC-PU-ETT and PVC-ETT) will be concealed and packaged in an opaque sealed envelope so that the assignment will occur in a blinded fashion. The study ETTs will be provided in three internal diameter sizes: 7.0 mm, 7.5 mm, and 8.0 mm. Unless otherwise indicated, the size recommendation will be I.D. 7.0 for females, I.D. 7.5 for males, and I.D. 8.0 as clinically indicated. Non-study ETT will be also available for use in protected populations, and for patients with exclusion criteria, and for participants declining consent. Also, if a study device becomes unusable at the time of intubation, non-study ETT would be available as replacement for the study ETT. The intubation kits will be distributed by research personnel to Anesthesia, ICUs, and ED storage locations. Study device packaging will be tracked using a barcode system.
Study Duration:	The proposed enrollment period is 15 months, with an additional 6 months to ensure that all participants complete the follow up. The duration of enrollment assumes 40% losses from ineligibility and exclusions. The trial started enrolling at OHSU and 90 participants were randomized. These activities were conducted under the oversight of OHSU IRB. After closing enrollment at OHSU, the study will enroll participants at YNHH only. Study oversight will be transferred to Yale IRB, including review of all Community Consultation and Public Disclosure activities, and oversight for the Public Disclosure activities in the Portland area at the conclusion of the study. The projected total study duration is 5 years (2018-2023).
Participant Duration:	Participants will be monitored for occurrence of VAEs until extubation. An appropriate size and model matched replacement ETT will be kept at the bedside until successful extubation or ICU discharge.

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Participants will be monitored for other endpoints during ICU and hospital discharge, and until 6 months after extubation. At 6 months post-randomization, study participants will be evaluated in person either at our research facility space or at their residence for airway evaluation and related disorders, quality of life and cognitive impairment.

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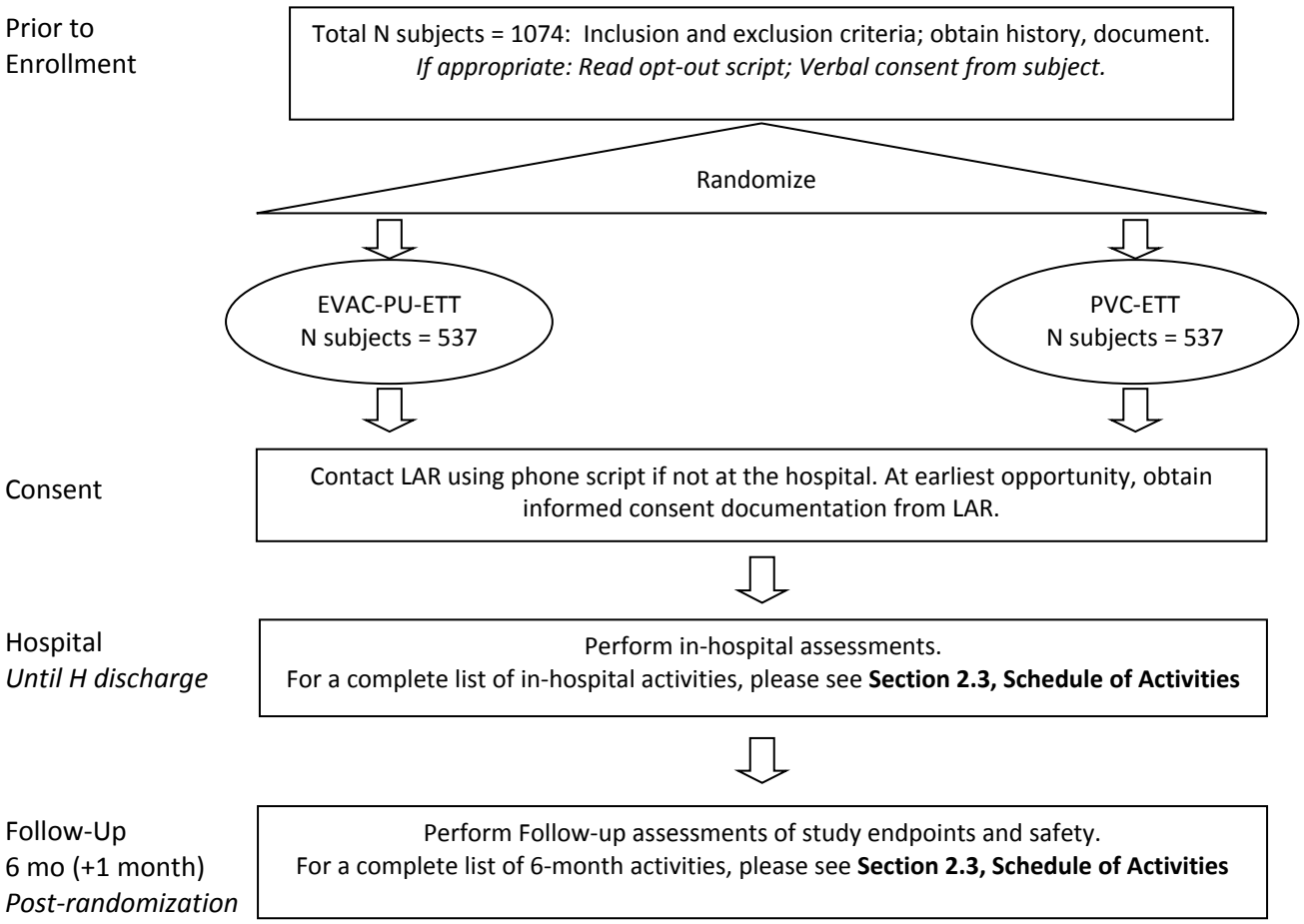
2.2 SCHEMA


Prior to Enrollment
Total N subjects = 1074: Inclusion and exclusion criteria; obtain history, document.
If appropriate: Read opt-out script; Verbal consent from subject.
Randomize
EVAC-PU-ETT
N subjects = 537
PVC-ETT
N subjects = 537
Consent
Contact LAR using phone script if not at the hospital. At earliest opportunity, obtain informed consent documentation from LAR.
Hospital
Until H discharge
Perform in-hospital assessments.
For a complete list of in-hospital activities, please see Section 2.3, Schedule of Activities
Follow-Up
6 mo (+1 month)
Post-randomization
Perform Follow-up assessments of study endpoints and safety.
For a complete list of 6-month activities, please see Section 2.3, Schedule of Activities

2.3 SCHEDULE OF ACTIVITIES (SOA)

	Study ETT Placement	ICU Day 1	ICU Day 2 to Extubation	ICU Discharge	Hospital Discharge	VAE Event [1]	Extubation	6-month Follow-up
Randomization assignment	X							
Daily screening for new mechanical ventilation or study ETT use	X							
Enrollment		X						
Pregnancy test [2]		X						
Informed consent		X						
Study ID number assignment		X						
Intubation location/details		X						
Baseline characteristics								
Demographics [3]		X						
ICU location		X						
Admission diagnosis		X						
Indication for MV		X						
CAP at admission [4]		X						
Charlson (history only) [5]		X						
Charlson (admit or history) [6]		X						
APACHE II		X						
Daily VAE/VAP surveillance								
FiO_2		X	X			X		
PEEP		X	X			X		
Temperature		X	X			X		
WBC		X	X			X		
Secretion quantity and quality		X	X			X		
Respiratory cultures		X	X			X		
Respiratory antimicrobials [7]		X	X			X		
CXR interpretation [8]		X	X			X		
VAP preventive measures								
Stress-ulcer prophylaxis		X	X					
Use of probiotics		X	X					
Enteral nutrition		X	X					
Oral chlorhexidine care		X	X					
Head of bed elevation >30°		X	X					
ETT cuff pressure compliance		X	X					
Daily sedation vacation		X	X					
Daily SBT		X	X					
Subglottic suction compliance		X	X					
Airway characteristics								
Cuff leak prior to extubation		X	X				X	
Post-extubation complications[9]				X	X		X	
Laryngeal/speech evaluation [10]								X
Device-related adverse event		X	X	X	X		X	X
Serious adverse event		X	X	X	X		X	X
ICU characteristics								
Mechanical ventilation duration		X	X				X	
Reintubation [11]				X	X		X	
Tracheostomy				X	X			
Surgical procedure				X	X			
PaO_2/FiO_2 ratio		X	X			X		

Daily SOFA		**X**	**X**	**X**			**X**	
Selected concomitant medications [12]		**X**	**X**	**X**			**X**	
Discharge disposition					**X**			
Quality of Life (Short Form-36)								**X**
Cognitive Function (NACC UDS)								**X**
Vital status				**X**	**X**			**X**
Cause of death				**X**	**X**			**X**

Abbreviations: ICU: intensive care unit; ETT: Endotracheal tube; MV: Mechanical Ventilation; CAP: Community-acquired pneumonia; VAE: Ventilator associated events; VAP: Ventilator-associated pneumonia; APACHE II - Acute Physiology, Age, Chronic Health Evaluation II; WBC: white blood count; CXR: chest x-ray; SBT: spontaneous breathing trial; SOFA - Sequential Organ Failure Assessment; NACC UDS: National Alzheimer's Coordinating Center Uniform Data Set.

[1] Ventilator associated events (VAEs) and ventilator associated pneumonia (VAP) are defined according to Centers for Disease Control and Prevention tiered definition and according to a "clinical" definition that also include a radiographic abnormality of new or progressive infiltrate.

[2] Pregnancy test – Standard of care test, results will be recorded in data set. Positive outcomes will be reported as eligibility criteria deviations.

[3] Demographic characteristics: race, gender, ethnicity, height, weight, age.

[4] Community-acquired pneumonia (CAP) is defined as newly acquired respiratory symptoms (cough, sputum production and/or dyspnea or tachypnea or fever or abnormal physical examination of the chest), and abnormal CXR due to the presence of a lung infiltrate diagnosed at admission or occurring within 2 days of hospital admission.

[5] Charlson - history: anemia, cerebrovascular disease, congestive heart failure, hemiplegia, hepatitis, myocardial infarction, ulcer disease.

[6] Charlson - current admit: acute or chronic myelogenous or lymphocytic leukemia or multiple myeloma, AIDS, alcohol abuse, chronic renal disease, cirrhosis, connective tissue disease, dementia, psychiatric disorder, diabetes, drug abuse, episodes of hepatic failure with encephalopathy or coma, HIV+, hypertension, lymphoma, peripheral vascular disease, immunosuppressive state/transplant, respiratory disease, solid tumor with metastasis, solid tumor without metastasis, tobacco use.

[7] Respiratory antimicrobials will be collected during the entire ICU stay to allow differentiation between possible community-acquired pneumonia or other nosocomial pneumonia.

[8] Chest x-ray: Interpretation (normal, focal, diffuse infiltrates), change (new or progressive), normal or abnormal.

[9] Post-extubation laryngeal dysfunction includes: use of post-extubation racemic epinephrine, helium/gas mix, reintubation within 24 hours.

[10] Six-month follow-up includes the evaluation of the following airway symptoms: Dysphagia, dyspnea at rest or during exercise, pharyngodynia, cough, respiratory secretions, symptoms of airways obstruction, other upper airway complaints. Speech evaluation: dsyarthria, voice change, aphonia, airway congestion, other symptoms, airway specialist consultation, history of tracheostomy or other surgery/procedures involving the airways, a diagnosis of laryngeal stenosis, tracheal stenosis or malacia.

[11] Reintubation: Non-study tube or Study tracking number, tube size, reintubation location/details.

[12] Concomitant medications: Proton pump inhibitors, H_2 blockers, sucralfate, neuromuscular blocking agents, respiratory antimicrobial use, indication for antimicrobial use (prophylaxis, empiric, pneumonia, non- respiratory infection).

3 INTRODUCTION

3.1 STUDY RATIONALE

The proposed study will be a randomized, controlled trial, conducted under Exception From Informed Consent (EFIC), comparing patients who undergo emergency tracheal intubation with one of two different ETTs, one of which is designed to prevent VAP: 1) An ETT with a PU cuff that is also fitted with a lumen to allow CASS (EVAC-PU-ETT); and 2) A standard ETT with a PVC cuff (PVC-ETT). Approximately 1,074 adult patients requiring endotracheal intubation in the ED or hospital for acute respiratory distress or failure will be randomly assigned in an equal fashion to be intubated with one of the two ETTs (537 patients in each group). Because endotracheal intubation is performed in an emergency setting, the unit of randomization will be the intubation kits containing, in a concealed manner, one of the two types of ETT. The intubation kits are placed in areas where emergency intubation teams receive their intubation equipment supplies. In order to maximize the potential benefit of the modified ETT for the prevention of VAP, it is imperative that the ETTs be available to the entire at-risk population. Thus, given that a sizable proportion of patients that undergo tracheal intubation and mechanical ventilation are intubated in the ED, it is important to include this cohort in the study population. The study is designed to allow all patients requiring emergency intubation to be potentially eligible for enrollment to ensure the applicability of the study findings to a generalizable setting of patients receiving emergency intubation outside the operating room. Endotracheal tubes will be concealed in opaque sealed envelopes so that the assignment will occur in a blinded fashion. The study ETTs will be provided in three internal diameter sizes: 7.0 mm, 7.5 mm, and 8.0 mm. Unless otherwise indicated, the size recommendation will be I.D. 7.0 for women, I.D. 7.5 for men, and I.D. 8.0 as clinically indicated. Non-study ETTs will be also available for use in protected populations, for patients with exclusion criteria, and for participants declining research participation. The kits will be distributed by research personnel to all ICUs storage locations, to the ED, and to high-risk patient care areas.

3.2 BACKGROUND

Nosocomial pneumonia is a common complication in critically ill patients, and it has been identified as by far the most common nosocomial infection, with an overall prevalence of 10%, ranging from 5 and 67%, depending on the patient population studied and the diagnostic criteria used.[1, 2, 3-8] Several studies indicate that mechanical ventilation is the greatest risk factor for the development of nosocomial pneumonia.[9-13] Ventilator-associated pneumonia (VAP) accounts for 80-90% of cases of nosocomial pneumonia in ICU patients.[11, 14, 15] VAP appears to be independently associated with increased morbidity, as measured by increased duration of mechanical ventilation, ICU and hospital length of stay.[16-19] Large studies have reported mortality associated with VAP that ranged from 24 to 54%,[4-7, 17, 20] with an attributable mortality between 5% and 48%.[13, 16, 17, 21-23] To increase surveillance accuracy and

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obviate the inconsistencies in the diagnosis of VAP, the CDC proposed a revised, structured approach to define respiratory infectious complications in mechanically ventilated patients under the overall designation of ventilator-associated events (VAEs).[24] The stepwise, algorithmic approach includes ventilator-associated conditions (VAC), infection-related ventilator-associated complications (IVAC), and "possible" VAP (Appendix I). The new classification system appears to have higher discrimination in predicting hospital mortality compared to tracking of VAP alone.[25-27]

Pneumonia has negative effects on quality of life including physical functioning, general health, and vitality even long after recovery from disease.[28, 29] With preexisting comorbid conditions, several domains of the SF-36 scores (physical function, physical role function, general health, and vitality) were significantly lower at 12 or 18 months, and were even worse when pneumonia was associated with sepsis.[30, 31] Similar negative physical and mental effects have been observed in survivors of acute respiratory distress syndrome (ARDS),[32-34] and in sepsis survivors.[31] It is also well documented that critical illness alone is associated with a decrease in long-term quality of life among previously healthy older patients admitted to a medical ICU.[35] Furthermore, several reports suggest that persistent voice disorders, possibly related to airway complications, are associated with reduced quality of life in the domains of physical functioning, emotional well-being and social functioning.[36-38]

Likewise, pneumonia, sepsis, and acute lung injury have a negative and lasting effect on cognitive function and have been associated with increased risk of dementia in some studies.[31, 39-41] In a longitudinal cohort of the EDEN trial – where over 80% had pneumonia or sepsis as ARDS risk factor – 20 to 30% demonstrated cognitive impairment.[33, 34] Importantly, cognitive impairment has been identified as one of the outcomes patients were least willing to accept.[42] Considering this growing body of clinical and experimental evidence suggesting that systemic infection, especially pneumonia, can lead to long-term effects on quality of life and cognitive function,[31, 39-41, 43] interventions aimed at VAP prevention have the potential to greatly impact and improve clinical care and patient quality of life.

VAP is preceded by bacterial colonization of the trachea in most cases.[1, 44-48] The source of colonization is likely to be bacterial contamination of oropharyngeal secretions that leak through folds in the endotracheal tube (ETT) cuff into the trachea.[46, 49-51] Microaspiration below an inflated high-volume, low pressure ETT cuff has been shown to occur in virtually 100% of cases,[49, 51] and it is reduced in the semi-recumbent position.[52-55] Interventions that prevent tracheal microaspiration reduce the incidence of VAP.[63,64]

Several strategies to prevent VAP have been investigated,[45, 56] and they are primarily focused on five areas: 1) Selective decontamination with the reduction of digestive tract, airway, and ETT colonization with pathogenic bacteria;[57-62] 2) Improvement of pulmonary secretion clearance by rotational therapy;[56, 63] 3) Prevention of microaspiration of oropharyngeal secretions by semi-recumbent positioning;[52, 53, 64] 4) Prevention of ETT bacterial colonization by coating the ETT with silver chloride;[62] and 5) Prevention of

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microaspiration via alterations in ETT design. This proposal will focus on prevention of microaspiration via alterations in ETT design with continuous aspiration of subglottic secretions combined with modification of the cuff material. This topic remains the most controversial, yet the most promising since it could have the greatest effect on VAP prevention.

One innovation in ETT design is the placement of an orifice just above the tube cuff connected to an externalized lumen that allows intermittent suction of secretions that may pool in the space between the laryngeal aperture and the ETT cuff. The removal of these secretions may prevent or minimize microaspiration, tracheal colonization with bacteria, and ultimately VAP. Several randomized trials and observational studies have investigated subglottic ETT suctioning.[65-73] A meta-analysis examined data from five of these studies and estimated an approximately 50% reduction in the risk of VAP due to subglottic suctioning based on the pooled results (relative risk = 0.51, 95% CI 0.37-0.71),[74] and the time to occurrence of VAP was delayed by 3.1 days (95% CI 2.7-3.4). A more recent meta-analysis on CASS incorporating 17 studies found a lower incidence of VAP.[75] This is generally consistent with most trials where some have found significant reductions in risk of VAP,[66, 70, 72] though only per-protocol analyses have found reductions in ICU length of stay and mortality. However, a prospective, observational study of 250 patients found no effect of subglottic suctioning on the risk of VAP.[71] Likewise, a newer study found no significant differences between intermittent and continuous suctioning in the incidence of early or late-onset VAP or mortality.[76] The degree of effectiveness of CASS in reducing the occurrence of VAP remains unclear because of several limitations in the data from the randomized trials that limit their strength and generalizability, primarily due to patient selection,[65, 68-70, 73] failure to perform intention-to-treat analysis and post-randomization exclusion of patients may have introduced bias,[65, 68, 69] lack of application or reporting of other strategies to reduce VAP, and lack of economic evaluation data.

Another approach to reduce secretion leakage around the ETT is to modify the composition of the cuff material to prevent channel formation on the surface of the inflated cuff. Several studies have found that ETT cuffs composed of PU or silicone prevent leakage of dye around the cuff in comparison with conventional cuffs composed of polyvinylchloride (PVC), both in vitro and in vivo.[77-86] A small randomized trial in patients undergoing cardiac surgery found that tracheal intubation with a PU-cuffed tube was associated with a reduced incidence of early postoperative pneumonia compared to intubation with a PVC-cuffed tube (23% vs 42%).[87] A retrospective study comparing VAP rates before and after introduction of a PU-cuffed tube found that VAP rates were reduced from 5.5/1000 to 2.8/1000 ventilator days.[88] A recent quasi-randomized controlled trial compared two cuff shapes composed of PVC or PU in 604 patients, and found that cuff shape or material did not affect VAP rates, although it may delay leakage.[89] However, a randomized trial that compared a tube that featured both a PU cuff and a subglottic aspiration port for CASS with a conventional tracheal tube in medical-surgical ICU patients found a significant reduction in VAP among patients receiving the specialized tube (22% vs. 8%).[72] None of the randomized trials were powered to detect a difference in VAP, duration of

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mechanical ventilation, ICU length of stay, or mortality. Thus, as concluded in a systematic review of these laboratory and clinical studies, it is unclear if PU cuffs lead to a reduction VAP.[90]

3.3 RISK/BENEFIT ASSESSMENT

3.3.1 POTENTIAL RISKS

Modification of the ETT design to prevent microaspiration (CASS-ETT) is one of several approaches to VAP prevention. ETTs that allow continuous aspiration of subglottic secretions or are equipped with PU cuff have been investigated in several randomized trials, with the weight of evidence suggesting a reduction of VAP associated with this intervention. The EVAC-PU-ETT has been recommended or suggested for use as a VAP preventative strategy by the American Thoracic Society and the Centers for Disease Control and Prevention. The EVAC-PU-ETT has been clinically used at many institutions to prevent VAP. However, there has been no systematic prospective study of the EVAC-PU-ETT to evaluate for both the efficacy of the tube for the prevention of VAP and for the safety of the tube as compared to a standard ETT to ensure there is no higher risk of airway injury related to subglottic suctioning.

Our previous pilot prospective randomized trial did not establish differences in risks between the PVC-ETT and the EVAC-PU-ETT. It remains uncertain if the EVAC-PU-ETT which has been demonstrated as a strategy for VAP prevention is also as safe as the standard ETT. There is equipoise to address the study question as there is insufficient evidence to claim one type of ETT is more effective and safe than another at preventing VAP.

This comparative effectiveness trial is designed to provide more rigorous effectiveness and safety evaluation of the EVAC-PU-ETT. We hypothesize the modified ETT with subglottic suctioning reduces the occurrence of VAP, is as safe as the PVC-ETT and does not pose an increased risk of laryngeal and/or tracheal injury.

The PVC-ETT and the EVAC-PU-ETT are FDA-cleared for clinical use (tracheal intubation). They will be used in this study in accordance with their FDA-cleared clinical indications and manufacturer recommendations. The use of these ETTs are considered medically recognized standards of care (see Appendix III for the ETT product labels).

It may be difficult to differentiate side effects of the ETT from complications patients who undergo intubation experience regardless of the type of ETT used. The product labels for both ETTs show no differences in the type, nature, or severity of complications between the tube types. Device-related complications are considered the same. Some subjects will receive the EVAC-PU-ETT and they would not otherwise receive this ETT type outside of the study. However, both ETTs we will use are medically recognized standards of care and there is no known differential in risk between the two treatments.

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From clinical experience, it is expected that the EVAC-PU-ETT is as safe as the PVC-ETT. For these reasons, we believe that subjects enrolled in this study will be exposed to the same risks if they were outside of the study.

This study will specifically evaluate the following immediate, short, and long-term device-related complications involving laryngeal anatomy and function that are also outlined in the product labeling:

Immediate risks:

- Airway complications at the time of tube insertion
- Need to change/reduce the pre-assigned size of the tube

Short-term risks:

- Stridor immediately after extubation
- Requirement for stridor treatment
- Reintubation within 24 hours due to upper airway complications such as stridor or obstruction

Long-term risks (6 months after extubation as identified by a phone interview)

- Tracheostomy
- Persistent throat discomfort or pain
- Stridor
- Residual hoarseness or change in voice (dysphonia)
- Dyspnea
- Whether dyspnea symptoms are attributable to upper or lower airway disease (certainly due to upper airway, probably, possibly, or unrelated).

Section 9.2 outlines how the study team will assess airway complications for safety of the ETT type during the study.

We do not expect differences in risks at insertion between the PVC-ETT and the EVAC-PU-ETT. However, while the tubes have the same internal diameter, the EVAC-PU-ETT tube has a slightly larger external diameter (due to the additional port) which effectively increase the outer diameter by 0.5 points. This may mean a different tube is requested prior to the intubation attempt or it is requested after a failed attempt is made. If this happens because the outer diameter of the tube is thought to be a problem, a non-study tube will be used. Specifically, if a <7.0 size is needed, then it will not be a study tube since alternative sizes are not available for this study. We will monitor insertion complications, including the need to insert smaller size tubes.

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Complications related to mechanical ventilation are not research risks and are instead due to standard of care which subjects would be exposed to outside of the study. However, certain symptoms, like dyspnea, will not be distinguishable between device and ventilator. Assessment of risks will primarily focus on complications to upper airway which are more closely related to the breathing device than the ventilator use. For the trial, we will document whether the symptoms are thought to be related to upper vs lower airway dysfunction (evidence of pulmonary disease or condition), and we will compare the frequency between the two groups.

This study will evaluate cognitive function. We do not expect cognitive changes to represent side effects of the ETT. We hypothesize that decreased cognitive function is a consequence of infection (VAP) as a result of neuroinflammation. We hypothesize that patients that do not experience infection or hypoxemia resulting from pneumonia should have less cognitive dysfunction. If the EVAC-PU-ETT is protective from VAP, then the intervention group should also have less cognitive dysfunction. Therefore, side effects of cognitive dysfunction are not research risks, and are instead risks of the condition they would be exposed to outside of the study.

This study increases the risk of invasion of privacy as patients will be enrolled into this emergency medicine study without his or her consent. We anticipate most subjects will be enrolled in the study under a waiver of consent because this patient population may not immediately have the capacity to provide consent to be in the study.

3.3.2 POTENTIAL BENEFITS

The intervention ETT is known to prevent ventilation associated pneumonia (VAP). This study will allow for the controlled evaluation of the comparative effectiveness and safety of a polyurethane-cuffed endotracheal tube with subglottic suctioning for prevention of VAEs. There are several benefits that could result from this research for the subjects, their family, as well as society. The greater benefit for the subject would be a reduction in the incidence of VAP (some patients may not develop VAP as a result of the intervention), with a resulting reduced duration of mechanical ventilation, length of stay, and cost, with no increased safety issues identified. All these outcome benefits will result in a reduction in institutional and societal costs. Indirect benefits will be shared by family members and society as a whole.

4 OBJECTIVES AND ENDPOINTS

Primary Aims (Objectives)	**Primary Specific Aim:** We will determine if EVAC-PU-ETT is as safe as PVC-ETT and if long-term patient quality of life and cognitive function are better in EVAC-PU-ETT, compared with PVC-ETT. As primary effectiveness endpoint, we will determine if the effect of EVAC-

	PU-ETT on quality of life (physical and mental component summary), as measured by the 36-item Short-Form General Health Survey, is better compared with PVC-ETT, at 6 months after randomization. An additional patient-centered endpoint will be the proportion of patients cognitively impaired, assessed by the National Alzheimer Coordinating Center's Uniform Data Set.
Secondary Aims (Objectives)	**Secondary Specific Aims:** We will determine if EVAC-PU-ETT is as safe as PVC-ETT. We will also determine if EVAC-PU-ETT reduces Infection Related Ventilator-Associated Complications (IVACs) and is more cost effective than PVC-ETT. **Aim 1.** For our safety endpoint, we will evaluate the safety profile of EVAC-PU-ETT based on airway-related complications, compared with the PVC-ETT, at 6 months after randomization. **Aim 2.** To determine if the EVAC-PU-ETT is effective in reducing the incidence of Center for Disease Control (CDC)-defined IVACs and Ventilator-Associated Events (VAEs) compared with PVC-ETT. **Aim 3.** To perform economic evaluation (cost-consequence approach) of quality of life of patient and the healthcare resource utilization and cost for hospitals of EVAC-PU-ETT compared with PVC-ETT.
Primary Endpoints	The study primary endpoints will be measures of **quality of life,** and **cognitive function** at 6 months after randomization. **Quality of life.** The patient interview will also include the evaluation of quality of life using the RAND version 1.0 of the Medical Outcomes Study 36-item Short-Form (SF-36) General Health Survey. This instrument includes eight sub-indices of the following types: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. It also includes a single item that provides an indication of perceived change in health. **Cognitive function**. At the six-month follow up, we will also assess cognitive function using a battery of tests assessing domains previously demonstrated to be potentially affected by periods of respiratory distress and validated in both normal aging and cognitively impaired populations. The core battery will consist of measures from the National Alzheimer Coordinating Center's Uniform Data Set (UDS): 1) Montreal cognitive assessment (MoCA), a global cognitive screen which has been shown to be much more sensitive than the Mini Mental Status Examination; 2) Craft Story Recall (an analogue to the Logical Memory subtest of the Wechsler Memory Scale), measuring immediate and delayed verbal contextual recall; 3) Benton Complex Figure test, which measures executive function and visuospatial ability, as well as

	visuospatial recall; 4) Digit Span, a test of attention and working memory; 5) Trail Making, Parts A and B, measures of attention and divided attention/working memory; and 6) semantic and phonemic verbal fluency test. Advantages of using the UDS are that it contains tests sensitive to cognitive impairment following respiratory illness that have been validated in older impaired and unimpaired populations, is freely available via the National Alzheimer Coordinating Center website, provides normative data and a normative calculator that are easily accessible online, and permits comparison with a nationwide database of older adults. Additional tests will be included to ensure specific impairments in patients with respiratory illness are adequately assessed: 1) Hopkins Verbal Learning Test-Revised – HVLT-R), a measure of declarative verbal list learning and memory, which allows evaluation of the participant's ability to use semantic clustering strategies during recall, which may be disrupted following acute or prolonged respiratory illness; 2) Coding (previously termed "Digit symbol", from the Wechlser Adult Intelligence Scale-4th ed [WAIS-IV], 2008, PsychCorp), a measure of speed of information processing /working memory. Participants will be considered cognitively impaired if any test is 2 standard deviations or greater below the age, sex, education adjusted mean, or if two tests are 1.5 standard deviations or greater below the mean, consistent with previous studies in this area. As we will not have access to neuropsychological tests prior to illness, we will include a measure of premorbid ability, the Test of Premorbid Functioning (TOPF, 2009, PsychCorp), in order to gauge whether current performance on cognitive measures may represent a change from previous levels of function.
Secondary Endpoints	**Safety.** Safety endpoints include clinical measures intended to evaluate the direct effect of the device at the site of placement. To evaluate the effect of the ETT at the local level we will be assessing subjective and objective measures of laryngeal anatomy and function, in addition to any device-related adverse events. We will record: 1) airway complications at the time of ETT insertion; 2) the presence of cuff leak test prior to study ETT removal, as indicated by a difference between the inspiratory tidal volume (measured before cuff deflation) and the expiratory tidal volume (measured after cuff deflation) of at least 10% or >110 mL; 3) stridor immediately after extubation; 4) requirement for stridor treatment (racemic epinephrine, helium-oxygen gas mixture); or 5) reintubation within 24 hours due to upper airway complications such as stridor or obstruction. Long-term safety will be assessed by ascertaining the persistence of airway sequelae six months after randomization using a standardized questionnaire via in-person interview. Data collected include the presence of persistent throat discomfort or pain, residual hoarseness, change in voice, and dyspnea. ***The main secondary clinical efficacy endpoint*** will be the incidence of CDC defined Infection-Related Ventilator-Associated Complications (IVAC)

	occurring during the ICU stay from enrollment until ICU discharge. An IVAC event is defined by a 14-day period, starting on the day of onset of worsening oxygenation. For this study, we will use the CDC proposed tiered approach algorithm that encompasses ventilator associated conditions (VAC), infection related ventilator-associated complication (IVAC), and possible VAP. ***Step 1:* VAC (≥1 required)**: 1) Daily min FiO_2 increase ≥0.20 (20 points) for ≥2 days **- OR** 2) Daily min PEEP increase ≥3 cm H_2O for ≥2 days (after two days of stable or decreasing daily minimum values) ***Step 2: IVAC***: 1) Temperature >38.0ºC OR <36.0ºC **- OR** 2) White blood cell count ≥12,000 or ≤4,000 cells/mm^3 **- AND** 3) A new antimicrobial agent is started and is continued for ≥4 days. ***Step 3: Possible VAP***: Criterion #1: Positive cultures of one of the following specimens collected within +/- 2 days of onset of VAC, meeting quantitative or semi-quantitative thresholds, without requirement for purulent respiratory secretions: 1) Endotracheal aspirate; 2) Bronchoalveolar lavage; 3) Protected specimen brush; 4) Lung tissue - **OR** Criterion #2: Purulent respiratory secretions **AND** a positive culture of one of the following specimens (qualitative culture, or quantitative/semi-quantitative culture without sufficient growth to meet Criterion #1): 1) Sputum; 2) Endotracheal aspirate; 3) Bronchoalveolar lavage; 4) Lung tissue; 5) Protected specimen brush. **Other secondary endpoints related to VAP** 1) Incidence of ventilator-associated events (VAEs); 2) Respiratory antimicrobial use; 3) VAP risk using a “clinical" definition for interpretation of the study findings in the context of previous literature where clinical definitions were used; 4) Occurrence of early- *versus* late-onset IVAC and time to first IVAC event. Early-onset IVAC is defined as IVAC occurring within four days of tracheal intubation while late-onset VAP is defined as VAP occurring 5 days or later. **Additional secondary clinical endpoints** 1) 28-day ventilator-free days; 2) Daily Sequential Organ Failure Assessment (SOFA) score; 3) Length of ICU and hospital stay; 4) In-hospital and 6-month mortality comparison between the two groups.

5 STUDY DESIGN

5.1 OVERALL DESIGN

This will be a single-site randomized, controlled, phase 2 trial, conducted under EFIC, comparing the safety, long-term patient quality of life, and cognitive function of patients who undergo emergency tracheal intubation with one of two different ETTs, one of which is designed specifically to prevent VAP: 1) An ETT with a PU cuff that is also fitted with a lumen to allow continuous subglottic suction (EVAC-PU-ETT); and 2) A standard ETT with a PVC cuff (PVC-ETT). 1,074 adult patients requiring endotracheal intubation in the Emergency Department (ED) or hospital setting for acute respiratory failure will be randomly assigned in an equal fashion to be intubated with one of the two ETTs. The first 90 patients have been randomized at OHSU and have completed study follow-up procedures, while the remaining 984 will be randomized at YNHH. Activities conducted at the first clinical site were overseen by the OHSU IRB. After closing enrollment at OHSU, the study will enroll participants at YNHH only. The trial will be overseen by the Yale IRB, including review of all Community Consultation and Public Disclosure activities, and oversight for the Public Disclosure activities in the Portland area at the conclusion of the study.

Because endotracheal intubation is performed in an emergency setting, the unit of randomization will be the intubation kits containing, in a concealed manner, one of the two types of ETT. The intubation kits are placed in areas where emergency intubation teams receive their intubation equipment supplies. In order to maximize the potential benefit of the modified ETT for the prevention of VAP, it is imperative that the tubes be available to the entire at-risk population. The study is designed to allow all patients requiring emergency intubation to be potentially eligible for enrollment to ensure the applicability of the study findings to a generalizable setting of patients receiving emergency intubation for respiratory failure or airway protection.

Surveillance for VAP will occur while patients are in the ICU until extubation, ICU discharge or death. A large proportion of patients is expected to be extubated within 48 hours. Although patients with early extubation are not considered to be at risk of VAP, they will be included in the study to adhere to the intent-to-treat approach, considering that the patient has been randomly assigned to one of the study treatment arms. Throughout the patient's hospitalization, data will be collected continuously from the time of randomization until hospital discharge or death.

The study will use clinical measures to address device safety and consequences of VAP reduction on long-term, patient-centered outcomes. At six months post randomization, all patients will have a structured in-person interview to screen for the presence of and assess airway symptoms or persistent sequelae of laryngeal dysfunction. Any need for consultation of a specialist for airway complaints will be recorded and information abstracted from the medical record, if appropriate. During the interview, we will record clinical measures intended to evaluate safety, quality of life, and cognitive function. If a visit

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to a specialist for evaluation and/or treatment of speech, swallowing, or breathing problems occurred, the medical record will be reviewed. Data pertinent to the continuing adverse event will be abstracted from the medical record.

Although randomization assignment occurs in a double-blind fashion, the study will subsequently be single-blind. Due to the different devices used and the presence of suctioning, it will not be possible to maintain the study as double-blind. To protect the integrity of the study from unmasking of investigators other than the primary caregivers, the adjudication of the VAP will follow an algorithmic, data-driven, objective approach. Likewise, the follow up airway assessment will occur in a blinded fashion. The statistician will be blinded to the randomization assignment, by labeling the randomization assignment as device A or B.

One interim analysis will be conducted when approximately 50 percent of the total sample has been collected. For details on planned interim analyses see **Section 9.4.6, Planned Interim Analysis.**

5.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed study will be a randomized, controlled trial, conducted under Exception From Informed Consent (EFIC), comparing patients who undergo emergency tracheal intubation with one of two different ETTs, one of which is designed to prevent VAP: 1) An ETT with a PU cuff that is also fitted with a lumen to allow CASS (EVAC-PU-ETT); and 2) A standard ETT with a PVC cuff (PVC-ETT). Approximately 1,074 adult patients requiring endotracheal intubation in the ED or hospital for acute respiratory distress or failure will be randomly assigned in an equal fashion to be intubated with one of the two ETTs (537 patients in each group). Because endotracheal intubation is performed in an emergency setting, the unit of randomization will be the intubation kits containing, in a concealed manner, one of the two types of ETT. The intubation kits are placed in areas where emergency intubation teams receive their intubation equipment supplies. In order to maximize the potential benefit of the modified ETT for the prevention of VAP, it is imperative that the ETTs be available to the entire at-risk population. Thus, given that a sizable proportion of patients that undergo tracheal intubation and mechanical ventilation are intubated in the ED, it is important to include this cohort in the study population. The study is designed to allow all patients requiring emergency intubation to be potentially eligible for enrollment to ensure the applicability of the study findings to a generalizable setting of patients receiving emergency intubation outside the operating room. The study ETT will be concealed and packaged in opaque sealed envelopes so that the assignment will occur in a blinded fashion. The study ETTs will be provided in three internal diameter sizes: 7.0 mm, 7.5 mm, and 8.0 mm. Unless otherwise indicated, the size recommendation will be I.D. 7.0 for women, I.D. 7.5 for men, and I.D. 8.0 as clinically indicated. Non-study ETTs will be also available for use in protected populations, for patients with exclusion criteria, and for participants declining participation. The kits will be distributed by the research team to the ED and area airway carts.

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5.3 JUSTIFICATION FOR DEVICE

We conducted an extensive literature review and meticulously examined the strengths and weaknesses of previous trials. We also took advantage of lessons learned from our own pilot trial. Taking into account all considerations above, we have determined that the best ETT candidate device associated with the highest potential of performing effectively in preventing microaspiration and demonstrating the highest safety profile is the CASS-ETT with PU cuff material. Our central hypothesis is that EVAC-PU-ETT is safe and superior to the standard PVC-ETT in reducing the occurrence of VAP and several of its long-term consequences. There is high potential to minimize the risk of VAP when consistently applying a VAP prevention bundle combined with the use and proper management of a specialized ETT. Since it is important to definitively determine the role of the device, for the intervention we chose the ETT with the highest potential of reducing microaspiration.

5.4 END OF STUDY DEFINITION

At 6 months post-randomization, study participants will be evaluated in person either at our research facility space or at their residence for airway evaluation and related disorders, quality of life and cognitive impairment. A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in **Section 2.3, Schedule of Activities (SOA)**.

The end of the study is defined as completion of the 6 month in-person follow-up visit.

6 STUDY POPULATION

6.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. ≥18 years of age
2. Requiring emergency endotracheal intubation in the ED or in-hospital for acute respiratory distress or failure
3. A study intubation kit containing the study ID number must have been used for the emergency intubation
4. Admitted to the ICU and receiving mechanical ventilation

6.2 EXCLUSION CRITERIA

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An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients electively intubated in the operating room whether or not they require subsequent ICU admission
2. Use of a non-study designated intubation kit (such as nasal intubation, tracheotomy, intubation occurring at a location not supplied with the study intubation kits)
3. Patients with permanent tracheostomy
4. Protected populations including children (age <18 years), pregnant women, or prisoners
5. Evidence of unwillingness to participate in a research study as documented in the patient's electronic health record, or at the time of intubation if there is opportunity to read the opt-out script.

6.3 SCREEN FAILURES

Screen failures are defined as participants meeting inclusion criteria but who have a study ETT inserted in a condition or situation meeting one or more of the exclusion criteria listed in **Section 6.2, Exclusion Criteria**.

6.4 STRATEGIES FOR RECRUITMENT AND RETENTION

We will be monitoring enrollment very closely throughout the recruitment period and examine reasons for suboptimal accrual. In a first step, modifiable causes, such as reinforcing provider training in study eligibility and procedures, will be addressed on an ongoing basis. In case of more serious concerns, the advice of the Advisory Committee and DSMB on enrollment optimization will be sought. If necessary, possible strategies to expand enrollment might include extending eligibility to emergency cases performed in the operating room, supplying additional locations where emergency intubations are less common, opening enrollment to out-of-hospital intubations (as in the pilot study), or including satellite locations.

Once a participant enrolls in this study, the study site will make every effort to retain him/her for six months of follow-up to preserve the integrity of the study and to minimize possible bias associated with loss due to dropouts. To enhance participant retention, patients or their legally authorized representative (LAR) will be adequately educated during the informed consent process. Study staff will be trained to explain to the participant or their LAR the importance of the follow-up visit and the scientific relevance of their data for the study and the potential deleterious effect that missing data could on the trial's integrity and credibility. Appropriately worded informed consent forms will enable patients to make more informed decisions about their willingness to participate in continued follow-up

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without feeling pressured to doing so. A clinical medical records release form will allow review of the patient's outside medical record when consultation of a specialist is required due to the airway problem. To minimize losses to follow-up for the long-term evaluation, several retention strategies will be used. These include collecting contact information of primary care provider, participant permanent address, several alternate contact persons knowledgeable in the whereabouts of the study participant, and location of hospital discharge disposition. In addition, participants will receive $100 compensation for their participation via a Bank of America pre-paid debit card upon completion of the 6-month follow up visit. Several methods have been systematically evaluated to maximize retention including optimizing contact and scheduling methods, visit characteristics, and participant and study personnel relationships.[118] Procedures will therefore be developed to enlist family, friends or other multiple contacts to ensure that appointments are kept. To ensure adequate patient tracking, participant contact will be maintained between visits with cards, appointment reminders, and phone calls to establish rapport particularly in the early months. We will optimize study visits by offering flexible appointments, visiting participants at their residents, and making sure that the participants are not rushed during their visits. Lastly, we will ensure that study personnel are empathetic and are trained and managed to be culturally sensitive. We will also support the study personnel with frequent trainings and staff meetings. We will screen local obituaries, and we will use the Connecticut Department of Public Health's State Vital Records Office to identify patients lost to follow-up due to death.

At time of enrollment the research coordinator will collect the participants' mailing address, contact number, email address as well as contact information for an emergency contact who will know how to get in touch with subject, as well as the primary care physician information. The study coordinator will initiate follow-up contact with the patient beginning four to six weeks prior to the six-month mark from the patient's enrollment. The study coordinator will attempt to contact the patient by telephone or email. Should the patient not respond within two weeks, the study coordinator will call the patient's emergency contact and request a current phone number for the patient.

7 STUDY INTERVENTION

7.1 STUDY INTERVENTION(S) ADMINISTRATION

7.1.1 SCREENING AND ENROLLMENT

Potential subjects enrolled will be identified through a three-prong process: 1) An automatically generated report listing all new patients admitted to the ICU and receiving mechanical ventilation will be generated daily. All patients listed in the report will be reviewed at the bedside to determine the presence of a study ID bracelet and confirm that a study device was inserted; 2) Self-addressed envelopes for campus mail to the study team provided in the intubation kits and containing the

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participant identification information; and 3) Used intubation kits deposited in return bins located in the ED and ICUs will be scanned for tracking and reconciliation of all study devices. In our previous pilot study experience, these strategies allowed 100% success tracking study devices and participants.[106] After identification, study personnel will approach the participant or authorized representative to obtain informed consent for continued study participation.

7.1.2 RANDOMIZATION

Because endotracheal intubation is performed in an emergency setting, the unit of randomization will be the intubation kits containing, in a concealed manner, either a PVC-ETT or EVAC-PU-ETT, assigned in a random and equal fashion. Both the opaque envelope and the study ETTs stored within will be labeled using a barcode system linked to the randomization number for identification and tracking.

7.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

7.2.1 ACQUISITION AND ACCOUNTABILITY

The intubation kits are placed in areas where emergency intubation teams receive their intubation equipment supplies. In order to maximize the potential benefit of the modified ETT for the prevention of VAP, it is imperative that the ETTs be available to the entire at-risk population. Thus, given that a sizable proportion of patients that undergo tracheal intubation and mechanical ventilation are intubated in the ED, it is important to include this cohort in the study population. The study is designed to allow all patients requiring emergency intubation to be potentially eligible for enrollment to ensure the applicability of the study findings to a generalizable setting of patients receiving emergency intubation outside the operating room.

All study endotracheal tubes (ETTs) will be numbered consecutively, and the randomization number will be linked to a barcode. Intubation kits, study ETT packaging, study bracelet, and the patient identification tracking form will be marked with a self-adhesive study barcode label. A fluorescent flyer with essential instructions will be inserted in the intubation kit requesting to 'place unused supplies in the designated collection bag'. It will be also requested to affix the patient label to the provider instruction sheet before returning to the study supplied return bin located in the ED and each ICU. Extensive training for the critical care, emergency department and anesthesiology teams, ICU nurse teams, and respiratory therapists will be ongoing to ensure appropriate handling of the study material. The return bins will be stored in designated locations of the specific clinical units and will be a check point to track the use of the intubation kits. If the patient is enrolled in the study, then the research coordinator will place a size- and model-matched ETT at the bedside in case later reintubation became necessary. The replacement ETT will be marked with the study ID number and will remain at the bedside until successful extubation or patient discharge from the ICU, whichever comes first. Unused intubation

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supplies will be recollected at that time, monitored for device expiration, repackaged as appropriate, and tracked on an ongoing basis.

7.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The study ETT manufacturing information is as follows:

ETT type: Standard (PVC-ETT)
Shiley Hi-Lo oral/nasal endotracheal tube, cuffed, hooded Murphy tip with Murphy eye
Manufacturer: Covidien/Medtronic
Manufacturer # (7.0MM): 86111
Manufacturer # (7.5MM): 86112
Manufacturer # (8.0MM): 86113

ETT type: EVAC (EVAC-PU-ETT)
Shiley EVAC oral endotracheal tube Seal Guard, Murphy eye
Manufacturer: Covidien/Medtronic
Manufacturer # (7.0MM): 110870
Manufacturer # (7.5MM): 110875
Manufacturer # (8.0MM): 110880

The study ETT will be concealed in opaque sealed envelopes so that the assignment will occur in a blinded fashion. The study ETTs will be provided in three internal diameter sizes: 7.0 mm, 7.5 mm, and 8.0 mm. Unless otherwise indicated, the size recommendation will be I.D. 7.0 for women, I.D. 7.5 for men, and I.D. 8.0 as clinically indicated. Non-study ETTs will be also available for use in protected populations, for patients with exclusion criteria, and for participants declining research participation.

Study ETT packages will labelled with a 6-digit bar code (XXXXXX) with the first two digits indicating ETT size (70, 75, or 80) and the last four digits indicating participant ID starting at 1001. For example, the first package will have the barcode 701001 (or 751001, or 801001), the second package will have the barcode 701002 (or 751002, or 801002), and so on. The bar code will be linked to randomization (PVC-ETT or EVAC-PU-ETT). In addition, a separate 4-digit sequence code (XXXX) will be created to capture the chronological order in which participants are enrolled by date and time.

7.2.3 PRODUCT STORAGE AND STABILITY

The intubation kits will be distributed by research staff to all ICUs storage locations, to the ED, and to all other high-risk patient care areas.

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7.2.4 PREPARATION

The opaque sealed airway packaging will be prepared by study personnel regularly to ensure there is always an adequate supply for all patients requiring emergent intubation.

The intubation kit will contain size 7.0, size 7.5, and size 8.0 standard or EVAC-PU-ETT with a barcode affixed to the packaging of the individual device, study wristbands for patient tracking, as well as a fluorescent flyer with the opt-out script and essential instructions for providers on where to recycle unused study supplies.

For when obtaining consent is not feasible and a LAR is not reasonably available, all study-related intubation kits will also include a script for nurses, respiratory therapists, or trained providers to read to a patient or their family member to provide an opportunity to object to the study, as soon as feasible, ideally before enrolling the subject in the study with the study tube.

7.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All possible measures to reduce bias due to the choice of the device have been taken by blinding caregivers to the treatment assignment ahead of time via concealment of the study tube in an opaque sealed envelope. However, double blinding cannot be maintained for the entire duration of the study because the study devices are visibly different. We realize that lack of double blinding could lead to the potential for bias. However, determination of primary and many secondary outcome measures and statistical analyses will be performed without knowledge of device assignment. Importantly, we have chosen objective measures for the primary and secondary endpoints, and standardized the way procedures are performed, thus removing subjectivity and variability. Crossovers will be minimized by maintaining a spare ETT of the same model and size at the bedside during the ICU stay, up to 24 hours after extubation or until ICU discharge, whichever comes first. If crossovers occur, the study will follow an intention-to-treat approach. There will be situations when patients will be diagnosed with pneumonia using clinical criteria or in the absence of respiratory cultures. In secondary analyses, we will evaluate a “clinical” diagnosis of VAP and respiratory antimicrobial use as endpoints.

7.4 STUDY INTERVENTION COMPLIANCE

This study relies on the cooperation of patient caregivers. Providers need to ensure appropriate functioning of the EVAC-PU-ETT suction port. Study personnel will play a key role in ensuring adequate adherence to the suctioning instructions throughout the intubation period, and consistent implementation of the VAP prevention bundle. Research personnel will monitor the study very closely during enrollment. Research coordinators will encourage adherence by providing daily reminders to

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check correct functioning of the device port and the correct amount of wall suction applied to it. Technical complications of ETT care such as obstruction of the suction port, rupture of the cuff, or endoluminal obstruction will be recorded. In addition, we will monitor adherence to expected VAP prevention bundles, and provide regular caregiver feedback. We expect that our extensive education and training process, along with daily verification by the study research coordinators will allow achieving optimal adherence to the study and clinical protocols.

7.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the electronic case report form (eCRF) are concomitant prescription medications, over-the-counter medications and supplements.

7.5.1 RESCUE MEDICINE

The study site will only supply ETTs for the 24 hours following extubation. In emergency situations outside this window, a new study intubation kit can be used if available in an accessible location or routine care ETTs can be used as rescue devices.

Although the use of rescue device is allowable at any time during the study, the use of rescue devices should be avoided if study ETTs are available. The date and time of rescue device placement must be recorded. For any events of a difficult airway requiring the placement of a surgical airway (tracheotomy), the date and time of rescue device placement must be recorded.

8 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 ADDRESSING INADVERTENT ENROLLMENTS

Due to this EFIC trial design and the short therapeutic window in an emergency medicine setting, we anticipate scenarios where a patient who does not meet the inclusion/exclusion criteria, may be inadvertently enrolled in the study. A deviation related to an inadvertent enrollment of a patient in one of these scenarios may be outside of the reasonable control of the research and occur based on what is considered the most readily available clinical information at the time of randomization into the study. The following four scenarios describe the unintentional, unavoidable protocol deviations in this EFIC study related to inadvertent enrollment and include a discussion of the potential risks and strategies to reduce the occurrences. The regulatory oversight and corrective action process is described in section 8.1.6.

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8.1.1 INADVERTENT ENROLLMENT OF A MINOR

A young adult of standard height and weight who appears older than their birth date has the potential to present to the ED unconscious, without family or witness, and in need of emergent endotracheal intubation. This rare scenario could lead to an inadvertent enrollment of a minor if a study ETT is used during intubation. Since the choice of the ETT size is clinically indicated and chosen based on body size and not age, there is not an increase in risk in using an appropriately sized ETT. There are no additional research risks involved in this type of inadvertent enrollment outside a minimal risk of breach of confidentiality.

If a patient is known to be a minor or found to be a minor, they should not be enrolled in the study and a standard of care ETT should be used instead. To minimize instances of enrollment of minors, prior to potentially enroll young adults into the study, subject identification (ID card or license) should be available for review. If (1) Identification is not available, (2) There is limited time to obtain a form of identification, and (3) It is not clear that the patient is above eighteen years of age, then the treating team should proceed with a standard of care endotracheal tube, and the patient will not be enrolled as a subject and randomized with a study tube.

The ED providers will be educated on the importance of confirming age prior to subject enrollment. The study team will review and confirm the subject identification process for all participants 18 to 21 years of age. The study team will provide feedback to the treating providers, as necessary. A log will be maintained by the study team of all subjects reviewed for identification confirmation.

For the ICU setting, a daily report of patients less than 18 years of age who are being treated in an adult ICU will be distributed to the study team as an additional tracking mechanism. When a minor is identified in an adult ICU, signage will be placed at bedside to notify the treating team to use a standard of care ETT if intubation is required.

8.1.2 INADVERTENT ENROLLMENT OF A PREGNANT WOMAN

A woman arriving to the ED needing emergent respiratory care may be unconscious and without family or witness to inform the treating staff of a pregnancy. Additionally, a woman could present to the ED in similar respiratory distress while also in the early stages of pregnancy and be unaware of her pregnancy status. These scenarios could lead to an inadvertent enrollment of a pregnant patient if a study ETT is used during an emergent endotracheal intubation. The choice of the ETT size is clinically determined and chosen based on body size and airway anatomy considerations in pregnancy. There is not an increase in risk in using a correctly sized ETT. There are no additional research risks involved in this type of inadvertent enrollment outside of minimal risks related to invasion of privacy and breach of confidentiality. Past the early weeks of pregnancy, pregnancy can be recognized based on clinical exam. All women of child bearing age have a pregnancy test performed on admission, in the context of clinical

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care. Whenever available and if there is time, providers are trained to verify these results in the medical record. If a patient is known to be pregnant or found to be pregnant based on testing, they should not be enrolled in the study and a standard of care ETT should be used instead.

A daily report of women who are pregnant in an adult ICU will be distributed to the study team as a tracking mechanism. When a pregnant woman is identified in an adult ICU, signage will be placed at bedside to notify the treating team to use a standard of care ETT if intubation is required.

8.1.3 INADVERTENT ENROLLMENT OF A PRISONER

While ED providers are trained to look for the presence of a police escort, physical restraints and/or prison attire, a person being detained in a drug treatment facility may present to the ED unrestrained, in plain clothing, and in respiratory distress. This scenario could lead to an emergent intubation using a study ETT. There are no additional research risks involved in this type of inadvertent enrollment outside of minimal risks related to invasion of privacy and breach of confidentiality.

If a patient is known to be a prisoner or found to be prisoner, they should not be enrolled in the study and a standard of care ETT should be used instead.

The ED providers will be educated on the importance of identifying if a patient is a prisoner prior to subject enrollment, if feasible. A daily report of prisoners in an adult ICU will be distributed to the study team as a tracking mechanism. When a prisoner is identified in an adult ICU, signage will be placed at bedside to notify the treating team to use a standard of care ETT if intubation is required.

8.1.4 INADVERTENT ENROLLMENT OF A RESEARCH OPT-OUT PATIENT

The Yale New Haven Health System offers an option for community members to opt out of research by adding this status to their electronic medical record prior to needing medical care. Due to the short therapeutic window in an emergency medicine setting, this status may be missed by the treating team and a study ETT could be used if emergency intubation is required. There are no additional research risks involved in this type of inadvertent enrollment outside of minimal risks related to invasion of privacy and breach of confidentiality. If a patient is known to have opted out of research at Yale University or their research opt-out status is found in the patient alerts field in EPIC, they should not be enrolled in the study and a standard of care ETT should be used instead.

The ED providers will be educated on the importance of confirming research opt out status prior to subject enrollment. The research opt-out status is documented in the electronic health record. A daily report of research opt-out patients hospitalized in an adult ICU will be distributed to the study team as a tracking mechanism. When a research opt-out patient is identified in an adult ICU, signage will be placed

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at bedside to notify the treating team that they should not be enrolled in the study and a standard of care ETT should be used instead.

8.1.5 TRAINING PLAN FOR ED STAFF

A study memo will be distributed to ED providers along with the faculty meeting and resident conference announcements. Research study staff will present monthly at two nursing huddle sessions to provide training reminders on the eligibility of the PreVent 2 trial in the ED setting. These frequent reminders will ensure new staff joining the department are trained on study inclusion and exclusion criteria. The quarterly memos will be printed and stored in the regulatory binder. Attendance sheets from the nursing huddle sessions will be stored in the in-person training log.

8.1.6 REGULATORY MANAGEMENT AND CORRECTIVE ACTION PROCESS OF DEVIATIONS INVOLVING AN INADVERTENT ENROLLMENT

Upon discovery, the sponsor-investigator will be notified immediately of the protocol deviation, and the deviation will be reviewed as part of regular monitoring duties. If a patient is discovered to be inadvertently enrolled into the study under a scenario described above, the patient will be withdrawn, and no data will be collected. Notification of subjects and family about an inadvertent enrollment will be tailored to each incident, and depending on the incident, will likely involve a call between the sponsor-investigator and the participant.

The sponsor-investigator will review the deviation and determine if the inadvertent enrollment meets the definition of an unanticipated problem (UP) or an unanticipated device effect (UADE). A report of the inadvertent enrollment will be submitted to the IRB via following the reporting requirements of Yale University IRB. If the deviation is an UP involving risks to human subjects, including an adverse event that is considered an UP or UADE, the sponsor-investigator will submit the report to the IRB and FDA within the required reporting timeframe. As a part of the review and management of the deviation, the sponsor-investigator will identify what necessary actions can be made to reduce the likelihood of a similar type of inadvertent enrollment, and to determine if the protocol needs to be amended. A corrective action plan may be initiated by the study team or the IRB.

8.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects may be withdrawn from the study at their own request or at the request of their legally acceptable representative, or in case of inadvertent enrollment.

Individuals enrolled in the study who become incidentally incarcerated after enrollment will be withdrawn from continued participation until they are no longer incarcerated.

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Participants will not be replaced if they withdraw after initial enrollment, and the data will be collected and included in the analysis up to the time of withdrawal.

A patient who is inadvertently enrolled fails to meet eligibility criteria; subjects inadvertently enrolled will be withdrawn from the study and their data removed. They are not considered a subject of planned enrollment.

8.3 LOST TO FOLLOW-UP

Obtaining complete data is a high priority for this trial because missing data could compromise the validity of the entire study. A participant will be considered lost to follow-up if he or she fails to return for the 6-month follow-up visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to appear for the 6-month follow-up visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant. These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable after several attempts, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

We will capture deaths among participants lost to follow up using various mechanisms, including review of the medical record, contacting the legal next of kin, or the contact provided at the time of study enrollment. For patients who are lost to follow up, we will also contact the primary care physicians and safety net clinics to ascertain the participant's vital status. In addition, local obituaries and newspapers will be screened for potential identification of lost to follow-up study participants.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 EFFICACY ASSESSMENTS

The initial study intervention (randomization and placement of a study device [tracheal intubation]) will be performed under exception from informed consent since the event will occur in an emergency situation. At the first available opportunity, an attempt will be made to obtain written informed consent from the participant or the authorized representative to continue participation in the study. Subjects

who have been randomized will be identified within 24 hours of intervention (tracheal intubation), and an attempt to approach the patient or more likely their legally authorized representative will be made immediately upon identification. In some cases, it may be difficult to identify the LAR immediately, but every effort will be made to obtain informed consent within 72 hours of randomization. Throughout the patient's hospitalization, data will be collected continuously from the time of randomization until hospital discharge or death.

A summary of the clinical data variables and definitions are listed below:

Baseline variables

Demographics: Patient demographic characteristics include age in years on the day of hospital admission, gender, race, ethnicity, weight and height, and county/state of residence. Participants' address and contact information will be maintained separately from the case report form and the study datasets, and linked via the study ID number, to enable re-contacting the participants after hospital discharge.

Clinical variables

Intubation procedure: PVC-ETT patients will be treated according to usual care, while EVAC-PU-ETT patients will receive continuous subglottic suctioning until removal of the ETT. As per the manufacturer's recommendation, continuous low-pressure suction at -20 mm Hg will be applied to the suction port. Procedural details of the intubation procedures will be collected as part of standard pre-formed intubation procedure notes. These details include indication for tracheal intubation, ETT type and size, methods of preoxygenation, induction medication, and instruments used. To quantify difficulty with laryngoscopy and ETT insertion, we will record the number of laryngoscopy attempts, and use of gum-elastic bougie to guide insertion of the tube. Furthermore, immediate complications will be gathered including aspiration noted during laryngoscopy, pharyngeal and tracheal injury, and extent of oxygen desaturation.

ICU admission and stay: Patient characteristics recorded will be demographics, APACHE II score, main reason for ICU admission, presence of community acquired pneumonia at admission, and indication for mechanical ventilation. In addition, patients' history of and current comorbidities will be collected and summarized using the Charlson comorbidity index. Variables that will be collected to derive outcome measures are: date of hospital admission, date of ICU admission, date/time of tracheal intubation (=time of initiation of mechanical ventilation), date/time of tracheal extubation (=time of discontinuation of mechanical ventilation), date/time of reintubation(s) and subsequent extubation(s) (if applicable), date and time of tracheotomy (if applicable), start and end date of each respiratory antimicrobial cycle initiated within 6 hours of intubation and while on mechanical ventilation, date of ICU discharge, date of hospital discharge, and date of death.

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Post-extubation laryngeal dysfunction: Lack of cuff leak prior to study ETT removal, post-extubation upper airway obstruction, as evidenced by stridor requiring treatment (racemic epinephrine, helium-oxygen gas mixture) or resulting in re-intubation within 24 hours, will be recorded by observation and/or review of the medical record.

Monitoring VAE/VAP events: Patients will be monitored in the ICU until extubation, discharge or death. All patients will be monitored for the occurrence of VAP (see Appendix I for CDC definition of ventilator associated events) during the ICU stay. Diagnosis and treatment of VAP are standardized and their identification will be left to the judgment of the primary physician in charge of the patient. We will record all VAP events diagnosed based on respiratory cultures, all bronchoscopically and invasive diagnostic tests for pneumonia performed, and events of clinical VAP criteria based on both CDC criteria and a based on a clinical diagnosis.

Patient monitoring: Vital signs and physiologic variables will be monitored hourly until ICU discharge. The amount, color, and frequency of suctioning of endotracheal aspirates will be recorded daily. Isolates and quantity of respiratory cultures, and antimicrobial administration for respiratory indication will be collected.

VAP bundles and concomitant treatments that affect VAP: 1) Semi-recumbent position by capturing head of bed position (% of time >30° as automatically recorded by electronic beds); 2) stress ulcer prophylaxis, enteral calorie intake; 3) performance of oral hygiene, 4) use of neuromuscular blocking agents; 5) documentation of cuff pressure and application of subglottic suctioning; 6) Daily sedation vacation and spontaneous breathing trial (SBT).

VAP Treatment: Initial antimicrobial therapy is directed by hospital-wide guidelines. Use of respiratory antimicrobials and their duration will be collected.

During the ICU stay we will also collect the daily SOFA. As a summary measure, we will compute the mean of the daily score during the ICU stay.

Hospital stay variables: After discharge from the ICU, patients will be followed to obtain information on safety, disposition and antimicrobial treatment for VAP.

6-month follow-up: All patients will be followed-up six months after randomization with a structured in-person interview to screen for the presence of and assess airway symptoms or persistent sequelae of laryngeal dysfunction (Appendix II).[106] Any need for consultation of a specialist for airway complaints will be recorded and information abstracted from the medical record if appropriate. The clinical medical records release form collected at the time of informed consent will allow access to the subject's outside medical record for data related to the breathing problem. Quality of life will be also assessed, as measured by the physical component summary and the mental component summary of the Medical

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Outcomes Study 36 Item Short-Form (SF-36) General Health Survey (Appendix IV).[120, 121] We will also assess cognitive function using a battery of tests assessing domains previously demonstrated to be potentially affected by periods of respiratory distress and validated in both normal aging and cognitively impaired populations.[125-128] The core battery will consist of measures from the National Alzheimer Coordinating Center's Uniform Data Set (UDS – Appendix V):[129, 130] 1) Montreal cognitive assessment (MoCA), a global cognitive screen which has been shown to be much more sensitive than the Mini Mental Status Examination; 2) Craft Story Recall (an analogue to the Logical Memory subtest of the Wechsler Memory Scale), measuring immediate and delayed verbal contextual recall; 3) Benton Complex Figure test, which measures executive function and visuospatial ability, as well as visuospatial recall; 4) Digit Span, a test of attention and working memory; 5) Trail Making, Parts A and B, measures of attention and divided attention/working memory; and 6) Semantic and phonemic verbal fluency test. The follow-up visit will take from 60 to 75 minutes to complete.

Adverse Events (AE) monitoring: Any device-related AE will be recorded and evaluated for intensity, seriousness, causality in relationship to the study ETT, and actions taken. In the case of a device-related AE, the subject will be treated by the primary physician or referred for care, as appropriate. Additional details on AE and serious AE reporting are detailed in the Human Subject Section.

Economic variables

Healthcare resource utilization data will be obtained through extracts of electronic health record information for specific service items (i.e., x-rays, respiratory cultures, use of antimicrobials, etc.). The institution's direct cost (not charge) for billable items will be obtained from financial records of the cases as the measure of the cost. The cost of the device itself will be taken from the institution's supply purchase price (with sensitivity analysis for public reports of the price). The main consequence/outcome variables include: quality of life dimensions in SF-36, their summarized preference-based utility score from the SF-6D, neurologic function score, and mortality. Differential cost and consequence outcomes will be calculated for each arm.

9.2 SAFETY AND OTHER ASSESSMENTS

Safety in regard to airway trauma induced by tracheal intubation will be assessed by evaluating the short-term effects of the ETT on the airway including subjective and objective measures of laryngeal anatomy and function, in addition to any device-related adverse events. We will record: 1) airway complications at the time of ETT insertion; 2) documentation of a cuff leak prior to study ETT removal; 3) stridor immediately after extubation; 4) requirement for stridor treatment (racemic epinephrine, helium-oxygen gas mixture); or 5) reintubation within 24 hours due to upper airway complications such as stridor or obstruction.

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In addition, long-term safety will be assessed by ascertaining the persistence of airway sequelae six months after randomization using a standardized questionnaire via in-person interview (or phone interview). Data collected include complaints of airway symptoms and a speech evaluation.

9.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

9.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3.3 CLASSIFICATION OF AN ADVERSE EVENT

9.3.3.1 SEVERITY OF EVENT

The clinical intensity of an unanticipated problem or AE will be classified as described below. For problems or events where the intensity changes over time, the maximum intensity observed during the whole duration will be documented.

Severity of Event	Mild	Signs and symptoms that can be easily tolerated, ignored, and disappear when the subject is distracted.
	Moderate	Symptoms cause discomfort but are not tolerable, cannot be ignored, and affect concentration.
	Severe	Symptoms affect usual daily activity.

9.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The causal relationship of an AE to the study protocol will be classified using the following terminology. The given criteria for each term are neither exhaustive nor required to be fulfilled in total for the selection of the respective term:

Relationship to Study Intervention	Unrelated	The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event) or could readily have been produced by a number of other factors.
	Suspected	An AE that follows a reasonable temporal sequence from the initiation of study procedures. Data with sufficient evidence or argument to suggest a causal relationship.
	Certain	The AE is clearly related to the study procedures.

9.3.3.3 EXPECTEDNESS

Expectedness of (serious) adverse events will be assessed by the medical monitor. An unexpected AE is one where the nature or intensity is not consistent with available information. Furthermore, reports that add significant information about the specificity or severity of a known, already documented, adverse reaction constitute unexpected AEs. For example, an AE that is more specific or more severe than expected would be considered “unexpected”.

9.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant’s condition deteriorates at any time during the study, it will be recorded as an AE.

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Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator will record all reportable events with start dates occurring any time after randomization until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

9.3.5 ADVERSE EVENT REPORTING

For the duration of patient therapy, the investigators will be responsible for monitoring and recording 1) Unanticipated problems (UPs); 2) Protocol deviations (PDs); 3) Adverse Events (AEs); 4) Serious Adverse Events (SAEs). The following AEs are expected for the study population: abrasion of the arytenoid cartilage vocal process, cartilage necrosis, cicatrix formation, consequences of failure to ventilate including death, damage to the perichondrium, development of dense or diffuse fibrosis invading the entire glottic area, emphysema, endobronchial aspiration, endobronchial intubation (hypoxemia), endotracheobronchial aspiration, epistaxis, esophageal intubation (stomach distension), excoriated membranes of the pharynx, eye trauma, fibrin deposition, formation of subglottic web, fracture-luxation of cervical column (spinal injury), fragmentation of cartilage, glottic edema (supraglottic, subglottic, retroarytenoidal), granuloma of the inner arytenoid area, infections (laryngitis, sinusitis, abscess, respiratory tract infection), inflammation, intermittent aphonia and recurrent sore throat, laryngeal fibrosis, laryngeal granulomas and polyps, laryngeal obstruction, laryngeal stenosis, laryngeal ulcers, laryngotracheal membranes and webs, membranous glottic congestion, membranous tracheobronchitis, mild edema of the epiglottis, mucosal sloughing, paresis of the hypoglossal and/or lingual nerves, perforation of esophagus, perforation of the trachea, pneumothorax, replacement of the tracheal wall with scar tissue, respiratory obstruction, retrobulbar hemorrhage, retropharyngeal abscess, retropharyngeal dissection, rupture of the trachea, sore throat, dysphagia, stricture of nostril, stridor, subglottic annular cicatricial stenosis, submucosal hemorrhage, submucous puncture of the larynx, superficial epithelial abrasion, swallowed tube, synechia of the vocal cords, teeth trauma, tissue burns, tracheal bleeding, tracheal stenosis, trauma to lips, tongue, pharynx, nose, trachea, glottis, palate, tonsil, etc., traumatic lesions of the larynx and trachea, ulcerations exposing cartilaginous rings and minor erosions at cuff site, ulcerations of lips, mouth, pharynx, ulcers of the arytenoid, vocal cord congestion, vocal cord paralysis, vocal cord ulcerations, and death.

All UPs and AEs reported spontaneously by subjects at any point will also be documented. Any medically concerning symptom will be followed until it reaches a satisfactory conclusion, becomes stable, or clinical judgement indicates that further evaluation is not warranted.

9.3.6 SERIOUS ADVERSE EVENT REPORTING

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Descriptions of individual serious adverse events (SAEs) and unanticipated problems will be reported as specified in the DMSB charter. The investigators will provide a written notification of reportable events to the DMSB and funding agency in accordance with deferral regulations. All serious adverse events will be followed until resolution or stabilization.

9.3.7 REPORTING OF PREGNANCY

Pregnancy will be determined via screening test provided to all women as part of standard care, so that women who test positive will be excluded. Women will not be excluded based on lactation status.

9.4 UNANTICIPATED PROBLEMS

9.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

9.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

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- Study Information: Title, PI, IRB#, Sponsor/award #, IND/IDE#
- Number of subjects enrolled to date and currently actively involved in research procedures.
- Date of UP, Date notified of UP
- Classification of the Experience Type: On protocol UP for subjects, Off protocol UP, or Other Unanticipated Problem
- Participant ID, if applicable
- Description of event
- Relationship of the device to the UP.
- Basis for UP determination: Analysis as to why the event represents a "problem" for the study and why it is "unanticipated". For instances of increased frequency or severity, it must state how the frequency or severity diverges from the expected.
- Response Plan. Description of proposed actions, including modifications, to be taken by investigators in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported to the IRB within 7 calendar days of discovering the information.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

Our central hypothesis is that EVAC-PU-ETT is as safe as the standard PVC-ETT and is superior to the standard PVC-ETT in reducing the occurrence of VAP and several of its long-term consequences.

The primary objectives of the proposed trial are to compare the clinical safety and effectiveness of EVAC-PU-ETT compared with PVC-ETT. The primary clinical endpoints will be: safety, quality of life, and cognitive impairment. Safety, measured as long-term laryngeal injury, will be tested for equivalence between the two treatment groups, or more precisely, that the EVAC-PU-ETT treatment is "non-inferior" to the PVC-ETT treatment. Quality of life will be assessed using the RAND Short Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS). For cognitive impairment, patients will be considered cognitively impaired if their global cognition scores are at least 1.5 standard deviation (SD) below the population mean (for comparable patients with moderate TBI) in at least two global cognition scores or more than 2 SD below the population mean for a single global cognition score. Safety will be analyzed using a sequential design with one interim analysis. The primary aims for quality of life and cognitive impairment will be evaluated for superiority of the EVAC-PU-ETT treatment using a fixed sample design. The treatment effect with be measured as the difference in probability risks, between the treatment groups, for the safety and cognitive impairment outcomes. The

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treatment effect for the quantitative quality of life outcomes will be represented as differences in means.

10.2 SAMPLE SIZE DETERMINATION

Power and Sample Size Determination

The trial uses a fixed sample design. We assumed a prevalence of cognitive impairment of 0.40 for this at population, a sample size of N=1074, we require a minimum risk difference of 0.09 ($q = p1 – p0 < -0.09$) to attain statistical power of at least 80 percent. We assumed a prevalence of cognitive impairment of 0.40, however, the risk difference of 0.09 attains the targeted level of power or higher, for a prevalence in a reasonable range (e.g., 0.2-0.8). To achieve power of at least 80 percent for the targeted sample size of N=1,074, we require a difference in the means to be greater than 0.17 standard deviations on a standardized scale. For the SF-36 mental component summary (MCS), for example, if the SD is conservatively equal to 30, then the minimum difference in the mean MCS scores will need to be approximately 5.1 points (i.e., min difference = 0.17*SD = 0.17*30). For the physical component summary (PCS), if the population SD were 40 points, the minimum difference would be 6.8 points (min difference = 0.17*40). These power and effect size calculations assume an independent, two-sample test, an alpha level of five percent and all statistical tests are two-sided tests.

The target sample size for the study is 1,074 patients (537 per treatment arm), in order to achieve power of 80% for each test of the primary outcomes. The study is powered for meaningful minimum effect sizes to detect treatment differences in the primary endpoints. The statistical software STATA vers. 15 (Stata Corporation, College Station, TX) and R have been used to compute the statistical power.

Based on 2016 data, emergency intubations occurred primarily in the Emergency Department (ED) and in the hospital: approximately 200 intubations were performed in the ED and 404 intubations occurred in the hospital, yielding approximately 600 emergency intubations per year. With a projected enrollment period of 36 months, we anticipate adequate feasibility to accrue the required sample size.

Missing Data

The primary analysis described above provides valid inference if the missing response data is missing at random (MAR). However, in the case that the data are not missing at random (NMAR), the results of the proposed analyses may be biased. We will perform sensitivity analyses to assess the impact of the missing outcome data. We will employ standard multiple imputation methods to assess the degree to which the primary analysis may be affected by the missing data. Patient retention will be key to the successful completion of this study, and we will take several measures to maximize retention. We expect missing data due to “losses to follow up” to be minimized by our efforts. We will make every reasonable effort to retain the patients through follow-up to preserve the integrity of the study and to minimize

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possible bias associated with loss due to dropouts. We realize that these investigations of missing data or accruing additional patients to meet targeted sample sizes are not foolproof substitutes to remedy missing data.[8] We intend to make every reasonable attempt to maximize the rate of follow up in our sampled population. We will minimize the loss of follow-up data by continuing to have clear performance standards in the protocols to achieve high quality trial conduct, including high levels of data capture. We will continue to monitor and carefully educate providers as well as patients or their representatives during the informed consent process regarding the scientific relevance, and we will also monitor data collection to ensure quality standards are met, including targeted levels of data capture.

Changes to the Statistical Analysis Plan

Changes to this statistical analysis plan will be documented via a formal addendum that includes rationale, new procedures, and potential differences from prior plan.

10.3 POPULATIONS FOR ANALYSES

An intent-to-treat (ITT) population will be defined as all adult patients whose trachea was intubated with either a EVAC-PU-ETT or PVC-ETT from one of the study kits and admitted to any adult Intensive Care Unit (ICU). Approximately 1,074 patients will be included.

10.4 STATISTICAL ANALYSES

10.4.1 GENERAL APPROACH

The statistical analysis plan (SAP) for the final statistical report contains the planned analyses indicated in the study protocol.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Analysis of Safety Primary Endpoint

One objective of this study is to establish that the experimental treatment, EVAC-PU-ETT, has a safety profile that is not inferior to the standard treatment, PVC-ETT. For this aim, we will conduct a non-inferiority analysis and test that the underlying population risk of laryngeal injury for the EVAC-PU-ETT treatment group is not statistically higher than the population risk of laryngeal injury for the PVC-ETT treatment group. To evaluate the non-inferiority of laryngeal risk of the EVAC-PU-ETT treatment, we specify a non-inferiority bound that the difference in the true risk probabilities is less than or equal to 0.05. That is, $q = p1 – p0 < 0.05$, where p1 denotes the risk of laryngeal injury for the EVAC-PU-ETT treatment group, p0 denotes the risk of laryngeal injury for the PVC-ETT treatment group and therefore,

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q, denotes the difference in the two risk probabilities. The test of hypothesis for the primary endpoint is a two-sample difference in risk in a group sequential design with one planned interim analysis. The analysis will be conducted when approximately 50 percent of the total sample has been collected. The group sequential stopping rule is based on 2.5 percent significance level and a one-sided stopping rule with an O'Brien-Fleming boundary. The interim analysis would take place when approximately 537 (269 patients per study arm) have been accrued. At the time of the interim analysis, the trial would be stopped if the estimated risk difference, p1-p0, is greater than the safety boundary of 0.0956, indicating EVAC-PU-ETT is significantly more harmful than PVC-ETT. Evaluation of the estimated differences will be obtained using standard, fixed-sample maximum likelihood estimates (MLEs). The MLEs provide valid point estimates for evaluating the group sequential design stopping rules. At the conclusion of the study, the estimated difference, confidence intervals and associated p-values require adjustment, accounting for the interim analyses. We consider bias adjusted estimates [4] and Rao-Blackwell adjusted estimates [5] to correct for the bias in the fixed sample MLEs. Sample mean ordering [5] will be used to adjust confidence intervals and p-values.

Specifically, we will evaluate whether there is a difference in the laryngeal injury risk probabilities for the two treatments, we will use maximum likelihood estimation (binomial family) with an identity link function. The statistical model used for this analysis will be: $p(X) = \beta 0 + \beta 1 X$ where p(X) denotes the laryngeal injury probability and X is an indicator denoting the treatment assignment (1 = EVAC-PU-ETT, 0 = PVC-ETT). The identity link function makes the interpretation of parameter for the treatment effect, $\beta 1$, be equal to $\beta 1 = p(1) - p(0)$, which is exactly the risk difference, q, noted above. In the Prevent pilot study, the estimated risk of laryngeal injury was 0.39 for the PVC-ETT treatment group and 0.38 for the EVAC-PU-ETT treatment group. Assuming an estimated risk difference less than or equal to 0.05 for the targeted sample size of N=1074 (537 patients per treatment arm) for the pre-specified alpha-level and statistical design, the statistical power for concluding non-inferiority of the EVAC-PU-ETT treatment group would be 80 percent.

Analysis of Quality of Life Primary Endpoint

We will evaluate whether there are differences in quality of life measures between treatment groups by comparing mean scores. Separate analyses will be conducted for the two endpoints. The statistical model will be linear regression, $\mu(X) = \beta 0 + \beta 1 X$, where $\mu(X)$ denotes the mean SF-36 score, X is an indicator denoting the treatment assignment as before. The test for a treatment effect is denoted by, $\beta 1 = \mu(1) - \mu(0)$. We will use robust inference so that our tests will be valid for modest departures in modeling assumption. Additionally, we will transform the scores to reflect "percent of healthy life". This transformation of the SF-36 measures provides easily interpretable variables and allow for the retention of patients that die during the study. As noted previously, the design for this endpoint is a fixed sample design. To have power of at least 80 percent for the targeted sample size of N=1074, we require a difference in the means to be greater than 0.17 standard deviations on a standardized scale. These

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power and effect size calculations assume an independent, two-sample test, an alpha level of five percent and all statistical tests are two-sided tests.

Analysis of Cognitive Impairment Primary Endpoint

To evaluate whether there is a difference in the risk of cognitive impairment between the two treatments, we will use the same fixed sample methods used for the primary safety endpoint. We will estimate the difference in the probability of cognitive impairment for the two treatments using maximum likelihood estimation (binomial family) with an identity link. We will use robust (sandwich) standard error estimates in the test statistics and confidence intervals to remedy possible minor violations of modeling assumptions. The design for this endpoint is a fixed sample design. We assumed a prevalence of cognitive impairment of 0.40 for this at population, a sample size of N=1074, we require a minimum risk difference of 0.09 ($q = p1 – p0 < -0.09$) to attain statistical power of at least 80 percent. We assumed a prevalence of cognitive impairment of 0.40, however, the risk difference of 0.09 attains the targeted level of power or higher, for a prevalence in a reasonable range (e.g., 0.2-0.8).

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Analyses of Secondary Endpoints

Important secondary analyses will be conducted to compare means between the EVAC-PU-ETT and PVC-ETT treatments for quantitative outcomes (e.g., domain scores for the SF-36, cost, length of stay) using linear regression. For binary outcomes we will use logistic regression with robust (sandwich) standard error corrections. Comparison of survival outcomes between the EVAC-PU-ETT and PVC-ETT treatments (e.g., time to extubation, time to discharge from the ICU) will be performed using log rank test statistics. We will compare 6-month mortality between the two treatment groups using 6-month mortality estimates from the treatment groups' Kaplan-Meier curves. We will compare mean hospital length of stay, mean ventilator-free days and the mean SOFA scores between EVAC-PU-ETT and PVC-ETT using censored regression analysis. We will investigate whether the proportion of IVAC and VAEs differs between EVAC-PU-ETT and PVC-ETT among the subgroups of critically ill patients defined by gender and race. Formal comparisons between the treatment groups and patient subgroups will be investigated by fitting logistic regression models with robust variance estimates. We will perform omnibus tests of appropriately specified interaction terms between treatment assignment and patient subgroups. The mean and median overall per patient costs will be assessed for each randomized group, along with the clinical and hospital outcomes (consequences). We will investigate the mean difference in cost between the use of EVAC-PU-ETT and PVC-ETT. Cost will be defined in two ways: service-price and billable costs. We will formally test the difference in mean cost by using linear regression analysis with robust variance estimates. Inference on mean cost will be valid provided the sample size is moderately large (e.g.,

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greater than 200 patients).[7] We will use regression analysis to determine if there are greater/lesser benefits/risks in patient subgroups in the economic analysis. We will test for differences in median costs using randomization tests. All hypothesis tests described above will be two-sided. Test results will be deemed statistically significant if the associated p-values of the tests are less than 5 percent.

10.4.4 SAFETY ANALYSES

Safety endpoints include clinical measures intended to evaluate the direct effect of the device at the site of placement. To evaluate the effect of the ETT at the local level we will be assessing subjective and objective measures of laryngeal anatomy and function, in addition to any device related adverse events. We will record: 1) airway complications at the time of ETT insertion; 2) stridor immediately after extubation; 3) requirement for stridor treatment (racemic epinephrine, helium-oxygen gas mixture); or 4) reintubation within 24 hours due to upper airway complications such as stridor or obstruction. Long-term safety will be assessed by ascertaining the persistence of airway sequelae six months after randomization using a standardized questionnaire via in-person interview. At the in-person interview, participants will be administered a structured interview to collect information for residual complaints involving the upper airway and any airway problems requiring the consultation of a specialist (Appendix II). Data collected include the presence of persistent throat discomfort or pain, residual hoarseness, change in voice, and dyspnea. If a visit to a specialist for evaluation and/or treatment of speech, swallowing, or breathing problems occurred, the medical record will be reviewed. If moderate to severe airway symptoms are identified, one the PIs will evaluate the airway and will refer the patient to the primary care provider or to a specialist, as appropriate.

Adverse Events: As defined in 21 CRF 312.32. Tabulation or summary of AEs will be reported at each DSMB meeting and annually to IRB.

10.4.5 BASELINE DESCRIPTIVE STATISTICS

For the baseline descriptive statistics, we will present overall sample summary characteristics, e.g., mean, standard deviations, and percentages. We will also provide summaries of the baseline characteristics stratified by treatment assignment to describe the patient population and to evaluate the balance in the randomization assignment. We will also provide information on data completeness and retention to follow up.

10.4.6 PLANNED INTERIM ANALYSIS

The test of hypothesis for the primary endpoint is a two-sample difference in risk in a group sequential design with one planned interim analysis. The analysis will be conducted when approximately 50 percent of the total sample has been collected. The test of hypothesis for the primary endpoint is a two-

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sample difference in risk in a group sequential design with one planned interim analysis according to the design specified in Section 10.4.2.

10.4.7 SUB-GROUP ANALYSES

We will investigate whether the proportion of IVAC and VAEs differs between EVAC-PU-ETT and PVC-ETT among the subgroups of critically ill patients defined by gender and race. Formal comparisons between the treatment groups and patient subgroups will be investigated by fitting logistic regression models with robust variance estimates. We will perform omnibus tests of appropriately specified interaction terms between treatment assignment and patient subgroups.

Also, we will use regression analysis to determine if there are greater/lesser benefits/risks in patient subgroups in the economic analysis.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1.1 INFORMED CONSENT PROCESS

11.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant. Due to the emergent situation leading to study enrollment, most participants will be incapacitated at the start of the study intervention. Written documentation of informed consent will be obtained at the earliest feasible opportunity after starting the intervention, either by the participant after regaining decisional capacity, or by the LAR once identified. A copy of the signed consent form will be given to the participant or LAR after written consent has been obtained.

11.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

This study involves emergency situations with an extremely narrow therapeutic window, minimal risk of harm to subjects, and involves no procedures for which written consent is generally required outside of the research context, it qualifies for the “exception from informed consent required for emergency research” outlined in FDA regulation 21CFR50.24.

The need for emergency endotracheal intubation is a clinical decision that is based on the patient’s condition and the likelihood of significant morbidity or mortality without intervention. In this situation, the therapeutic window for interventional care may be seconds to minutes. In the vast majority of cases,

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this therapeutic window represents insufficient time to contact a LAR for consent. In addition, any delay in these emergency situations could be detrimental to the patient. All aspects of clinical care that follow the placement of the device will occur according to usual care. We will make every effort to contact a legal representative during the therapeutic window to ask for consent prior to intubation with a study tube rather than proceeding without consent. However, the need to obtain consent will not impede the clinical need to intubate a patient as the provider sees fit. Emergency intubation will not be delayed as a result of waiting to obtain LAR consent for this study.

It is unlikely that an individual subject may be conscious and able to make heath care related decisions. In the event that a patient meets the entry criteria and is awake and alert, the patient is still under considerable duress due to the acute injury. In this situation, an opt-out script informing the patient that he/she is being enrolled in a research study and their right to immediate refusal along with a brief description of the study will be read to the subject by any of the following: trained providers performing the procedure, the ICU nurse, or the respiratory therapist in the ICU. For patients “opting-out,” a non-study tube from standard supply will be used for intubation.

Prior to randomization, there may be other evidence that an individual does not wish to participate in a study. For instance, a LAR or family member is able to communicate a subject’s unwillingness to participate in research studies or there is evidence in the individual’s electronic health record. If we learn that a family or patient is opposed to participating in the research prior to randomizing the patient, then we will not be randomized into this study and the subject will receive a non-study ETT.

If the subject or the LAR is not immediately available to provide consent during the therapeutic window, the research coordinator will attempt to contact the subject’s LAR through hospital discharge as described below.

After the therapeutic window, the research coordinator will attempt to contact the subject’s LAR through hospital discharge. A summary of these efforts will be documented in the study attempted consent logs. The study team will attempt to obtain informed consent for continued participation in the study upon identification of the subjects via the daily intubation and ventilation reports, as well as communication from the team performing the intubation procedure. If the study participant is legally competent but is physically unable to talk or write, an unbiased witness who is neither a study team member nor a family member of the participant can sign the witnessed line on the consent form to enter the patient into the trial. The unbiased witness must observe the consent process.

For the majority of enrolled subjects, it is assumed that patients themselves will be unable to give informed consent due to critical illness, tracheal intubation, and administration of sedative and analgesic drugs, all of which may cloud consciousness, impair communication and decisional capacity. When it is appropriate to obtain informed consent, the patient’s clinical team will be asked for

permission to approach the patient's LAR in person to consent for continued participation in the study at the earliest feasible opportunity.

When it is appropriate, a member of the study team will meet with the LAR to explain why the subject was included in the study without his/her informed consent. The study team will provide the details about the research study and will ask for continued participation in this study. The study team will obtain informed consent. Consent forms will be Institutional Review Board (IRB)-approved and include HIPAA Authorization. The study team will also obtain a signed clinical medical records release form to allow review of the patient's outside medical record when consultation of a specialist is required. The LAR will be asked to read and review the documents. The study team will explain the research study to the LAR and answer any questions that may arise. A verbal explanation will be provided in terms suited to the LAR's comprehension of the purposes, procedures, and potential risks of the study and of the rights of the research participant. During the consent process, the details of the study will be reviewed along with potential risks and benefits, the endpoints of interest, and the process by which these endpoints are evaluated. The LAR will have the opportunity to carefully review the written consent form and ask questions prior to signing. The LAR must be informed that participation is voluntary and that the participant may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the LAR and the participant for their records. The informed consent process will be conducted and documented in the source document. The rights and welfare of the participant will be protected by emphasizing to the LAR that the quality of the participant's medical care will not be adversely affected if they decline to participate in this study.

When face-to-face communication with the LAR is not possible (for instance due to individual being out of town), then the study team will make contact by phone and send information with the consent form by registered mail, email, or by fax with "read receipts" in order to provide this information in a timely fashion and to obtain signatures for the consent form.

If the LAR is told about the research study and the subject's condition improves, the subject will also be informed about the research as soon as is it feasible. The LAR, or subject will be given the opportunity to object to the study and refuse participation or withdraw from the study at any time without penalty or loss of benefits to which the subject is otherwise entitled. If the subject or LAR chooses to withdraw from the study after randomization, the study team will discontinue data collection on the patient at that time but will retain the data collected up until the time of withdrawal.

11.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the

Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

This study may be discontinued at any time by the DSMB's and or responsible IRB's recommendation. The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funder, IRB and/or Food and Drug Administration (FDA).

11.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored on a secure server. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured

and password protected. At the end of the study, all study databases will be de-identified and archived on a secure server.

11.1.4 FUTURE USE OF STORED DATA

The de-identified, archived data will be stored on a secure server and made available via the NIH/NHLBI Biologic Specimen and Data Repository Information Coordinating center (BioLINCC) for use by other researchers including those outside of the study.

11.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
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11.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including ethics, EFIC clinical trial experience, long term follow-up, pulmonary critical care, and biostatistics. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to NIH staff.

11.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the PI will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the

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protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

11.1.8 DATA HANDLING AND RECORD KEEPING

11.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

A large portion of data collection will be performed by abstracting data captured in the electronic medical record and merged with the data automatically abstracted from the electronic health record. A subset of the data collection will require manual chart abstraction. In addition, study specific questionnaires and case report forms will be used for additional data collection at extubation and at the 6-month follow up. Study personnel will enter data from source documents corresponding to a participant's day on-study into the case report form (CRF) when the information corresponding to that day is available. Study participants will not be identified by name on any study documents to be collected by the Sponsor or authorized designee, but will be identified by a unique study ID.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs) and expected adverse reactions data) and clinical laboratory data will be entered into the eCRF, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

11.1.8.2 STUDY RECORDS RETENTION

The Sponsor or authorized designee must make study data accessible to regulatory authorities upon request. A file for each participant must be maintained that includes the signed Informed Consent and copies of all source documentation related to that participant. The Investigators must ensure the reliability and availability of source documents from which the information in the eCRF was derived. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

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11.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the NHLBI Program Official and the site investigator. Documentation must include: 1) Detailed narrative describing the deviation, how the deviation was discovered, the risks the subjects were exposed to and the measures taken to minimize risk; 2) A detailed corrective action plan to prevent similar deviations in the future.

Protocol deviations must be tracked in a protocol deviation log. Protocol deviation logs should be submitted at the time of continuing review. Research teams should review the protocol deviation logs periodically and determine if the deviations indicate a larger systemic problem with the implementation of the research. Appropriate corrective measures should be taken to rectify any systemic problems.

Further details about the handling of protocol deviations will be included in the MOP.

11.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-

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reviewed journals. Consistent with NIH policy within three years after the completion of the last 6-month follow up visit, the data management unit will create public use data sets with documentation appropriate for independent use by an investigator external to the study.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

11.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with The National Heart, Lung, and Blood Institute (NHLBI) has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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11.2 ABBREVIATIONS

AE	Adverse Event
CAP	Community-Acquired Pneumonia
CASS	Continuous Aspiration of Subglottic Secretions
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ED	Emergency Department
EFIC	Exception From Informed Consent
ETT	Endotracheal Tube
EVAC-PU-ETT	Polyurethane-Cuffed Endotracheal Tube with Continuous Aspiration of Subglottic Secretions
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
HVLT-R	Hopkins Verbal Learning Test-Revised
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IVAC	Infection Related Ventilator-Associated Complications
LAR	Legally Authorized Representative
LSMEANS	Least-squares Means
MAR	Missing At Random

MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MLE	Maximum Likelihood Estimates
MoCA	Montreal Cognitive Assessment
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NACC UDS	National Alzheimer's Coordinating Center Uniform Data Set
NCT	National Clinical Trial
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NMAR	Not Missing At Random
OHRP	Office for Human Research Protections
OHSU	Oregon Health & Science University
PCS	Physical Component Summary
PD	Protocol Deviation
PI	Principal Investigator
PU	Polyurethane
PVC	Polyvinylchloride
PVC-ETT	Polyvinylchloride-Cuffed Endotracheal Tube
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	RAND version 1.0 of the Medical Outcomes Study 36-item Short-Form General Health Survey
SMC	Safety Monitoring Committee
SNP	Single Nucleotide Polymorphisms
SOA	Schedule of Activities
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
TBI	Traumatic Brain Injury
TOPF	Test of Premorbid Functioning
VAC	Ventilator Associated Conditions
VAE	Ventilator-Associated Events
VAP	Ventilator Associated Pneumonia
UDS	National Alzheimer Coordinating Center's Uniform Data Set
UP	Unanticipated Problem
US	United States
WAIS-IV	Wechlser Adult Intelligence Scale-4th ed
YNHH	Yale New Haven Hospital

11.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	04/13/2020	Original version	
2.0	08/31/2020	Addressing Community Consultation and Public Disclosure plan.	Clarifying CC and PD plan through the end of the trial.
2.1	04/12/2021	Addressing unplanned protocol deviations related to enrollment outside of the inclusion/exclusion criteria.	Clarifying inadvertent enrollments and the regulatory and corrective action process that follow.
2.2	04/28/2021	Updating the format, frequency, and tracking of training in the Emergency Department.	Providing clarification of ongoing provider training during participant enrollment.

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