

Oral Suction Intervention to Reduce Aspiration and Ventilator Events: NO-ASPIRATE

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Approach

Patients who are intubated and treated with MV are at a high risk for microaspiration of secretions,¹⁵ and subsequent development of VAC.³⁶ VAC include infectious and noninfectious complications that result in increasing oxygenation needs after a period of stability on MV.¹⁶ Many factors contribute to microaspiration: gastric distention and reflux,^{100,101} enteral tube feeding,¹⁰¹⁻¹⁰³ underinflation of the ETT cuff,¹⁰⁴ longitudinal folds that develop in the ETT cuff,¹⁰⁵ ventilator settings (low PEEP),¹⁰⁶⁻¹⁰⁸ lower head of bed position (gastric contents),¹⁰¹ sedation, and reduced level of consciousness.¹⁰¹ Nursing interventions that have been shown to

reduce the incidence of microaspiration and/or VAP in critically ill, adult patients include an aspiration risk-reduction protocol targeting head of bed elevation, management of high residual enteral feeding volumes,¹⁹ suctioning oral secretions prior to repositioning,^{23,24} and continuous suctioning of oral secretions.²² Device related interventions are also important, such as control of the ETT cuff pressure and insertion of the SS-ETT.^{85-88,109-111} In clinical practice, we have observed that nurses are managing feedings per protocol, maintaining the head of bed elevation, and cleansing the mouth with antiseptics; respiratory therapists are maintaining the ETT cuff pressure in a targeted range; and many patients have a SS-ETT. We have also observed that nurses use suction swabs and tonsil suction devices for removing oropharyngeal secretions.

Preliminary Studies: High Resource Utilization, Large Volume of Secretions, Oral Suction Strategies

Our preliminary work has focused on airway management of critically ill patients who require MV. We found that development of VAP is associated with up to \$40K per case in additional costs, along with longer LOS.^{13,112} Our work has identified that frequency of oropharyngeal suction varies widely, and that the tonsil suction device is preferred.²⁶⁻²⁸ In a simulated laboratory setting, we determined that the oropharyngeal suction catheter was more effective than either a suction swab or tonsil suction device in removing oropharyngeal secretions.⁹⁹ Two oropharyngeal suction catheters are included in oral care kits used on MV patients at the study site to be used concurrently with tooth brushing; however, average use is only 0.8 per day.⁹⁵ Many patients have large volumes of oropharyngeal secretions that can be potentially aspirated.^{25,93,113} In preliminary work, we suctioned an average of 7.5 mL of secretions within a 4-hour interval, although volumes as high as 25 mL were removed.²⁵ Secretion removal can be achieved with ≤ 3 suction passes with the oropharyngeal suction catheter over an average total duration of 48.1 seconds.²⁵ We have not identified any issues when using the oropharyngeal suction catheter.^{25,93} *In a recent pilot study of 13 critically ill subjects, we found that all subjects had α -amylase present in the oral secretions, and 6 (46%) had α -amylase detected in the first tracheal sample.⁹³ The study was done to test α -amylase procedures and the intervention. A second specimen obtained one to four hours later (when ETT suctioning was needed) showed only 4 subjects (31%) with α -amylase in the tracheal secretions, and a lower value in those positive.* The study established our ability to measure α -amylase in the APH Specialty Diagnostic Laboratory with precision and quality controls. It also provided data that microaspiration frequently occurs in our study population and may be reduced with this simple intervention. Our co-investigator, Dr. Mehta, has studied biomarkers for microaspiration.¹¹⁴⁻¹¹⁸ He also provides oversight for the laboratory, including developing the procedures for quantifying α -amylase. These multiple preliminary studies informed our decision to focus on enhanced removal of oral secretions, using an oropharyngeal suction catheter, on a 4-hour schedule, with α -amylase as our primary outcome measure.

Design

A prospective, 2-group, single-blind, randomized clinical trial design is planned. The design will allow us to test the impact of the NO-ASPIRATE intervention on outcomes of microaspiration and VAC.

Aims and Hypotheses

Our primary aim is to compare the effects of the NO-ASPIRATE intervention versus usual care on microaspiration in critically-ill intubated patients on MV. Patients often have high volumes of oropharyngeal secretions, and despite existing interventions, microaspiration occurs. Regular removal of secretions that accumulate in the oropharynx is intended to decrease the volume or potential load, and thus reduce microaspiration. Our working hypotheses are that subjects in the NO-ASPIRATE group will have a reduction in microaspiration as measured by the percentage of tracheal specimens that are positive for α -amylase (1.1) and *mean values of α -amylase* (1.2).

A secondary aim is to compare the effects of the NO-ASPIRATE intervention on development of VAC and duration of VAC-free days. By reducing the risk for microaspiration, VAC should be reduced. Our working hypotheses are that the subjects in the NO-ASPIRATE group will have a lower rate of VAC (2.1) and longer duration of VAC-free days (2.2). Another secondary aim is to explore changes in the ratio of α -amylase in the tracheal aspirate versus the mouth over time. Our working hypothesis is that subjects in the NO-ASPIRATE group will have a lower tracheal/oral α -amylase ratio over time (3.1).

Setting and Sample

Setting. The study will be conducted in the ICUs at Orlando Regional Medical Center (ORMC), a division of Orlando Health. ORMC is an 808-bed tertiary care facility that specializes in trauma, emergency care, cardiology, orthopedics, neurosciences, and internal medicine. The hospital serves a 5-county area in Central Florida area with a diverse population of 2.8 million people.¹¹⁹ The ICUs include Trauma (14 beds), Neuroscience (16 beds), Multi-System (10 beds), and Cardiac (10 beds). Nursing and respiratory care practices for airway management are standardized across units. The patients are managed by a team of either

medical or surgical intensivist physicians. Our co-investigator, Drs. Jimenez, is chief of the medical critical care service. Dr. Penoyer is the Director of the Center for Nursing Research, and Dr. Sole holds an appointment as a nurse scientist, in addition to her faculty role. The APH Pediatric Specialty Diagnostic Laboratory is part of Orlando Health, and will run the α -amylase assays. Dr. Mehta (co-investigator) provides leadership for the laboratory, and is an expert in biomarkers of microaspiration. Drs. Talbert and Xan are faculty members at UCF and will be involved in data management and analysis. Team members have worked together on many previous studies, including our R21.

Sample. Subjects (n=560) will be enrolled if they meet the following **inclusion criteria**: 1) 18 years of age or older; 2) orally intubated with ETT and treated with MV; 3) 24 hours or less since intubation; and 4) expected to be intubated for at least 36 hours after enrollment. **Exclusion criteria** are: 1) documented aspiration at time of intubation; 2) *intubation to treat known aspiration*; 3) treatment with rescue MV therapies (high-frequency oscillator ventilation or extracorporeal membrane oxygenation); 4) re-intubation for any reason; 5) contraindications to receiving the intervention (e.g., oral injuries); 6) history of lung or head/neck cancers that may produce α -amylase in the lungs; 7) history of disease that affects saliva production (e.g., Sjögren's syndrome); and 8) prisoners. Eligible subjects are available. In fiscal year 2012, 1,641 patients were treated with MV on the study units (median=4 days; mean=6.2 days). On average, 28 patients are ventilated each day. Patients on MV are split between the medical and surgical intensivist teams, providing a diversity of diagnoses. We will have a large pool of patients who are highest risk: trauma, burn, and neurological conditions.⁴⁸

Power Analysis. We used data from our pilot work and input from our consultants to estimate sample size and attrition. *A final sample size of 400 will allow us to detect a 15% reduction in the proportion of specimens that are positive for α -amylase (primary aim) at an alpha level of .05 with a power of .87 (H1.1). The sample size will be able to detect differences in mean values of α -amylase with an effect size (d) of .25, alpha .05, and power of .80 (H1.2). Since VAC, our secondary aim, is a newer measure, we used data from recent studies to provide sample estimates. A final sample size of 400 will allow us to detect a 12.7% reduction in VAC with an alpha of .05 and power of .80 (H2.1). We will overenroll by 40% to account for attrition, for a targeted enrollment of 560 subjects.*

Procedures

Study procedures have been developed after many of the ones we have used successfully in previous studies. We also incorporated procedures described by Nseir,¹⁰⁹ Metheny,^{18,19} Munro (our consultant),^{73,80} and other researchers who have conducted intervention studies to prevent complications in MV patients.

Screening and Enrollment of Subjects. *A convenience sample of eligible subjects will be enrolled after ICU admission, within 24 hours of intubation. Our goal is to enroll subjects as soon as possible to maximize the effects of the intervention. Munro demonstrated the ability to recruit similar patients within 24 hours,^{73,120} and we will use her expertise as we implement the study.* Nseir used a 48-hour recruitment window in a study testing an intervention (control of ETT cuff pressure) on microaspiration.¹⁰⁹ We will develop a checklist to ensure that inclusion criteria are met at time of enrollment. The Project Director (PD) or research assistant (RA) will be available for 18 hours each day, 7 days per week, to facilitate enrollment. RAs will be trained registered nurses or respiratory therapists who have experience caring for patients on MV. The PD will coordinate all staffing and will develop a master schedule; flexible and variable shifts will be offered to ensure coverage for enrollment and delivering the intervention. We have a plan in place to ensure coverage and are committed to success.

Randomization. Our biostatistician will oversee the process of randomization of subjects to either the NO-ASPIRATE or usual care group. He will develop a blocked randomization procedure, using different sized blocks, to ensure balanced assignment without being able to predict group assignment.¹⁶⁶ Because many subjects will be intubated with the specialized SS-ETT (about 65% from historical data), we will stratify randomization by type of ETT to ensure that approximately half of those with and without the SS-ETT are randomly assigned to each group. Stratification will help to address type of tube as a potential confounding variable, and will allow for secondary sub-group analysis. A member of the study team not involved in data collection will place group assignments for each type of ETT in numbered, sealed, opaque envelopes. Upon enrollment, study personnel will identify the type of ETT, and open the appropriate envelope to determine group assignment. Only study team members who provide the intervention will know the subjects' assigned groups. ICU personnel, as well as subjects and family members, will be blinded to the assignment.

Intervention. Following enrollment, the RA will collect baseline data, implement the assigned intervention (NO-ASPIRATE or usual care/sham), and collect specimens. The RA will then implement the intervention as designated by study arm every 4 hours. *Figure 4 summarizes the procedures for each group.*

To control for possible differences in usual oral care practices, the RA will perform oral cleansing and suctioning with a suction swab after delivering the NO-ASPIRATE or sham intervention using the hygiene components from the oral care kit. The RA will also perform tooth brushing every 12 hours. Oral antisepsis will be done after obtaining specimens for α -amylase. Some subjects may require additional oral suctioning for secretion management; staff will use the available tonsil suction device for oral suctioning in-between the scheduled interventions and document in the medical record. Additional necessary oral suctioning will be recorded and controlled for, if applicable.

NO-ASPIRATE Intervention. The NO-ASPIRATE intervention involves enhanced suctioning of the mouth and oropharynx every 4 hours with an oropharyngeal suction catheter. The catheter is 8.25" (21 cm) long (see Figure 2D) and is one that we tested in the simulated setting as being most effective in removing oropharyngeal secretions.⁹⁹ *Figure 5 compares secretion removal with a suction swab (usual care) versus the oropharyngeal suction catheter. This length and pliability of the oropharyngeal suction catheter facilitate manipulation of the catheter around the ETT to reach secretions in the oropharynx. In contrast, suction swabs and tonsil suction devices are shorter and rigid, and do not reach secretions that pool in the oropharynx.*

During the intervention, the oropharyngeal suction catheter will be repositioned to reach both sides of the mouth and the oropharynx. Suctioning will be done using standard suction pressures until secretions are no longer audible or visible, for a duration of about 45 seconds.²⁵ ¹²¹ We have performed this procedure in previous studies without any adverse issues, such as gagging or oral trauma.^{25,93}

However, subject response will be observed and the procedure will be stopped if intolerance is noted.

Usual Care/Sham Intervention. A usual care/sham intervention will be delivered to those in the usual care group. Trained RAs will insert the suction catheter into the subject's mouth and mimic the suction procedure for 45 seconds without occluding the suction port. The usual care/sham intervention will be done every 4 hours.

Data Collection. Data will be collected at enrollment and at regular intervals (Table 1), including demographic and physiological data to describe the sample and *test equivalence between groups*. We will also collect data related to factors that might influence microaspiration and development of VAC to assist in interpretation of findings and be used as possible covariates in statistical analyses. *We anticipate having 4 to 6 subjects enrolled at a time. This estimate was based on consultation with Dr. Munro and designed to ensure adequate time to deliver the intervention, enroll new subjects, and record data from the medical record.* Additionally, at this rate of accrual, laboratory will be able to regularly process the α -amylase assays.

The PD will maintain a list of all enrolled subjects and will organize them according their geographic location. Approximately 20 minutes per subject will be allotted for delivering the intervention and obtaining specimens.

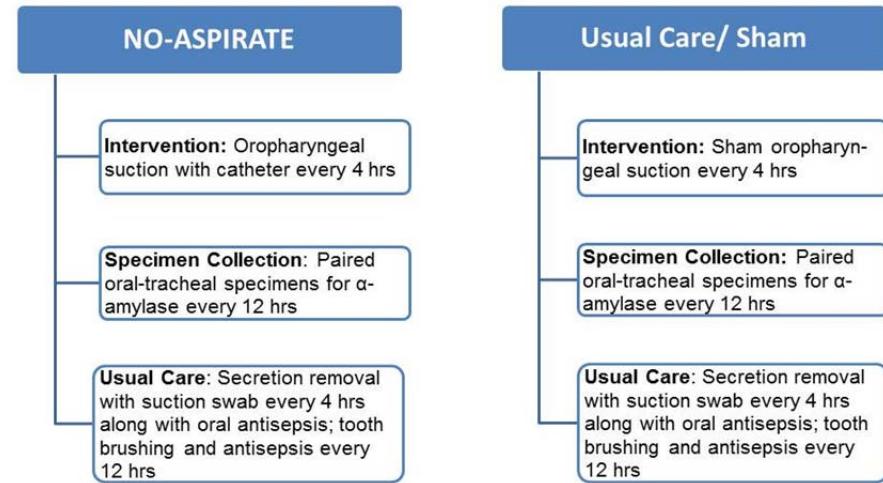


Figure 4. Procedures for NO-ASPIRATE and Usual Care Groups
Figure 4. Procedures for NO-ASPIRATE and Usual Care Groups. The NO-ASPIRATE group includes intervention (opharyngeal suction with catheter every 4 hrs), specimen collection (paired oral-tracheal specimens for α -amylase every 12 hrs), and usual care (secretion removal with suction swab every 4 hrs). The Usual Care/Sham group includes intervention (sham oropharyngeal suction every 4 hrs), specimen collection (paired oral-tracheal specimens for α -amylase every 12 hrs), and usual care (secretion removal with suction swab every 4 hrs). Some subjects may require additional oral suctioning for secretion management; staff will use the available tonsil suction device for oral suctioning in-between the scheduled interventions and document in the medical record. Additional necessary oral suctioning will be recorded and controlled for, if applicable.

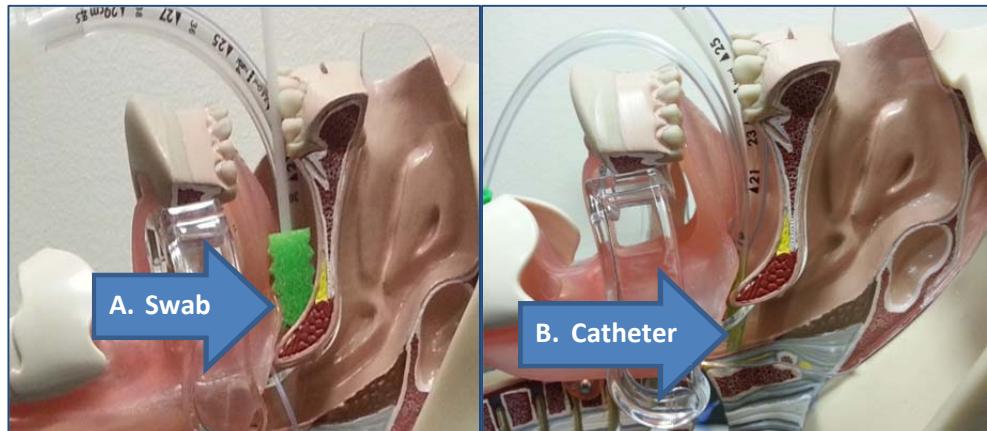


Figure 5. Comparison of Suction Devices. A, Swab; B, Suction catheter; note that catheter reaches the posterior oropharynx.

Scheduled times for the intervention will be determined (e.g., 0800, 1200, 1600 military time). The RA will begin the shift and deliver the intervention per study arm to the first scheduled subject. The procedure will be repeated until the intervention has been delivered to all subjects per schedule. Hand hygiene and infection prevention measures will be strictly followed. We will allow a 30-minute window before and after the scheduled time to deliver the intervention to account for patient care activities. If the subject is off the unit during the scheduled time, it will be delivered upon return to the unit. Delays or omissions in providing the intervention will be recorded in the study record. These data will allow us to calculate the number of scheduled interventions that are completed each day (dose), which may be useful in interpreting findings.

Table 1: Variables and Data Collection

Variable	Source	When	Purpose
Outcome Variables			
Outcome: Microaspiration; % tracheal specimens positive for α -amylase; mean value of α -amylase in tracheal secretions	Assays of α -amylase in tracheal aspirate	Enrollment Every 12 hours Duration: up to 14 days while intubated	<i>Aim 1—Microaspiration</i>
Outcome: Ventilator-Associated Condition (VAC)—yes/no <i>Subset:</i> Infection-Related Possible VAP Probable VAP	Medical record data: <ul style="list-style-type: none">• Ventilator: PEEP, FiO_2• Temperature• WBC / culture results• New antibiotics / duration	Daily Assess for 2 days beyond the last intervention	<i>Aim 2—VAC</i>
Outcome: Ratio of α -amylase in tracheal and oral secretions	Assays of α -amylase from paired tracheal and oral specimens	Enrollment Every 12 hours Duration up to 14 days	<i>Aim 3—tracheal/oral ratio of α-amylase</i>
Demographic Data			
ETT information (time of intubation, type ETT, size ETT)	Observation Medical Record	Enrollment	Describe sample Stratify by ETT type
Age, gender, ethnicity, diagnoses	Medical Record	Enrollment	Describe sample Compare groups
Comorbidities: COPD; immune-compromise; chronic heart, liver, or renal failure	Medical Record	Enrollment	Describe sample Compare groups
Acuity and outcomes: APACHE II, APACHE IV, SAPS, ventilator days, LOS	Hospital database	Completion of participation in study	Describe sample Test group equivalence
Physiological status: vital signs, oxygen saturation, sedation level	Medical Record	Enrollment Daily (am)	Describe sample Test equivalence
Potential Risk Factors for Microaspiration and VAC			
Backrest elevation (daily average)	Observation	Every 4 hours	Test equivalence
GI data: tubes, nutritional support; gastric residual, distention; vomiting	Medical Record Observation	Enrollment Daily (am)	Test equivalence
ETT: min, max, mean daily cuff pressure; repositioning; cuff issues	Medical Record	Daily	Test equivalence
Oral care: additional interventions, type of antiseptic	Medical Record Intervention documentation	Daily	Test equivalence
GI medications: H_2 blockers, proton pump inhibitors, antacids, sucralfate	Medical Record	Enrollment Daily (am)	Test equivalence
Mobility and transport off unit	Medical Record/observation	Every 4 hours	Test equivalence

Paired specimens of oral and tracheal aspirates for α -amylase. The RA will obtain an oral specimen for α -amylase at enrollment and every 12 hours (concurrently with a tracheal aspirate) to compute the tracheal/oral ratio. Oral secretions will be collected into a trap during the NO-ASPIRATE or usual care/sham intervention. Following this procedure, a tracheal aspirate will be obtained for detection of α -amylase. Although Weiss detected α -amylase in BAL specimens up to 72 hours post intubation, others have suggested more frequent collection.^{46,97} Obtaining specimens every 12 hours will provide longitudinal data regarding microaspiration, and facilitate identification of clinical factors that contribute to its occurrence. The RA will suction the subject's ETT per standard procedure (closed ETT suction with hyperoxygenation via the ventilator before the procedure) to retrieve tracheal secretions into a specimen trap. We tested these procedures in a preliminary study.⁹³ Since ETT suctioning should be done based on identified need,¹²¹ the RA will assess the subject for cues identifying suctioning need before obtaining the specimen: audible crackles over the trachea, sawtooth

pattern on the ventilator flow waveform, cough, high peak inspiratory pressure, visible secretions, or changes in oxygen saturation.^{85,122} *If suctioning is not indicated at the scheduled time, the RA will collaborate with the subject's nurse to notify the RA if suctioning is clinically indicated within a 2-hour period to ensure complete collection of samples. Time of specimen collection (or omissions) will be noted. The usual care oral antisepsis done for all subjects will be done AFTER specimen collection to prevent contamination.* All oral and tracheal specimens will be frozen to -20° C until the assays are run. A compact medical lab freezer, used solely for purposes of this study, will be purchased and located on or near one of the study units for easy storage. Specimens will be regularly transported on ice to the APH Specialty Diagnostic Laboratory.

Endpoints. The intervention will be delivered per protocol until one of the following endpoints is met (whichever occurs first): 1) ETT removed (extubation); 2) tracheostomy performed; 3) 14 days of enrollment; or 4) other exclusion criterion met (e.g., rescue ventilation). *Extending the intervention to 14 days will allow us a better opportunity to address the secondary aim of VAC. At the study site, the median time to tracheostomy is 8 days; 85% of patients on prolonged MV undergo a tracheostomy by Day 14.*¹¹² *This duration of enrollment is longer than that reported in other intervention studies,*^{19,73,109} *and will allow us to test the effect of the intervention on both microaspiration and VAC prevention for an extended period. Subjects must be enrolled at least 36 hours to be included in analysis. Since the duration of MV varies and we want to assess the effect of our intervention on preventing microaspiration, we determined (with input from consultants) that a minimum enrollment of 36 hours would provide adequate samples to address the primary aim.*

Measurement of Primary and Secondary Outcome Variables

Microaspiration. Assays of the biomarker, α -amylase, in paired oral and tracheal specimens will be performed in the APH Pediatric Specialty Diagnostic Laboratory per standard procedures (See Appendix A). Laboratory personnel will be blinded to study group. Alpha-amylase activity in the paired samples will be analyzed using the Stanbio α -amylase LiquiColor Reagent Kit. The recommended procedure was modified for a microplate reader. Each run of samples is accompanied by two controls, and the controls are evaluated before results are released. A 10 μ l sample is placed in a microplate well, and 200 μ l of α -amylase LiquiColor reagent, which has been pre-warmed to 37°C, is added to each sample and mixed. The increase in absorbance is measured at 405nm in a spectrophotometer in 3-minute intervals for 9 minutes. The average change in absorbance is used to calculate a standard curve of α -amylase in μ mol/min/ml, which will be converted to U/L. *An α -amylase value of 0.6 μ mol/min/ml will be considered positive. No amylase should be detected; the value 0.6 μ mol/min/ml is the lowest possible concentration of amylase that can be detected with the method's analytic sensitivity. After detection, the total values of α -amylase in secretions will be recorded. Amylase that is detected would be either of oropharyngeal or gastrointestinal origin; however, in this setting and location of sampling, presence from pancreatic source would be unlikely. Indeed the additional step of using a specific inhibitor for salivary amylase was shown to be not necessary in airway samples during our preliminary study. The paired oral-tracheal samples evaluated in the preliminary study detected large amounts of α -amylase in the oral secretions of all subjects, and smaller amounts in those who also had positive results in tracheal secretions.*⁹³

To address Aim 1 and hypothesis 1.1, total values of α -amylase will be recorded, and each tracheal aspirate will be coded as either positive or negative for α -amylase. Dr. Mehta, also blinded to study group, will verify the results of each assay. The percentage of positive specimens for the biomarker will be calculated for each subject. For hypothesis 1.2, the mean values of α -amylase will be calculated.

VAC. VAC will be determined using the CDC/NHSN criteria (Figure 6, blue boxes).¹⁶ We will assess ventilator data (FiO₂ and PEEP) daily from the medical record to assess for worsening oxygenation status. Per consultation with Dr. Klompas, we will assess for VAC for 2 days beyond the last intervention. To address Aim 2 and hypotheses 2.1 and 2.2, we will record VAC as positive or negative. We will also record the time to VAC in days (0.1 day increments). Determination of VAC will be made by our intensivist co-investigator. The CDC/NHSN algorithm proceeds to determine if VAC is infection-related (grey part of algorithm).¹⁶ *Our primary endpoint is VAC as a broad complication that includes both infectious and noninfectious etiologies; however, we will also report possible and probable VAP in our analyses as applicable.*

Tracheal/Oral Ratio of α -Amylase. To address Aim 3 and hypothesis 3.1, the ratio of the tracheal value to the oral value of α -amylase for each paired sample will be calculated.

Training and Data Management

Personnel Training and Fidelity. The PI will be responsible for training and will be assisted by the PD in ensuring that all personnel are knowledgeable in their roles. At the beginning of the study, the PI and PD will develop a comprehensive study Operations Manual, which will include procedures and checklists for subject enrollment, delivery of the NO-ASPIRATE and usual care/sham interventions, data collection, and ongoing

reporting related to the study (e.g., IRB and DSMB). All study personnel will complete the required CITI training on protection of human subjects and will sign confidentiality agreements.

The PI and PD will train the RAs in all study-related procedures. Initial training for the NO-ASPIRATE intervention, the usual care/sham intervention, and specimen collection will be conducted in a simulation laboratory, followed by observation in the clinical setting. Inter-rater reliability will be established for delivery of the NO-ASPIRATE and usual care/sham interventions, and for review of the medical record for study-related data. A kappa of at least .90 will be achieved between data collectors. To ensure treatment fidelity, additional re-assessment and related training will be done every 6 months using a standard observation checklist.

Treatment fidelity and effect of usual care will be addressed by reinforcing existing protocols for head of bed elevation, daily interruption of sedation, and ETT cuff pressure (20-30 cm H₂O). During our every 4 hour rounds, we will monitor and promote adherence, and document potential issues. To control for usual oral care practices, we will deliver oral care suctioning and cleansing/antisepsis interventions to both groups. We will also record documentation of additional oral suctioning interventions and method/tolerance of enteral feedings. Although random assignment of subjects to groups should address potential confounders, we will compare data between groups and control statistically if differences are noted.

Data Management and Integrity. We will record data in electronic format, using spreadsheet or database software, on tablet or laptop computers that are password protected and used solely for the study. Computers will be stored in a locked secured area when not in use. We will use the software data validation features and/or filters for as many variables as possible to ensure accuracy of data entry, including missing data and out-of-range values. These features allow for drop down selection of findings, and specifications of parameters for values that are expected to be recorded. We have successfully used similar procedures in previous studies to ensure consistency and accuracy of data collection. Dr. Talbert will oversee data management and integrity for the study, and will be assisted by the PD. He has past experience in this role on NIH-funded grants, and is an expert at managing large databases. The PD will monitor study records to ensure completeness. Accuracy of the data collected from the EMR will be reviewed for 10% of subjects during the first month of the study. Errors will be corrected, and re-training will be done as necessary. Following the initial audit, 5% of the files will be audited quarterly for completeness and accuracy; we will create an audit trail to identify and correct issues and/or errors.¹²³ If causes of error other than random variation are identified, we will change our procedures.

Data Analysis

Subjects will be randomly assigned to each of the two treatment groups at 1:1 ratio. Before analysis, data will be carefully examined for accuracy. Every effort will be made to avoid missing data. Subject characteristics at baseline will be examined to ensure a sound balance on demographic variables between the two groups. For continuous demographic variables, independent two-sample *t* tests will be used to detect differences between the two groups. For categorical demographic variables, the Pearson's chi-square test will be used to examine differences between the two groups. If subject subsets are found to be significantly different for a demographic variable, then this variable will be included into the statistical models. All planned analyses will be based on the intent-to-treat (ITT) population, which consists of all subjects who have been randomized into the NO-ASPIRATE or usual care group. In all analyses, an alpha level of 0.05 will be used.

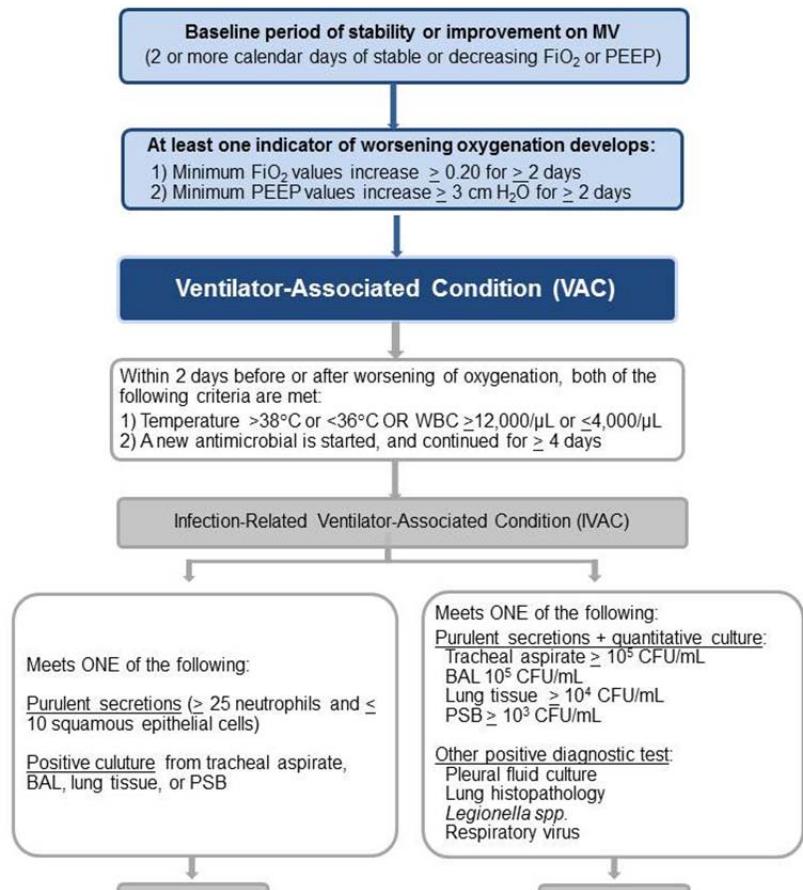


Figure 6. Algorithm for Determining VAC

Aim 1. To compare the effects of the NO-ASPIRATE intervention versus usual care on microaspiration of gastric and oral contents in critically-ill intubated patients. Hypothesis 1.1.

Subjects in the NO-ASPIRATE group will have a significantly lower percentage of tracheal secretions with α -amylase present as compared to those in the usual care group. **Analysis 1.1.** Percentages of tracheal secretions α -amylase present for both groups will be computed. The percentage difference between the two groups will be calculated along with the 95% confidence interval for the percentage difference. The logistic regression including covariates of interest will be used to assess the percentage difference adjusting for the prognostic covariates.

Hypothesis 1.2. Subjects in the NO-ASPIRATE group will have a lower mean value of α -amylase in tracheal secretions as compared to those in the usual care group. **Analysis 1.2.** Values of α -amylase in tracheal secretions will be collected for each subject every 12 hours during study. Treatment effect based on these values over time will be evaluated by the generalized linear models using the generalized estimating equation (GEE) method.^{124,125} In addition, the generalized linear models with prognostic covariates of interest will be used to assess change in mean values of α -amylase over time adjusting for prognostic covariates.

Aim 2. To evaluate the NO-ASPIRATE intervention versus usual care on VAC rate and time to occurrence.

Hypothesis 2.1. Subjects in the NO-ASPIRATE group will have a significantly lower rate of VAC as compared to those in the usual care group. **Analysis 2.1.** Percentages of VAC for both groups will be computed. The percentage difference between the two groups will be calculated along with the 95% confidence interval for the percentage difference. The logistic regression including covariates of interest will be used to assess the percentage difference adjusting for the prognostic covariates. **Hypothesis 2.2.** The number of VAC-free days will be longer in those in the NO-ASPIRATE group as compared to the usual care group.

Analysis 2.2. Time to VAC event for both the NO-ASPIRATE and the usual care groups will be assessed using the Cox proportional hazard model.¹²⁶ The hazard ratio and the 95% confidence interval of the hazard ratio of NO-ASPIRATE group versus the usual care group will be computed. The graphical display of the Kaplan-Meier estimators for both groups will be presented.¹²⁷ The Cox proportional hazard model with prognostic covariates of interest will be used to assess the difference adjusting for the prognostic covariates.

Aim 3. To explore changes in the tracheal-to-oral α -amylase ratio between groups over time.

Hypothesis 3.1. Subjects in the NO-ASPIRATE group will have a significantly lower tracheal/oral α -amylase ratio over time as compared to those in the usual care group. **Analysis 3.1.** Treatment effect on reducing tracheal/oral salivary amylase ratio over time will be assessed by the generalized linear models using the generalized estimating equation (GEE) method.^{124,125} In addition, the generalized linear models adjusting for prognostic covariates will be used to assess ratios over time adjusting for prognostic covariates.

Solutions to Potential Issues

Design. We are planning a single-blind RCT to test the NO-ASPIRATE intervention. Our goal is to blind the staff and subjects to the intervention group by using a sham treatment for those in the usual care group, which we believe to be a strength. Despite our efforts, knowledge of group membership may be identified.

Confounding Variables. Since we know that oral suctioning and cleansing practices vary widely, we will assume responsibility for oral care interventions for all subjects. This will allow us to truly test the effect of the NO-ASPIRATE intervention versus usual care. Since we will be delivering oral hygiene, we will communicate well with the nursing staff to avoid duplication of procedures. Prior to the study, we will provide information sessions for staff (nurses and RTs) to outline roles of study team members and reinforce existing protocols. We will assess the medical record for additional oral suctioning done by the staff. We will use standard unit supplies for usual care from the oral care kit, and label components to assess if supplies are used by others. Additional suction swabs and catheters are not available to the staff beyond those included in the kit. If the patient needs additional suctioning to manage secretions, the tonsil suction device is readily available. We will promote adherence to existing protocols for head of bed elevation, daily interruption of sedation for weaning assessment, enteral feeding management, and ETT cuff pressure. We will monitor these interventions during rounds, reinforce adherence, and document findings. We will record information related to potential confounders from the EMR. We will compare equivalence between groups and control statistically if indicated. Standard practices to prevent microaspiration could change during the study. We will monitor for potential influences of any new practices, and we will include them in the analyses if warranted. Random assignment of subjects to groups should address potential issues. We will also use the expertise of our consultants.

Biomarker of Microaspiration. Because our focus is on removal of oropharyngeal secretions, we are using α -amylase as a biomarker for microaspiration because it is a specific measure of migration of oral secretions from the oropharynx to the lungs. We considered measuring pepsin; however, it has a short window for detection after aspiration and is specific to gastric contents. Although α -amylase is a newer biomarker for

microaspiration, the rationale for its use is strong since α -amylase is present in oral secretions and detection in tracheal secretions indicates aspiration. We have spoken with other researchers who have tested this biomarker and are confident in our decision.⁴⁶ We have also specified exclusion criteria to ensure accuracy of findings (e.g., Sjögren's syndrome). Some researchers have used cultures of the endotracheal aspirate as a marker of microaspiration.^{15,109} However, culture results are not always precise, are expensive, and may be influenced by the oral care antisepsis. Using cultures only informs of microbial growth in secretions, not specifically aspiration of oral contents.

VAC as an Outcome Measure. The VAE algorithm published by the CDC/NHSN will be used to determine VAC.¹⁶ *The algorithm is a newly designated outcome measure, but it has been systematically tested and shown to identify events and related outcomes of mortality and length of stay.*^{6,17,31} It is possible that the algorithm will be modified before the study begins. In that case, we will modify the procedures to ensure that we collect data to determine VAC per the algorithm that is publicly available at the start. We will also monitor for changes throughout the study. We will use the expertise of our consultant, Dr. Klompas, as we design the electronic methods for recording data to determine VAC, and in interpretation of findings.

Staffing. We have developed a staffing plan to ensure coverage by study personnel 18 hours/day, 7 days per week. The PD will coordinate scheduling and develop flexible staffing options for coverage. Qualified individuals have offered to work as part-time RAs. We understand that the proposed project is complex; however, we are confident that we conduct the study as planned and will readily use our consultants' expertise.

Recruitment and Retention. *Although unanticipated delays in subject recruitment are common in studies of critically ill subjects, we have been successful in enrolling subjects with similar inclusion and exclusion criteria in prior studies. We have a strong working relationship with the medical staff, nurse managers, and staff nurses on the units. We will also use the expertise of our consultant, Dr. Munro, who has conducted large NIH-funded clinical trials with similar populations. We have identified a conservative approach for recruitment and retention of subjects over 36 months during the proposed 4-year study.* Our timeline has some flexibility, in that we can extend data collection by 3 months and achieve study goals. *Other trials may be conducted at the study site with similar inclusion criteria for enrollment. We will collaborate with other investigators at the study site to facilitate enrollment in the event of competing studies. These other trials have very restrictive inclusion/exclusion criteria, and only 1-2 potential subjects are enrolled in other trials at a given time. The number of potential subjects is large, and can support needs of multiple investigators.*

Project Timeline

We will conduct the study over 4 years (Table 2).

We have allocated 6 months to start the study, followed by enrollment over 36 months. The final year of the project will be devoted to analysis, dissemination of findings, and writing additional grant applications.

Summary

The study will add to the science related to a simple-to-implement, yet extremely important, enhanced oropharyngeal suction intervention to reduce microaspiration in intubated patients. Our preliminary studies have been logically and systematically conducted to guide this intervention study. The study has a great potential for improving patient outcomes and will provide data to develop evidence-based practices for secretion removal. Findings may also result in methods for earlier detection and treatment of potential aspiration. A strong multi-professional team, including internationally-known consultants, has been convened. Strong support for clinical research is provided by both the university and clinical setting.

Table 2: Project Timeline

Activity	Year	1				2				3				4			
		Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3
Convene team; develop Operations Manual; purchase supplies; IRB approval; hire and train staff																	
Consultation																	
Staff training/retraining																	
Subject enrollment, data collection, and management																	
DSMB review (ongoing)																	
Data analysis																	
Dissemination and final grant report																	

Human Subjects

A. HUMAN SUBJECTS INVOLVEMENT, CHARACTERISTICS, AND DESIGN

Describe the proposed involvement of human subjects in the work outlined in the Research Strategy section.

The population for this study is critically ill patients who have an ETT who require mechanical ventilation (MV) support. *Considering power analysis calculations, we propose to enroll 560 subjects to achieve a final sample size of 400 subjects randomized to either the NO-ASPIRATE or usual care group.* Subjects will be critically ill patients, age 18 and older, who are admitted to one of the ICUs at Orlando Regional Medical Center (ORMC): Trauma, Neuroscience, Multi-System (medical-surgical), and Cardiac. Subjects will have an oral ETT, and require MV as part of their treatment. The project population will include: women, children (age 18-20), elderly, inner city and rural, low-income groups, minority populations, and those with trauma as well as chronic disease.

Recent data from the study setting show that 65% of patients are male, with an average age of 53 years. Over half of patients admitted to the study units receive MV. Patients who are aged 18-20 represent 9% of the study population, and 36% are 65 years of age or older. Using similar inclusion and exclusion criteria as proposed in this study, we were able to enroll a diverse sample in prior studies.

Describe and justify the sampling plan, as well as the recruitment and retention strategies and the criteria for inclusion or exclusion of any subpopulation.

Subjects (n=560) will be enrolled if they meet the following inclusion criteria: 1) 18 years of age or older; 2) orally intubated with ETT and treated with MV; 3) 24 hours or less since intubation; and 4) expected to be intubated for at least 36 hours after enrollment. Exclusion criteria are: 1) documented aspiration at time of intubation; 2) intubation to treat known aspiration; 3) treatment with rescue MV therapies (high-frequency oscillator ventilation or extracorporeal membrane oxygenation); 4) re-intubation for any reason; 5) contraindications to receiving the intervention (e.g., oral injuries); 6) history of lung or head/neck cancers that may produce α -amylase in the lungs; 7) history of disease that affects saliva production (e.g., Sjögren's syndrome); and 8) prisoners.

The Project Director (PD) and Research Assistants (RAs) will make rounds in the units on a regular basis (in between the scheduled interventions) to assess eligibility of new admissions. The PD or RA will explain the study and seek informed consent from patients that are able to provide their own consent, or from the legally-authorized representative (LAR). The consent form will be available in Spanish, and translators are available at the Orlando Health system for those who do not read or speak English.

Adequate subjects are available to complete the study and represent a broad cross section of critically-ill patients. The number of MV patients per day averages 28 across the study units. *We conservatively estimate enrolling an average of 50 subjects per quarter. At this accrual rate, it will take 36 months for enrollment.* In our previous studies we have had adequate representation of children (18-20 years of age), women, and racial/ethnic minorities.

Our past experiences conducting research in the clinical setting with the same patient population will enhance our ability to recruit and retain subjects. The continued presence of the PD and RAs throughout the study should facilitate retention of subjects. RAs will be readily available to discuss the study and answer questions as they arise. We will also use our consultant, Dr. Munro, to guide us.

Explain the rationale for the involvement of special vulnerable populations.

We will include children ages 18-20 who meet eligibility criteria. Approximately 9% of the population is in this age range. In particular, younger patients are admitted to the surgical/trauma critical care service line. Patients with burn, trauma, and neurological injury are at highest risk for infection, and are often younger. Therefore, it is important to include this age group.

We will include the elderly as they are at an increased risk for complications of MV secondary to chronic illness and decreased immune response, and their mortality for VAC (lung injury) is higher than younger patients.¹²⁸ We will also include pregnant women because if they require MV, oral care interventions are not any different for them, and the NO-ASPIRATE intervention is enhanced oral care.

Although children less than 18 years of age are sometimes treated in the adult ICUs, we will exclude them because the VAC criteria specifically note applicability only to those 18 years of age and older.¹⁶

We will exclude prisoners.

Describe procedures for assignment to a study group. As related to human subjects' protection, describe and justify the selection of an intervention's dose, frequency, and administration.

Our biostatistician will oversee the process of randomization of subjects to either the NO-ASPIRATE or usual care group. He will develop a blocked randomization procedure, using different sized blocks, to ensure balanced assignment without being able to predict group assignment.¹⁶⁶ Because many subjects (about 65% to 70% from historical data) will be intubated with the specialized subglottic suction ETT (SS-ETT), we will stratify randomization by traditional or SS-ETT to ensure that approximately half of those with and without the SS-ETT will be randomly assigned to each group. This will help to address type of tube as a potential confounding variable, and will allow for secondary sub-group analysis. A member of the study team, who will not be involved in data collection, will place group assignments in sequentially-numbered, sealed, opaque envelopes for each type of ETT. Upon enrollment, study personnel will identify the type of ETT inserted, and open the appropriate envelope to determine group assignment. Only study team members who provide the intervention will know the subjects' assigned groups. Hospital staff members, as well as subjects and their family members, will be blinded to group assignment.

The NO-ASPIRATE or usual care/sham intervention will be administered by a member of the research team every 4 hours. The decision for this interval was based on the volume of oral secretions measured in our preliminary studies,²⁵ and non-experimental quality improvement studies that implemented oropharyngeal suctioning at 4- and 6-hour intervals.^{64,94} Concurrently with delivery of the interventions, paired specimens of oral and tracheal secretions will be obtained at baseline and every 12 hours for assays of α -amylase. Tracheal specimens will be obtained based on the subject's need for ETT suctioning.

List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.

Subjects will be patients in one of the ICUs at Orlando Regional Medical Center. The study team has extensive experience conducting clinical studies in these units. Three of our co-investigators are employees at the site. Dr. Jimenez is chairman of the corporate Critical Care Committee, which will facilitate communication across units. As Director for the Center for Nursing Research, Dr. Penoyer helps to establish collaborations between the university and hospital. Dr. Mehta oversees the APH Specialty Diagnostic Laboratory where the α -amylase assays will be run. Additionally, Dr. Sole has an appointment as a Nurse Scientist at the agency, which also facilitates collaboration and the ability to conduct research in the setting.

Data will be recorded in electronic means on password-protected computers. The subject's medical record number will be used to retrieve study-related data from the electronic medical record (EMR). All subjects will be issued a unique code that will be recorded in the research files. All data will be de-identified for final analysis and findings will be reported in aggregate. A key, pairing the medical record number and unique identification code, will be kept separate from all data in a locked file in Dr. Sole's research office at UCF. Access to this information will be limited and only on a "need-to-know" basis.

B. SOURCES OF MATERIALS

Describe the research material obtained from living individuals in the form of specimens, records, or data.

The research materials for this study include data from the subject's medical record and observation. Oral secretion and sputum specimens (endotracheal aspirate) for assays of α -amylase will be obtained at baseline and every 12 hours for up to 14 days. Specimens will be discarded after analysis. Demographic and physiological data will be obtained daily from the EMR. Data to determine presence of VAC will be obtained daily and for 2 days after the last intervention has been delivered. VAC-related data will be obtained from the EMR.

Describe any data that will be collected from human subjects for the project described in the application.

At baseline (enrollment), we will collect demographic, physiological, and ventilator data (Table 1). Data include age, gender, ethnicity, race, diagnosis, ETT information (type of tube and time of intubation), and severity of illness data. Physiological data will be obtained from the medical record at time of enrollment and per schedule (either daily or every 4 hours): temperature, vital signs, and sedation score. Information related to types of enteral tubes and nutritional support will be collected. Ventilator data will include mode of ventilation, set respiratory rate, positive end expiratory pressure, pressure support, and fraction of inspired oxygen. Ventilator data will assist in determining VAC. Temperature and results of tracheal aspirate cultures will be obtained from

the EMR for secondary analysis of infection or non-infection related VAC. Upon completion of the study, additional outcome data will include ICU length of stay, duration of mechanical ventilation and cost data from the hospital database for comparison of groups.

Indicate who will have access to individually identifiable private information about human subjects.

Study personnel who are collecting data from the EMR will have access to the medical record number to access study-related data. All data will be collected to meet HIPAA regulations and will be treated confidentially. All subjects will be issued a unique identification number so that data cannot be personally identified. All files (paper and electronic) will be coded with this identification number. Subjects' medical record numbers will be cross-referenced to identification numbers, and will be kept separate from all data collection forms in a locked cabinet in one of Dr. Sole's research offices. Access to information will be limited to the members of the research team on a "need to know" basis. All research team members will sign a confidentiality agreement and will complete mandatory CITI training for protection of human subjects. Results for presentation and publication will be presented in a way that individual patients cannot be identified.

Provide information about how the specimens, records, and/or data are collected, managed, and protected as well as whether material or data that include individually identifiable private information will be collected specifically for the proposed research project.

All data will be recorded electronically into the study database per the subject's unique identification number. Demographic and other physiological data will be retrieved from the subject's medical record. Observational data will be collected during the scheduled intervention times per the study protocol. Study personnel will record all data in electronic format using a password-protected tablet or laptop computer. Data will be backed up to a secure server at the College of Nursing.

C. POTENTIAL RISKS

Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the human subjects.

The probability of adverse consequences to participants is minimal. Removal of secretions is an independent nursing action that is routinely done but not per evidence-based protocol. We propose to enhance secretion removal through a protocol-driven procedure done every 4 hours. We do not anticipate that this frequency of oral suction poses a risk to subjects as nurses have the option to suction as needed with devices that they prefer to use, usually a suction swab or tonsil suction device. A recent study conducted in Asia tested a device that was kept in the mouth for continuous suction, and reported no adverse issues.²² We have observed that patients may awaken during oral care interventions, but that they fall back to sleep immediately after it is done. We have performed this procedure (NO-ASPIRATE) to obtain specimens in previous studies without any adverse issues, such as gagging or oral trauma.^{25,93} However, subject response will be observed as part of ongoing monitoring.

Oral care kits are standard for each patient, with supplies for oral suction, cleansing every 4 hours, and tooth brushing every 12 hours. We will use the same brand of oropharyngeal catheter that is packaged in the kits on a scheduled every-4-hour basis to those in the NO-ASPIRATE group.

All subjects will get usual care to prevent microaspiration, including head of bed elevation, management of enteral feedings, assessment of readiness to wean from MV, and management of ETT cuff pressure within recommended ranges. Many subjects will be intubated with the specialized subglottic suction ETT.

Trained members of the research team will implement the NO-ASPIRATE or usual care/sham interventions and collect data related to the study; all RAs will be experienced practitioners in management of patients on MV. Education and training is scheduled before beginning data collection and regularly throughout the study.

We will purchase all study-related supplies, including the oropharyngeal suction catheters, sputum traps, and materials needed to run the α -amylase assays. No additional costs will be associated with participation.

Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

No alternate treatments are identified.

D. RECRUITMENT AND INFORMED CONSENT

Describe plans for the recruitment of subjects and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.

Subjects will be recruited from the study units at Orlando Regional Medical Center. The PI, PD, or RAs will review the medical records of newly admitted patients to the study units. If a potential subject meets inclusion criteria, the study will be explained and a request for permission to enroll will be made to the patient (if alert and oriented and able to give consent) or the LAR. RAs will collaborate with the staff nurses, charge nurses, and the intensivist teams to assist in identification of potential subjects and to receive notification when the LAR is available. Our goal to enroll subjects as early as possible after admission; however, we need to ensure that the patient has been stabilized and that the patient or LAR is able to discuss participation.

Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent.

The PI, PD, or RAs will obtain consent from the patient (if competent to provide consent) or the LAR as soon as feasible after admission, within the designated enrollment period. Using data from previous studies, we expect that nearly all consents will come from the LAR. Study personnel will approach the patient or LAR, explain the study, and obtain consent for participation. From experience, we anticipate that 75% of LARs who are approached will give consent for participation. A standard script will be developed for explaining the study and answering study-related questions. The consent process will be available in both English and Spanish, and an interpreter will be available if needed through the hospital's translation services.

The consent form will include all required information: purpose, number of subjects, procedures, risks and benefits, measures to protect confidentiality, and the organization's required HIPAA statements. Consent will be documented. The patient or LAR will be given a copy of the signed consent form.

If during the course of the study, a subject becomes alert enough to understand the study and research processes, and the LAR has provided initial consent for participation, we will obtain verbal assent (nodding) or writing (yes/no) for continuation in the study from the subject. Should the subject gain sufficient cognitive ability to provide consent while enrolled, the study personnel will obtain his/her signature on the consent form.

The same procedures will be used for those 18-20 years of age, who are considered children for federal proposals. We will follow all rules and stipulations for enrolling this age group as specified by the ORMC IRB procedures. The IRB treats those 18 years of age and older as adults who are able to provide their own consent (<http://www.orlandohealth.com/pdf%20folder/IRB%20Policies%20&%20Procedures/11-14-08/400-Children06-2008.pdf>).

E. PROTECTION AGAINST RISK

Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.

During the study, patient safety will be of highest priority and all standards of care for the ventilated patient will be followed. All study team members delivering the intervention will receive training in both simulated and clinical settings before beginning the study, and periodic re-assessment of skills is scheduled throughout the study. *The NO-ASPIRATE or usual care intervention will be stopped if clinical signs indicate the patient does not tolerate the procedure. Intolerance will be assessed by a 20% or more increase in heart or respiratory rate or a decrease in oxygen saturation below 85%.* We will train RAs in all procedures, and monitor subjects for any adverse responses. The assigned critical care intensivist physician will be notified immediately should any serious adverse events occur during the study.

Subjects in both groups will have oral suctioning done every 4 hours. The NO-ASPIRATE group will be suctioned with the oropharyngeal catheter while the usual care/sham group will be suctioned with the swab. We will use the same type of oral hygiene equipment (catheter and swab) readily available in the oral care kits for the NO-ASPIRATE and usual care/sham interventions. We will regulate the suction pressure for oropharyngeal and ETT suction within recommended ranges. Subjects may awaken during the intervention. In our pilot work, 25% of subjects awakened during the procedure; however, they returned to their resting state immediately after the procedure. Any oral intervention has the potential to increase gagging; however, we have not noted that to be an issue with the oropharyngeal suction catheter in our preliminary studies.

Paired oral and tracheal specimens will be obtained for analysis of α -amylase. Tracheal aspirates will be obtained every 12 hours during a scheduled NO-ASPIRATE or usual care/sham intervention if clinical assessment indicates that the subject needs to be suctioned through the ETT. Suctioning will be done per standard procedures using the closed ETT suction system and recommended suction pressures. The subject will be hyperoxygenated via the ventilator before the procedure. ETT suctioning is regularly necessitated by the intubated patient and these same standards are followed when the patient is suctioned by the nurse or

respiratory therapist. We have used the same procedures in preliminary studies. Oral specimens will be obtained during the NO-ASPIRATE or usual care/sham intervention.

Existing standards of care to prevent microaspiration will be continued by the nursing and respiratory care staff. These interventions include head of bed elevation, management of enteral feedings, management of the subglottic suction ETT (if patient is intubated with the SS-ETT), maintaining the ETT cuff pressure within recommended ranges (20 and 30 cm H₂O), daily assessment of readiness to extubate, and oral antisepsis.

All data will be coded to ensure confidentiality of information. Members of the research team will be trained in measurement techniques and safety precautions for all interventions and related procedures. They will demonstrate proficiency in a simulated setting prior to initiation of the study, and on a regular basis.

Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a general description of the plan for data and safety monitoring of clinical trials and adverse event reporting to the IRB, the NIH and others, as appropriate, to ensure the safety of subjects.

The PI, Dr. Sole, will assume all responsibility for integrity and safety of the proposed study, and will provide close oversight of all aspects of the study. We do not anticipate adverse issues related to the study; however, we will be vigilant in our assessment to identify any issues and work in collaboration with our intensivist co-investigators. The NO-ASPIRATE intervention will be stopped if clinical signs indicate the subject does not tolerate it. The assigned intensivist physician will be notified immediately should any serious adverse events occur during the study.

At regular study team meetings, safety data will be reviewed, including compliance with the protocol, enrollment data, and any adverse events. Monthly meetings will be held, and will be convened more frequently if indicated. Should any standards of care that might influence the conduct of the study change during the study, meetings will be held accordingly to discuss their impact on the study. The protocol should be designated as no more than minimal risk; therefore, frequency of review and monitoring of data should be adequate. All reporting as required by the IRB will also be done per policy. All federal, state, local, university, and HIPAA regulations will be followed.

An independent **Data and Safety Monitoring Board (DMSB)** will be established to oversee the study and review any adverse events. (See H.)

F. POTENTIAL BENEFITS OF PROPOSED RESEARCH TO SUBJECTS AND OTHERS

Discuss the potential benefits of the research to research participants and others.

Those assigned to the NO-ASPIRATE intervention arm may have a reduced risk of microaspiration and VAC. It is also possible that subjects will have no direct benefit from the study. Patients in the future who are intubated and receiving mechanical ventilation may benefit from knowledge gained from this study.

Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

The NO-ASPIRATE intervention is an enhancement of existing standards of care focused on reducing the oral secretion load to prevent microaspiration and VAC. It will help to identify standard oral suctioning practices and assess the benefits. The potential benefit of the intervention to future patients is very high if it results in a reduced rate of microaspiration and VAC.

G. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.

Findings will be used to inform practice and establish standards of oral suctioning that can be incorporated into comprehensive airway management of the mechanically-ventilated patient. Knowledge of effectiveness of the NO-ASPIRATE intervention in a large sample of diverse critically ill patients will have great importance in influencing future practice to reduce microaspiration and prevent VAC. The study will yield important data to guide practice, and has the potential to influence types of oral care equipment that are most effective. It may also provide data for earlier detection of microaspiration, and guide treatment if needed.

Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

The study is associated with minimal risks in that all study-related procedures are considered part of the care of the mechanically-ventilated patient. The knowledge to be gained will help to identify effective methods and establish standards of practice to prevent microaspiration.

H. DATA AND SAFETY MONITORING PLAN

Since we are using a clinical trial approach, we will establish an independent Data and Safety Monitoring Board (DMSB) to oversee the study and review any adverse events. The DSMB will include an intensivist, a nursing manager, and a master's or doctoral-prepared critical care nurse. None of the members will be directly associated with the project. *The DSMB will be convened at the start of the study and will meet every 6 months thereafter. More frequent monitoring will be done if recommended by the DSMB or if issues are identified.*

In collaboration with the PI, Dr. Talbert (data manager) and the Project Director will prepare reports for the DMSB. The reports will include enrollment data and any issues or adverse events noted. The Board can request additional information to assist in safety monitoring. Written minutes of DSMB meetings with summaries of adverse events will be forwarded to the ORMC IRB and NIH according to established written procedures for each group. Determinations or recommendations for early stopping of the trial by the DSMB will be made if safety issues are identified.

Inclusion of Women and Minorities

Inclusion of Women

In the critical care units where patients will be enrolled, women represent 35% of patients who require mechanical ventilation. In our preliminary studies, we have recruited at least this percentage of women. We anticipate that enrollment in this study will be similar to the demographics of the study units. We will monitor demographic data on a regular basis to assess inclusion of women in the study. If issues are noted, we will identify and implement solution to ensure that women are represented.

Inclusion of Minorities

Patients who require mechanical ventilation represent racial and ethnic diversity. In a recently completed study, we found that Hispanic or Latino patients represented 14% of the population, and non-whites comprised 28% of the population. This diversity will facilitate our enrolling a diverse sample. Based on our enrollment calculations, we anticipate that 15% of our subjects will be Hispanic or Latino, and at least 25% will represent racial groups other than white. The PI will monitor enrollment data to ensure that minority populations are represented. We have achieved good diversity enrollment in previous studies conducted on the study units.