COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Project Title: Aspiration in Acute Respiratory Failure Survivors
Principle Investigator: Marc Moss MD

Objectives: Hypothesis and Specific Aims

Aim #1: To determine whether our 5-item decision tree algorithm is a more effective screening test to identify patients at high risk for post-extubation aspiration when compared to the 3-WST and the TOR-BSST.

Aim #2: To identify unique subphenotypes of patients with post-extubation aspiration based upon FEES-related measures of upper airway structure and function and determine their trajectories of recovery.

Aim #3: To determine the effects of ultrasound determined ETT size/tracheal diameter ratio upon post-extubation aspiration while accounting for other potential confounders including ETT cuff pressure.

Hypothesis: We hypothesize that our 5-item decision tree algorithm will more accurately identify ARF survivors at high risk for aspiration when compared to two standard tools: the Yale 3-ounce water swallow test (3-WST) and the Toronto Bedside Swallowing Screening Test (TOR-BSST), and ratio of ETT size/tracheal diameter determined with ultrasound may be a more accurate predictor of aspiration risk than ETT size alone

Study Design: Prospective cohort study of patients with acute respiratory failure who require mechanical ventilation for more than 48 hours.

Inclusion Criteria:

1. Admission to an ICU.
2. Mechanical ventilation with an endotracheal tube for greater than 48 hours. We will enroll COVID positive patients. Please see below for safety procedures.

Exclusion Criteria:

1. Contraindication to enteral nutrition administration.
2. Pre-existing history of dysphagia or aspiration.
3. Pre-existing or acute primary central or peripheral neuromuscular disorder.
4. Presence of a chronic tracheostomy (present prior to ICU admission).
5. Pre-existing head and neck cancer or surgery.
6. Coagulopathy resulting in uncontrolled nasal or pharyngeal bleeding.
7. Delirium for more than 72 hours after extubation as assessed by CAM-ICU.(75,76)
8. Extubated for greater than 72 hours.
9. Inability to obtain informed consent from patient or an appropriate surrogate.
10. Age < 18 years.

For Aim #1: Primary outcome variable: Using a PAS cutoff score of ≥6 on FEES, patients will be stratified by aspiration on any of the five consistencies. Sensitivity and negative predictive value will be the co-primary outcomes.

Statistical analysis: All relevant diagnostic accuracy statistics will be calculated for each screening tool. This includes sensitivity (co-primary), specificity, positive predictive value, negative predictive value (co-primary), area under the receiver operating characteristic (ROC) curve, and likelihood ratios.

For Aim #2: Methods: We will use all available patient data with an overall PAS score of 6,7 or 8 (positive for aspiration).

Longitudinal outcome variables: All study participants will be assessed for the following outcomes during their primary hospitalization: 1) time until return to baseline diet (in days), 2) Development of hospital acquired pneumonia according to CDC criteria, 3) Re-intubation, 4) Percutaneous feeding tube placement, 5) ICU length of stay, 6) Hospital length of stay, 7) Hospital mortality, and 8) Discharge location (home, long term acute care, acute rehabilitation hospital, nursing home, other).

For Aim #3: Primary independent variable: ETT size/tracheal diameter ratio.

Primary Outcome Variable: Aspiration (PAS score of ≥6) on the FEES with any of the feeding consistencies. A PAS score of ≥ 6 includes patients with both silent and non-silent aspiration.

Statistical Analysis: The primary outcome (aspiration) will be modeled using a multivariable logistic regression with ETT size/tracheal diameter ratio as one independent variable, and the confounders mentioned in the section above included as other predictor variables.

Overall Sample Size Determination: Based on enrollment data from our R21 grant, 8.8% (22/248) of patients withdrew between the non-invasive bedside evaluations and the performance of the FEES examination. An additional 5.2% (13/248) of patients had an incomplete FEES that could not be used in the final analysis. *Therefore, we will need to initially enroll 855 patients, and start the FEES exams on 789 patients to achieve our final sample size of 750 evaluable patients.*

For the over 1,000,000 patients that develop acute respiratory failure (ARF) each year, endotracheal tube (ETT) placement and mechanical ventilation are life-saving procedures.[1] Fortunately, 75% of these patients survive their critical illness.[2] However, post-extubation aspiration occurs in up to 44% of ARF survivors (330,000) and is associated with deleterious consequences including pneumonia, percutaneous feeding tube placement, long-term care admissions, and increased hospital mortality.[3-7] Our understanding of the epidemiology, screening and diagnosis, mechanisms, and therapeutic options for post-extubation aspiration is still in its infancy. *Through a multi-faceted approach, this proposal will establish the most accurate screening test to identify high-risk patients, facilitate the development of personalized therapies for post-extubation aspiration, and identify a novel modifiable risk factor (ETT size) that could dramatically improve the intubation process for all ARF patients.*

Our successful NINR-funded R21 award paved the way for this R01 proposal. In our multi-center and multidisciplinary prospective study of over 230 ARF survivors, we made three novel discoveries that will allow us to determine how to decrease the risk of post-extubation aspiration. First, using non-invasive bedside evaluations performed by speech language pathologists and fiberoptic evaluation of swallowing (FEES) examinations, we developed a 5-item screening decision tree algorithm that identifies patients at high risk for post-extubation aspiration.[8] Second, we identified laryngeal structure and swallowing function abnormalities that are associated with post-extubation aspiration, and we identified three potentially distinct subphenotypes of ARF survivors.[9] Third, we determined that ETT size is associated with an increased risk of post-extubation aspiration, and therefore may represent a modifiable risk factor for ARF survivors.[10]

These promising preliminary observations could pave the way for a paradigm shift in the care of ARF survivors. The crucial next step is a more in-depth study to expand upon our novel findings and establish new methods to identify, prevent, and treat post-extubation aspiration. Though the validity of our decision tree algorithm is promising, its efficacy needs to be compared to other currently used screening tools. We hypothesize that our 5-item decision tree algorithm will more accurately identify ARF survivors at high risk for aspiration when compared to two standard tools: the Yale 3-ounce water swallow test (3-WST) and the Toronto Bedside Swallowing Screening Test (TOR-BSST).[11-14] With FEES as our gold standard for detecting aspiration, we will determine the most effective method to identify patients at high risk for post-extubation aspiration.[15] The three ARF subphenotypes we identified may be associated with different trajectories of recovery, and represent unique patients who would benefit from different personalized therapies.[16-19] We will investigate these possibilities. Finally, ETT size alone may not represent the spatial parameters of the upper airway.[20,21] We hypothesize that ratio of ETT size/tracheal diameter determined with ultrasound may be a more accurate predictor of aspiration risk than ETT size alone. Ultimately, we will identify the most effective method to select the proper ETT size for all ARF patients and decrease the risk of post-extubation aspiration.

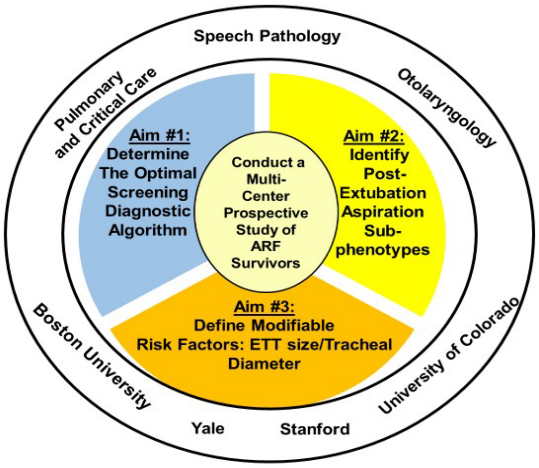


Figure 1: R01 Proposal Overview:

Outer circle represents our multidisciplinary and multi-center infrastructure.

We are the optimal multi-center research team to perform the proposed studies. Dr. Moss' interest in aspiration began with his 2000 *New England Journal of Medicine* article identifying the harmful effects of using blue dye to detect

aspiration in ARF patients.[22] Dr. Langmore developed the FEES procedure and is one of the pioneers of dysphagia-related research.[15,23-37] We have already worked collaboratively for many years as a four-center integrated research team (Colorado, Boston University, Stanford, Yale), and we will perform a prospective multi-center cohort study of *750 evaluable* ARF survivors to answer three complementary study questions (Figure 1).

Aim #1: To determine whether our 5-item decision tree algorithm is a more effective screening test to identify patients at high risk for post-extubation aspiration when compared to the 3-WST and the TOR-BSST.

Aim #2: To identify unique subphenotypes of patients with post-extubation aspiration based upon FEES-related measures of upper airway structure and function and determine their trajectories of recovery.

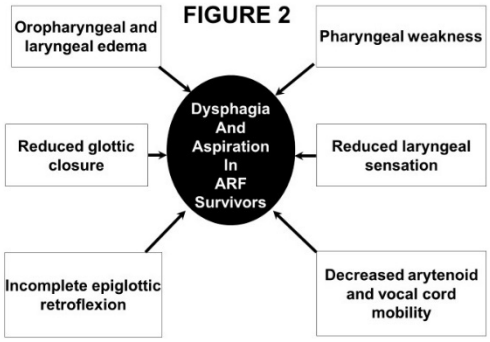
Aim #3: To determine the effects of ultrasound determined ETT size/tracheal diameter ratio upon post-extubation aspiration while accounting for other potential confounders including ETT cuff pressure.

SIGNIFICANCE: Post-extubation dysphagia and aspiration are common in survivors of acute respiratory failure (ARF). The care of ARF survivors costs an estimated $19 billion or 8.4% of all hospital expenses.[2] Due the COVID pandemic, the impact and prevalence of ARF has significantly increased. Up to 50% of hospitalized COVID patients develop ARF requiring intubation and mechanical ventilation.[38] All ARF survivors cope with a multiple consequences of their critical illness.[5-7,39-44] As summarized in our two clinical reviews, as many as 44% of ARF survivors develop post-extubation aspiration.[5,6] However, our understanding of the optimal ways to diagnose and treat post-extubation aspiration are relatively unknown.

There is no standardized method to screen and diagnose post-extubation aspiration. After extubation, ARF patients may receive a swallowing screening test to identify those at high risk for aspiration. When the screening test is abnormal, a speech language pathologist (SLP) may be consulted to perform a bedside evaluation of swallowing (BSE)**.** Our research group and others demonstrated that even the formal BSE does not identify accurately those ARF survivors at high risk for post-extubation aspiration.[8,14,45-47] Therefore, a new diagnostic algorithm is needed. We developed a five variable BSE-based decision tree screening algorithm that dramatically improved the detection of post-extubation aspiration. The five variables are easy to determine: length of mechanical ventilation, APACHE II score, voice quality, type of ICU, and a 2-ounce water swallowing assessment.[8] Though promising, our algorithm requires validation and comparison to other screening tools. The 3-ounce water swallow test (3-WST) and the Toronto Bedside Swallowing Screening Test (TOR-BSST) are two of the most used screening tests to identify patients at high risk for aspiration.[12-14] We will determine the most accurate screening test and establish that test as the standard method to identify patients that require further diagnostic testing such as a fiberoptic evaluation of swallowing (FEES) examination.

The mechanisms responsible for post-extubation aspiration are relatively unexplored. The broad post-extubation aspiration definition, defined as simply the detection of aspiration, is one barrier to the development of effective therapies. Different combinations of demographic and physiological factors may naturally cluster into previously undescribed subsets or phenotypes that may have different underlying mechanisms and may respond differently to treatments.[48] Most SLPs treat patients with aspiration by restricting oral nutrition, adjusting the consistency of their food or liquids, or with different swallowing maneuvers.[49-60] These interventions limit the chance of aspiration but do not treat the underlying cause of the swallowing dysfunction.[49-60] Using fluoroscopy, one study of eleven ARF survivors demonstrated that those who aspirate manifest a longer time to achieve laryngeal closure when compared to normal controls.[61] In our large cohort of 213 ARF survivors, we identified multiple abnormalities of laryngeal structure and function that were associated with post-extubation aspiration (Figure 2). In a *preliminary* analysis on the 70 ARF survivors with post-extubation aspiration, we identified three unique subphenotypes (see Preliminary data). However, 70 patients is insufficient to identify subphenotypes accurately. By prospectively following these ARF survivors, we will also determine whether the subphenotypes are associated with different trajectories of recovery and identify those patients who benefit from personalized therapies.

FIGURE 2

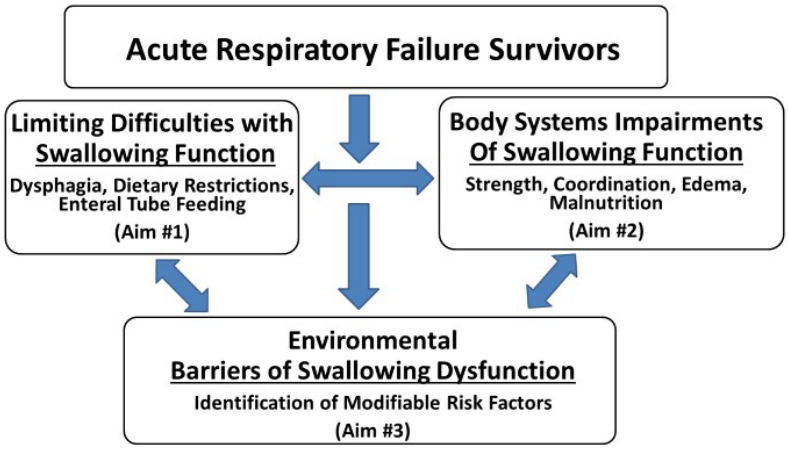


Endotracheal tube (ETT) size is a potentially modifiable factor that has been associated with post-extubation laryngeal injury.[10,62,63] There is no standard method for selecting the proper endotracheal tube size (diameter) for adults.[20,64,65] As a result, there is significant variability in the size of the ETT placed during intubation. The placement of a

smaller ETT may increase airway resistance, impede weaning from the ventilator, and inhibit the ability to perform bronchoscopy. The placement of a larger ETT has been associated with increased rates of laryngeal injury and post-extubation stridor.[62] We identified ETT size as a potential risk factor for post-extubation aspiration in a pilot study and replicated these findings in a larger multi-center prospective study.[10,63] However, ETT size alone may not be the most accurate measure of the spatial parameters of the upper airway and does not account for individual differences in tracheal diameter. Ultrasonography is a readily accessible and portable bedside instrument that easily and accurately measures tracheal diameter.[20,21,66] *We hypothesize that a higher ETT/tracheal diameter ratio may more accurately predict post-extubation aspiration than ETT size alone.* If correct, bedside ultrasound could be used prior to intubation to guide the selection of ETT size and minimize post-extubation consequences such as stridor and aspiration.

Levine's theoretical framework guides our long-term goal to assist ARF survivors return to a full and satisfying life within the constraints of their ARF recovery. These conservation principles direct nursing activities and rehabilitation efforts to regain the person's health and wholeness. Levine identified four principles of conservation: energy, structural integrity, personal integrity, and social integrity.[67,68] SLPs can improve patient's structural and personal integrity. In addition, the International Classification of Function (Figure 3) that highlights the interrelated role of generalized impairments (such as weakness) on function (in this case dysphagia) also guides this proposal. Collectively, this framework demonstrates that modifying the influence of personal factors and incorporating improved swallowing capabilities improves overall function and participation. Our proposal focuses on strategies to reduce the development of post-extubation aspiration and personalize the establishment of effective interventions that will prevent and treat post-extubation aspiration.

Figure 3: Theoretical Model



INNOVATION: Our research proposal is innovative in five specific ways.

1) We are the only multi-center and multidisciplinary group studying post-extubation aspiration and dysphagia.

2) This is the first study to compare different screening tools to detect patients at high risk for aspiration. Our results will establish one of these tools as the most clinically useful, and directly improve clinical practice.

3) We will use novel and innovative statistical techniques. Recursive partitioning analysis was an innovative method to develop an effective decision tree algorithm that streamlined the BSE evaluation and accurately identified patients at high risk for post-extubation aspiration.[69,70] Using the novel statistical approach of a latent class analysis, we will be the first group to identify subphenotypes of post-extubation aspiration.[16] These subphenotypes likely have different trajectories of recovery that are amenable to different interventions.

4) We will identify one of the first modifiable risk factors (the endotracheal tube/tracheal diameter ratio) for post-extubation aspiration, and the first group to utlize an ultrasound measure of laryngeal diameter to improve the selection of the proper sized endotracheal tube in adult ARF patients. This observation could dramatically enhance clinical practice for all ARF patients by facilitating the placement of the proper sized ETT and decreasing a variety of deleterious consequences such as post-extubation aspiration and stridor.

5) Our study design is innovatively efficient. FEES will serve as the gold standard test for Aims 1 and 3 and identify changes in laryngeal structure and function associated with subphenotypes of ARF survivors in Aim 2.

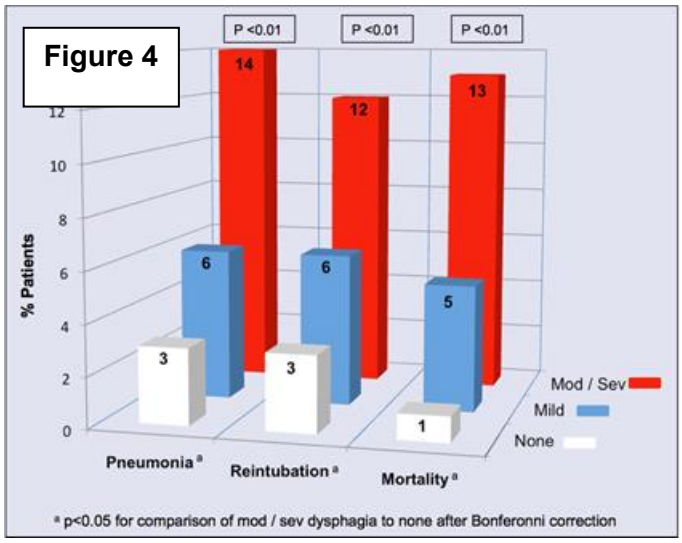
PRELIMINARY DATA:

I. General post-extubation data generated by our research group.

1. Longer duration of mechanical ventilation is associated with dysphagia.[71] We conducted a cohort study of 446 ICU patients who required mechanical ventilation and received a BSE. On the BSE, dysphagia was present in 84% of

patients (mild in 52% and moderate/severe in 48%). Longer duration of mechanical ventilation was independently associated with moderate/severe dysphagia (AOR 2.84 [1.78-4.56], p <0.01).

2. In ARF survivors, dysphagia is associated with prolonged hospitalization and delayed oral nutrition.[71] Dysphagia was independently associated with the composite outcome of pneumonia, re-intubation, or in-hospital death (AOR 3.31 [1.78-4.56], p<0.01) (Figure 4 on next page). Dysphagia was still present in 55% of patients at hospital discharge. Hospital duration was longer in ARF survivors with dysphagia compared to those without dysphagia (8 [5-15] days vs 5 [3-8] days after the BSE was performed, p<0.01). Patients with moderate/severe dysphagia were more likely to be kept NPO after the initial BSE (74% vs 15%, p<0.01) and receive a surgical feeding tube (15% vs 5%, p<0.01).



3. Our nationwide survey of SLPs identified current practices to diagnose aspiration in ARF survivors. [72] We designed, validated, and distributed a survey to 1,966 inpatient SLPs. Each survey included questions concerning SLP staffing and availability, and methods used in the diagnosis and treatment of dysphagia and aspiration. A total of 836 SLPs completed their survey (43%), 801 of whom were actively practicing. This survey represents the largest published study to date of SLP practices for ARF survivors.

4. There are currently no uniformly used diagnostic tests to detect aspiration in ARF survivors.[72] Based on our national survey, 0nly 29% of hospitals have formal guidelines for when critical care providers should consult SLPs in the evaluation of ARF survivors. When consulted, most SLPs performed the BSE on average 24 hours after extubation. Importantly, the majority of SLPs (60%) only use the BSE to identify swallowing dysfunction in ARF survivors. Gold standard tests (video fluoroscopy-VFSS and FEES) are not commonly used. VFSS and FEES are also more available and more utilized at university hospitals when compared to community hospitals (p < 0.01).

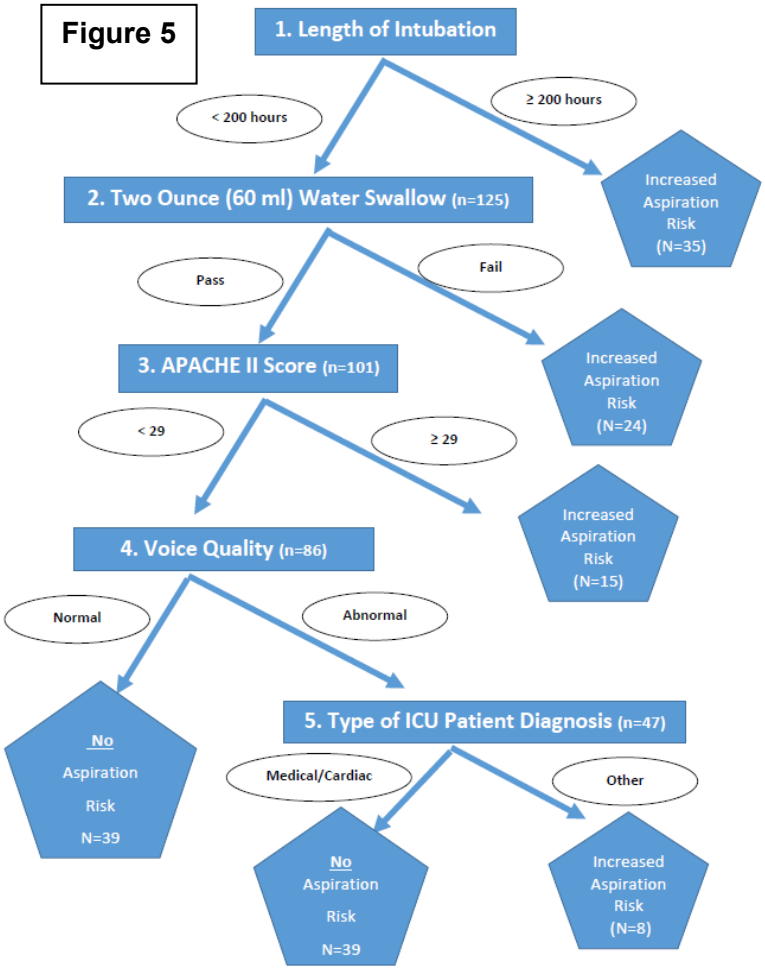
5. With the support from our NINR R21 award, we conducted a prospective multi-center cohort study of ARF survivors. From August 2015 until July 2018, 248 patients were enrolled at the four sites that will be included in this proposal (Colorado, Boston University, Yale, and Stanford); with the same investigators and research coordinators. A total of 22 subjects withdrew from the study before the FEES was performed, and an additional 13 patients had an incomplete FEES exam. Therefore, 213 patients were included in the final analyses. Median age was 57 (interquartile range 47 – 66) years, and 62% were male. Median duration of mechanical ventilation was 126 hours (interquartile range 72 – 206). Both the BSE and FEES exam were performed in the ICU. Median time from extubation to the BSE was 25 hours, and the FEES was completed 1 hour after the BSE. *This 213-patient cohort serves as the foundation for most of the preliminary data below.*

II. Data directly relevant to Aim #1:

6. Silent and non-silent post-extubation aspiration occur in ARF survivors. A total of 33% (70/213, 95%CI=26.6-39.2%) of patients aspirated on at least one FEES bolus consistency test. Non-silent aspiration (Penetration-Aspiration Scale (PAS) score = 6 or 7) was detected in 24% of patients and silent aspiration (PAS = 8) was detected in 14% patients. There were 11 patients (5%) with both non-silent and silent aspiration on different consistencies. Five adverse events occurred during this study. One patient vomited during FEES, and one vomited the night after the study; both of these episodes were considered to be associated with study-related events. Three patients developed transient respiratory failure after the FEES that were not considered study-related events. *Overall, this study demonstrated that the performance of FEES is safe in ARF survivors.*

7. We developed an accurate decision tree algorithm for detecting aspiration in ARF survivors. In order to develop a decision tree model, we used a recursive partitioning analysis to predict the development of aspiration on FEES examiniation.[73,74] To optimize sensitivity, the decision trees were not trimmed by cross-validation. All 175 possible demographic and BSE predictor variables were used as candidate predictors for aspiration. When compared to the gold standard FEES, the standard BSE detected aspiration with an accuracy of only 52% (95%CI =45-58%), a sensitivity of 83% (95%CI =74-92%), and negative predictive value of 81% (95%CI=72-91%). Our decision tree algorithm identified five variables for the final model of overall aspiration: duration of intubation, APACHE II score, voice quality, type of ICU: medical/cardiac vs. other, and a 2-ounce water swallowing assessment. Our decision tree algorithm improved the sensitivity to 95% (95%CI = 90-98%), and negative predictive value to 97% (95%CI = 95-99%). The overall algorithm is displayed in Figure 5 (next page). If our diagnostic algorithm was used as a screening test, then nearly half (49%) of patients would be accurately identified as not being an aspiration risk and would require no further diagnostic testing to detect aspiration, and the misclassification of these ARF patients would decrease by over 30%.

Figure 5



III. Data directly relevant to Aim #2:

8. We identified specific abnormalities in laryngeal structure that are associated with post-extubation aspiration. With over 30 years of FEES experience, Dr. Langmore independently scored the different components of the FEES examination including: velar closure, vocal cord/arytenoid mobility, glottic closure, epiglottic retroflexion, laryngeal elevation/arytenoid lift, base of tongue retraction, pharyngeal wall medialization, secretions, and laryngeal sensation. Our otolaryngologist (Dr. Fink) also scored the FEES for vocal fold mobility, laryngeal edema, and vocal cord granulation tissue. Each of the *variables in the four general categories were associated with post-extubation aspiration:* (1) Laryngeal closure: reduced glottic closure, incomplete epiglottic retroflexion, decreased arytenoid mobility, and vocal fold immobility. (2) Weakness: reduced pharyngeal medialization. (3) Laryngeal sensation: decreased sensation and presence of upper airway secretions. (4) Anatomical: Airway edema (usually arytenoid).

In most cases, the same variables were significantly associated with aspiration, whether the bolus was ice/liquid or puree/nectars/solids. In a multivariable analysis, two variables remained significant: pharyngeal medialization (Odds ratio = 2.57, 95% CI = 1.16-5.84, p = 0.019) and airway edema (Odds ratio = 3.24, 95% CI 1.44-7.66, p = 0.004).

9. Swallowing function is also associated with post-extubation aspiration. For all consistencies, the median overall swallowing time was 0-1 second; range from 0-22 seconds for ice/liquids, and up to 240 seconds for solids. The average swallowing time for the ice/liquid bolus consistencies was associated with aspiration of the ice/liquid boluses, although not significantly, aspiration: 2.6±2.5 seconds vs. not aspiration 2.0 ± 1.8 seconds, p = 0.051. For each consistency, the timing of aspiration during the swallow is demonstrated in Table 1. Reduced sensation was significantly associated with spillage of liquids (p= 0.03) and was significantly associated with penetration into the laryngeal vestibule before the onset of the swallow (p = 0.04). Altered pharyngeal medialization was significantly associated with the residue for nectar/puree/solid consistencies (p= 0.047).

TABLE 1	Aspiration Frequency	Time of Aspiration		
		Before the Swallow	During the Swallow	After the Swallow
All boluses	33% (70/213)	10% (7/70)	90% (63/70)	23% (16/70)
Ice	8% (18/213)	17% (3/18)	89% (16/18)	28% (5/18)
Thin liquid	27% (54/197)	9% (5/54)	96% (52/54)	19% (10/54)
Nectar thick	8% (17/210)	18% (3/17)	88% (15/17)	47% (8/17)
Puree	3% (7/205)	0% (0/7)	86% (6/7)	71% (5/7)
Solid	2% (3/176)	33% (1/3)	100% (3/3)	67% (2/3)

10. We identified potential subphenotpyes of ARF survivors. For our 213 patients, we examined patient demographics, physical exam characteristics, and BSE and FEES results. Overall, 63 variables were included as predictor variables. Using a forward stepwise multinomial regression model, we refined the list of candidate predictors for further analysis. Examining the 70 ARF survivors with aspiration of any consistency on the FEES examination, we identified three potential subphenotypes of ARF survivors: 1) patients with more upper airway edema (57%, n=40), 2) patients with predominantly neuromuscular weakness (37%, n=26), and 3) patients with focal signs of vocal cord immobility (6%, n=4). The first cluster with upper airway edema were younger, more likely to be female, more likely to be non-white, and have lower Charlson scores. The second cluster with a predominance of weakness had longer times of mechanical ventilation and higher rates of renal disease.

IV. Data directly relevant to Aim #3:

11. We identified that ETT size is associated with an increased risk of post-extubation aspiration.[10] We first conducted a prospective pilot cohort study of 45 ARF survivors to determine the accuracy of the BSE. In the multivariable analysis, we identified that ETT size of 8.0 or greater was associated with aspiration, p=0.03. Based on these results, we systematically collected information regarding the ETT in our larger prospective cohort study of 213 patients and observed similar findings. In both studies, the treating physicians independently selected the ETT size. The distribution of ETT size was 8.0 mm or greater (48%), 7.5 mm (35%), 7.0 or smaller (17%). Overall, one third (n=70) of patients aspirated on at least one bolus on FEES examination. In the multivariable analysis, ETT size (≤7.5 vs. ≥8.0) was significantly associated with patients exhibiting aspiration (p=0.016, OR=2.17, 95% CI=1.14-4.13).

12. We can measure ETT/tracheal diameter ratio and determined that tracheal diameter does not change during the duration of endotracheal intubation. We enrolled six intubated patients within 24 hours of intubation and obtained serial tracheal ultrasounds until extubation. The ETT/tracheal diameter appears to be normally distributed and ranges from 0.51-0.87. Using a paired analysis, there does not appear to be changes in tracheal diameter over time (.70 vs. .67). This study is ongoing, and we will add supplemental preliminary data after the primary submission regarding tracheal diameter that is permitted due to COVID-19.

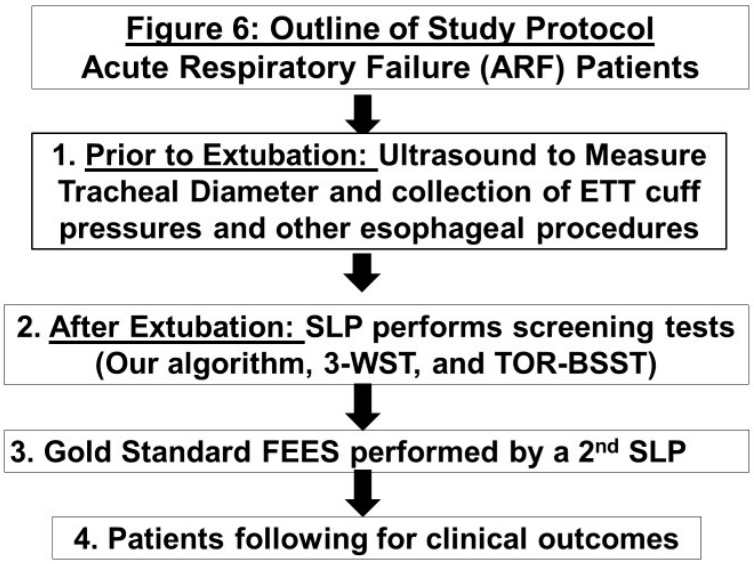
Methods:

Screening and Informed Consent: We created an integrated multi-center network between the Colorado, Boston University, Yale, and Stanford that has already performed all aspects of the research proposed in this application. All four institutions already had a long history of dysphagia and aspiration research involving critically ill patients. We already developed a HIPAA compliant cloud-based system that shares and stores all of the information in the case report forms including the FEES videos. A total of 350 ICU beds will be screened on a daily basis. (Table 3). Consecutive patients will be screened for enrollment prior to and regardless of whether the SLP service was consulted by the primary team. Surrogate of patients meeting enrollment criteria will be approached for informed consent prior to extubation.

Tracheal Ultrasound: Part of the study protocol is to obtain a tracheal ultrasound within 72 hours prior to extubation. Because it is a very low risk procedure, we propose to be able to perform the tracheal ultrasound with a waiver of informed consent if we are unable to consent a surrogate within this time frame. If we are subsequently unable to obtain informed

consent for the remaining study procedures or if the surrogate or patient declines enrollment, then we will discard the ultrasound images. No other study related procedure would be performed without a signed consent from the patient or their surrogate. All patients will be re-consented once they regain cognitive ability and decisional capacity. See Figure 6 for the overall study design and flow.

Collection of Demographical and Clinical Information: After obtaining informed consent, we will collect demographic information, and obtain ETT cuff pressures that are collected every 4-6 hours as part of standard of care at all four study hospitals. In addition, we will record the presence and duration of other oral, nasal, and esophageal tubes placed during mechanical ventilation.



Performance of the three Screening Tests: The three screening tests (outlined below and in Table 4) will be performed before the FEES examination. One SLP will perform the screening tests. To account for the potential learning effect of the patient through participating in one of the water swallow tests, the order of the two 2-ounce water swallow tests (included in our algorithm and the TOR-BSST) and the 3-WST will be performed in random order for each study participant. We considered randomizing the order of the screening exams and the FEES examination. However, in practice the non-invasive screening tests will always be performed prior to FEES.

Screening Test A. Our five-item decision tree algorithm: Three of the components (length of mechanical ventilation, APACHE II score, type of ICU) will be extracted from the medical record. The SLP will then assess the voice quality and perform the 2-ounce water consistency assessment. The voice quality will be scored as (normal vs. abnormal defined as aphonic, hoarse, or wet). The 2-ounce water test will be administered via a straw controlled by the patient. The SLP may assist in holding the cup. The SLP will wait for 10 seconds following the completion of the trial before recording the results for that consistency. Five outcomes (cough, throat clearing, vocal quality change, change in breath sounds, or stridor) will be recorded.

Coughing: Dichotomized as a single cough within 10 seconds after diet administration (yes/no).

Throat Clearing: Dichotomized as a throat clearing sound within 10 seconds after diet administration (yes/no).

Change in vocal quality: Baseline vocal quality will be assessed initially and dichotomized as normal/abnormal. Transitions from normal to abnormal vocal quality during feeding will be recorded.

Change in breath sounds: Breath sounds will be assessed before and 10 seconds after the examination by auscultating over the larynx at the thyro-cricoid space during quiet breathing. Patients will be classified as "gurgling" or "non-gurgling." Gurgling is a low/medium-pitched rattling sound on inhalation or exhalation.[81]

TABLE 4: Comparison of Three Screening Tools

Our Algorithm	3-WST	TOR-BSST
Our 2-oz. water test	3-oz. water test	The TOR-BSST 2-oz. water test
Length of ventilation		Tongue movement
APACHE II		Baseline voice
Voice quality		Post voice
Type of ICU		

Stridor: Dichotomized as present or absent in 10 seconds.

Screening Test B. Three-Ounce Water Swallow Test (3-WST): Championed in ARF patients by our Yale colleagues, the 3-WST will be performed according to standard procedures. Patients will receive three ounces of water and will be instructed to drink the entire amount, via a cup or straw, completely and without interruption (the cup can be held to the patient's mouth by the SLP).[74;76;109] The 3-WST will be scored as pass/fail. Criteria for failure of the 3-WST are: the inability to drink the entire amount, coughing or choking up to 1 minute after completion, or the presence of a wet-hoarse vocal quality.

Screening Test C. Toronto Bedside Swallowing Screening Test (TOR-BSST): Though originally developed for stroke patients, the TOR-BSST has been used more broadly for other patient populations.[12,82,83] More recently, the TOR-BSST was studied in critically ill patients (manuscript currently under review). Designed to be administered by nurses, we will have our study SLPs complete the 4-hour TOR-BSST training program. Dr. Rosemary Martino (TOR-BSST developer) will provide our study SLPs access to the TOR-BSST educational videos and modules to enhance study fidelity (see Dr. Martino's letter of support). For consistency, we will have study SLPs assess each of the four components of the TOR-BSST; including assessment of baseline voice, tongue movement, ability to swallow water and post-voice quality. The ability to swallow water is assessed using the 2-ounce water swallow test according to the TOR-BSST protocol.

Gold Standard Testing: the FEES Protocol

Within 4 hours of the completion of the BSE, another SLP or investigator who is blinded to the results of the three screening tests will administer the FEES examination. Vital signs, including blood pressure, heart rate, and oxygen saturation will be recorded through the entire procedure. Developed by Dr. Langmore, the FEES will be performed according to her standardized protocol.[34,35] Initially, the SLP will examine various aspects of upper airway structure and function prior to delivering liquid or solids. These tasks comprise Part 1 of the FEES examination and include structural movements that are not visible during swallowing. Overall we will assess nine components that will be scored similarly to our R21 scoring system: 1. velar closure, 2. vocal cord/arytenoid mobility, 3. glottic closure, 4. epiglottic retroflexion, 5. laryngeal elevation/ arytenoid lift, 6. base of tongue retraction, 7. pharyngeal wall medialization, 8. secretions, and 9. laryngeal sensation. Laryngeal sensation will be assessed by observing the laryngeal adductor reflex (LAR): patient response to a light touch to the aeryepiglottic folds bilaterally with the tip of the laryngoscope.[9] The FEES will also be scored for three components of laryngeal function: 1. vocal cord immobility; 2. granuloma formation; and 3. airway edema. Each of these functions will be quantified as none, mild, moderate, severe using our previous scoring system.

Table 5: Order, type and quantity of each bolus consistency

	Type	IDDSI score	Different Quantity and Order
Ice	Ice Chips	7 - 0	1) ½ teaspoon 2) Full teaspoon
Nectar Thick Liquids	Pre-thickened apple juice	2	1) 5 ml – level teaspoon 2) 15 ml presented in medicine cup 3) 2 ounce via straw, patient controlled (may assist in holding the cup)
Pureed Solids	Applesauce	4	1) 5ml puree – level teaspoon 2) 10 ml puree – heaping teaspoon
Thin Liquids	Water	0	1) 5 ml – level teaspoon 2) 15 ml presented in medicine cup 3) 2 ounce via straw, patient controlled (may assist in holding the cup)* 4) 3 ounce water swallow test (3-WST)*
Solids	Graham Cracker	7	1) ¼ piece – instruct to chew before swallowing

*= The order of the 2 ounce water and the 3-WST will be randomized

Subsequently, the SLP will assess swallowing function with food and liquid trials (Part 2 of the exam). The SLP will administer five standard consistencies: ice chips (International Dysphagia Diet Standardization Initiative consistency (IDDSI) = starting at 7 and then transition to 0), nectar thin liquids: pre-thickened apple juice (IDDSI = 2), pureed solids: applesauce (IDDSI =4), thin liquids: water (IDDSI = 0), and solids: graham cracker (IDDSI =7) in successive boluses that increased are in size.[84-87] Table 5 outlines the order, type and quantity of each bolus. All boluses will be administered unless considered unsafe by the treating SLP. This safety determination will be left to the discretion of the SLP based on the patient response to the prior bolus. If there are clinical signs of aspiration with a smaller bolus of one consistency, the remaining boluses of that consistency can be skipped. The smallest bolus of the next consistency would then be administered.

Scoring of the FEES Examination: All FEES examinations will be video and sound recorded and stored in a HIPAA compliant cloud-based system. From the recordings, Dr. Langmore will perform a blinded review of the determinants of laryngeal structure and swallowing function on the FEES examination and determine a Penetration Aspiration Scale (PAS) score for each boluses (Table 6).[88] A PAS score of 6 or greater represents aspiration. A PAS score of 6-7 represents non-silent aspiration, and a score of 8 represents silent aspiration. To obtain an interrater reliability, an experienced SLP at Boston University will over read 10% of the FEES. In addition, Dr. Fink will score three variables: vocal fold mobility, presence of laryngeal edema, and presence of granulation tissue on the vocal cords. The swallowing onset time will be determined for each bolus defined as the time from first

Table 3: PAS scoring system

Scale	Enters airway?	Relationship to vocal folds	Ejected from airway?	Effort made to eject?
1	No	--	--	--
2	Yes	Above	Yes	--
3	Yes	Above	No	--
4	Yes	Contacting	Yes	--
5	Yes	Contacting	No	--
6	Yes	Below	Yes	--
7	Yes	Below	No	Yes
8	Yes	Below	No	No

bolus visualization until swallow onset. We will assess the residue after each bolus defined as residue in the pharynx/ laryngeal vestibule after a swallow.

How will we ensure our study protocol will be performed safely in COVID positive patients? Drs. Moss and Langmore were part of the multidisciplinary team that developed the International Dysphagia Research Society guidelines for speech language pathology related procedures in COVID positive patients.[97] When caring for a patient with suspected or known COVID-19, we will ensure that personal protective equipment (PPE) is provided to study personnel including an N95 mask, a face shield for eye protection, gloves, and an isolation gown. Study personnel will be fitted with PPE in accordance with OSHA standards and will receive training to demonstrate competency in properly donning, doffing, and disposing or disinfecting PPE equipment. Only the minimal number of essential personnel will be present to perform the screening testing and FEES examination while maintaining permissible physical distancing between members during the procedure and ideally performing the study procedures in a negative pressure room.

Monitoring of SLP protocol fidelity: Study fidelity has the dual purpose of monitoring and enhancing both the performance of the study and the assessment of the outcome variables.[98-100] We will monitor our study in five domains: study design, provider training, protocol delivery, receipt, and enactment.

1. Screening tests and FEES examinations will only be conducted by SLPs that are specifically trained for this study. All of the study SLPs will have at least two years of experience in performing bedside evaluations and FEES examinations and will have prior experience working with critically ill patients and survivors of ARF. All of the study SLPs participated in our R21 protocols.

2. We already developed a study manual for consistent performance of all study procedures.

3. All SLPs will undergo formal training in the conduct of all three screening tools including the required 4-hour training for the TOR-BSST (see support letter from Dr. Rosemary Martino)

4. Prior to the start of the study, Dr. Langmore will conduct individual in-person training sessions at each site. She will observe each SLP until they are able to implement the protocol independently. During subsequent annual visits, Dr. Langmore or her designee will conduct repeat training for all study SLPs. In the event of travel restrictions due to the COVID pandemic, we will conduct virtual video conference sessions.

5. FEES will be video recorded. Dr. Langmore will review the videos for quality and protocol fidelity to optimize the FEES examinations between her annual visits. We will determine the interrater reliability for all components of the FEES by having 10% of exams over read by a second reader.

6. We will have monthly calls to review specific cases and videos to assure consistency in the protocol.

Additional Methods for Specific Aim #1: To determine whether our 5-item decision tree algorithm is a more effective screening test to identify patients at high risk for post-extubation aspiration when compared to the 3-WST and the TOR-BSST.

Primary outcome variable: Using a PAS cutoff score of ≥6 on FEES, patients will be stratified by aspiration on any of the five consistencies. Sensitivity and negative predictive value will be the co-primary outcomes.

Statistical analysis: All relevant diagnostic accuracy statistics will be calculated for each screening tool. This includes sensitivity (co-primary), specificity, positive predictive value, negative predictive value (co-primary), area under the receiver operating characteristic (ROC) curve, and likelihood ratios. The gold standard outcome will be aspiration as defined by the PAS score ≥6 on the FEES. In order to test for differences in diagnostic accuracy statistics between our 5-item decision tree algorithm, the 3-WST, and TOR-BSST, we will use paired tests of two proportions (McNemar's tests). As a secondary analysis, we will utilize a multivariable logistic regression with the three screening tools as candidate predictors to infer whether the 5-item algorithm adds significantly to the predictive capabilities of either of the two other screening tools.

Sample Size Calculation and Feasibility: Based on enrollment data from our R21 grant, 8.8% (22/248) of patients withdrew between the non-invasive bedside evaluations and the performance of the FEES examination. An additional 5.2% (13/248) of patients had an incomplete FEES that could not be used in the final analysis. *Therefore, we will need to initially enroll 855 patients, and start the FEES exams on 789 patients to achieve our final sample size of 750 evaluable patients. Our past success is the best predictor of future study enrollment.* During our R21 award, we were able to maintain an enrollment rate of one patient/week for each individual site or four patients/week combined, when all four sites were active. If we enrolled four patients per week, we would enroll approximately 200 patients per year. Therefore, we will need to enroll patients for 4.25 years to enroll 855 patients. On average, there are 5,463 mechanically intubated critically ill patients each year at the four hospitals combined. Therefore, we need to enroll 3.6% (one out of 28 patients) of these patients into our

study to meet our enrollment criteria. For our budget estimates, we were conservative, and they are based on enrollment of 210 patients/site or 840 total patients (extra 51 patients) that will start the FEES to achieve 750 evaluable patients.

Our final sample size of 750 patients who complete the protocol will ensure that the width of the 95% confidence interval (2 times the margin of error) for each diagnostic accuracy component is at most 5% for especially low/high values (<0.1 or >.9), and at most 7.3% for any value between .25 and .75. This sample size yields 80% power to detect a difference of 0.094 (9.4%) in either the sensitivity or negative predictive value of our 5-item decision tree compared to either screening method. This power estimate is based on dual two-sided McNemar tests assuming a 2.5% level of significance (achieves a 5% family-wise type I error rate), a baseline prevalence of 30% aspiration, and 20% discordant pairs.

Anticipated Results, Limitations, Additional Considerations, and Future Directions: We anticipate that our algorithm will be the most accurate screening test for post-extubation aspiration. Even if this assumption is incorrect, this study will establish one of the three tools as the optimal screening test for post-extubation aspiration. The results of this aim will enhance clinical practice by improving the screening and diagnosis of post-extubation aspiration and inform SLPs when additional studies such as FEES are necessary. We will also be able to determine the interrater reliability of the interpretation of the FEES examination. Understanding the areas of the FEES that are most prone to variability will assist in the development of improved educational modules for teaching FEES performance and interpretation. Additional considerations could include determining if the screening tools accurately predict dysphagia defined as a PAS score of 3-5. The impact of COVID-19 on post-extubation aspiration is unknown. In the proposal, we will be able to define the epidemiology of post-extubation swallowing dysfunction and aspiration in COVID patients who survived their ARF. Future studies could explore how to best disseminate and implement the optimal screening tool to enhance its utilization. We will also need to identify the optimal healthcare professionals (such as nurses, nursing assistants, or SLPs) who can accurately perform the optimal screening test.

Additional Methods for Specific Aim #2: To identify unique subphenotypes of patients with post-extubation aspiration based upon FEES-related measures of upper airway structure and function and determine their trajectories of recovery.

Methods: We will use all available patient data with an overall PAS score of 6,7 or 8 (positive for aspiration).

Longitudinal outcome variables: All study participants will be assessed for the following outcomes during their primary hospitalization: 1) time until return to baseline diet (in days), 2) Development of hospital acquired pneumonia according to CDC criteria, 3) Re-intubation, 4) Percutaneous feeding tube placement, 5) ICU length of stay, 6) Hospital length of stay, 7) Hospital mortality, and 8) Discharge location (home, long term acute care, acute rehabilitation hospital, nursing home, other).

Statistical Analysis: Based our prior studies, we estimate that conservatively 30% of patients will have post-extubation aspiration; resulting in a cohort of approximately 225 ARF survivors with aspiration. Baseline clinical and FEES assessments of laryngeal structure and pharyngeal/laryngeal function will be considered as class-defining variables in an unsupervised clustering/classification framework. Statistical analyses will be conducted using R. We will fit a series of models using all of the enrolled subjects, starting with a 1 class solution and sequentially increasing to K classes, where K is the largest number supported by the data. Criteria for model selection will based on the Bayesian Information Criteria, the Vuong-Lo-Mendell-Rubin (VLMR) likelihood ratio test, and the size of the smallest class. The best fitting classification model will be interpreted in terms of class homogeneity (i.e., similarity among those assigned to the same class) and separation (i.e., differences between those assigned to different classes) and will be inspected for classification certainty by evaluating model entropy and the classification probabilities for each class.

How will we account for missing data? Based on the results of our previous trial, missing data will occur. For example in the derivation of our diagnostic algorithm, 25% of patients were missing at least one data point. The majority of missing data was from the larger volume liquid and solid consistency trials in the BSE and FEES when the patients had aspiration concerns with lower volumes. Since we will not be performing the BSE, we anticipate have less missing data. We will use a modified version of regression-based imputation.[101]

1. We will regress the non-missing data against selected predictors from the fields with no missing data. Regression models will be selected by forward stepwise selection with AICc as the selection criterion.[102] AICc, a sample-size-corrected version of AIC, is a fairly liberal model selection criterion compared to BICand variants such as ICL-BIC; the purpose here was to ensure that all relevant predictors were included.[103]
2. From the regression models, we will predict the missing elements using the corresponding predictor elements. Continuous predictions will be rounded as appropriate, and negative predictions will be set to zero since none of the fields in the data can take negative values.

3. For each regression, we will calculate the pseudo-R^2 value. The pseudo-R^2 will be used in preference to simple R^2 for the linear regression models to maintain consistency with the multinomial regression models.[104]
4. We will calculate a quality score for the fields with imputed values as the product of the pseudo-R^2 and the proportion of non-missing elements. Fields with a high regression pseudo-R^2 and few missing elements will be considered more reliable for further analysis.

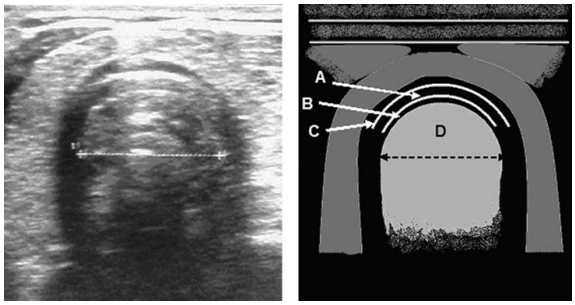
Incorporating outcomes: Once the number of classes are determined, the associations between class and clinical outcomes listed on the previous page will be examined using a method that accounts for uncertainty in class specification.[105-108] This method incorporates the degree of uncertainty of class membership.

Sample size: Preliminary data suggest we should be able to classify patients into 3-4 clusters, and that these clusters will be of unequal size. Assuming we arrive at 3 clusters with a class allocation of 1:3:5, our sample size of N=225 will yield 80% power to detect a standardized effect (Cohen's f) of f=0.20 in each of our outcomes. If instead we arrive at 4 clusters with a class allocation of 1:2:3:4, we will have 80% power to detect a difference of f=0.22 between clusters for each outcome.

Alternative Analysis: As an alternative analysis to unsupervised clustering approach, we will utilize elastic net penalized regression models to assess directly which variables or groups of variables are associated with each of the longitudinal outcomes listed above. Models will be tuned using 10-fold cross validation. For these elastic net models, the issue of correlated features (of which we expect many) will be mitigated by the ridge (L2) component of the penalty. Features that are not at all related to the outcome will be deselected by the L1 (lasso) component of the penalty. This result will yield a sparse prediction equation for each outcome.

Anticipated Results, Limitations, Additional Considerations, and Future Directions: Similar to our preliminary data, we anticipate that we will identify at least three distinct phenotypes with different trajectories of recovery. One limitation is that we are not performing electrophysiological assessments of swallowing muscles. These procedures are difficult to perform and the needle examination would likely decrease participation enthusiasm for the study. If there is a phenotype that is more characterized by laryngeal edema, then those ARF survivors should have a more rapid recovery than those characterized by weakness. As an additional consideration, we will collect a peripheral neuromuscular examination and determine whether peripheral neuromuscular weakness in swallowing (defined as decreased pharyngeal medialization) occurs in those patients with peripheral weakness. We could also consider performing diaphragmatic ultrasonography, again to see if upper airway neuromuscular weakness is associated with diaphragmatic weakness. We could also perform additional analyses for the patients with dysphagia (PAS score of 3-5), to see if subphenotypes exist for the cohort of patients with dysphagia but not aspiration. Future studies could determine whether the suphenotypes are stable over time, and whether they respond differently to interventions. For example, an edema subphenotype, may be more responsive to corticosteroids, and a neuromuscular weakness subphenotype may be more responsive to therapeutic exercises or electrical stimulation.

Additional Methods for Specific Aim #3: To determine the effects of an ultrasound determined ETT size/tracheal diameter ratio upon post-extubation aspiration while accounting for other potential confounders. We hypothesize that a higher ETT size/tracheal diameter ratio will be associated with an increased risk of post-extubation aspiration. ETT size selection will be at the discretion of the treating physician. Based on our two studies involving over 250 patients, there is sufficient variability in the ETT size in this patient population (see section 11 of our Preliminary Data).[10,63]



Primary independent variable: ETT size/tracheal diameter ratioprior to extubation, we will perform an ultrasound to measure tracheal diameter. Ultrasonography measurements will be performed in B-mode with a linear probe (40 mm length, frequencies 7–15 MHz) placed on the midline of the anterior neck. To avoid any confusion between the cricoid cartilage and a tracheal ring, the procedure will begin with the location of the true vocal folds (paired hyperechoic linear structures with respiratory and swallowing mobility).[20] Then, the probe will be moved caudally to visualize the cricoid arch. The transverse air-column diameter will be measured at the cephalic half of the cricoid cartilage which is narrower than the caudal part (Figure 7) (4,6). We know the external diameter of each of the ETTs that will be used in this study (see Table 7). None of the sites use ETTs with externally attached suction ports or other specialized ETT. However, if practice changes, we will adjust the external diameter of the ETT accordingly. The tracheal diameter and external diameter of the ETT will be measured in millimeters. By dividing the external diameter of

the ETT by the external diameter of the trachea, we will determine the ETT/tracheal diameter ratio. For example, if the tracheal transverse diameter is 15.1 mm, and the patient has an 8.0 ETT (external diameter of 11.0 mm), the ratio would be 11.0/15.1 or 72.8%.*To standardize the timing of the ultrasound, all ultrasound images will be obtained prior to extubation during a spontaneous breathing trial.* We will then upload all images to our already established cloud-based, encrypted, HIPAA compliant and University of Colorado information technology approved Citrix ShareFile.

Strategies to ensure interrater reliability for the ultrasound measurements of tracheal diameter: We will utilize similar strategies to our prior FEES training to maintain rigor and reproducibility in the ultrasonographic procedure and the tracheal diameter measurements across the four sites: 1) Ultrasonography has become a common test performed by critical care personnel. We will limit the test performance to a few trained ultrasound hospital-certified personnel (mainly the site PIs). 2) A tracheal ultrasound manual will be developed. 3. Dr. Moss will conduct individual virtual training sessions for each designated investigator. He will observe each investigator until they are able to implement the protocol independently. Using the saved images, interrater and intra-rater reliability will be established among the raters until agreement of at least 80% is reached. 4. On our monthly calls, we will review cases and videos to assure protocol consistency.

TABLE 7: ETT Diameters

Internal Diameter (mm)	External diameter (mm)
6.0	8.2
6.5	8.8
7.0	9.6
7.5	10.2
8.0	11.0
8.5	11.6

Figure 7: Cricoid cartilage is a round hypoechoic structure (the medulla (A)) with hyperechoic edges (the internal (B) and external (C) perichondrium). The air-column (D) appeared hyperechoic and created a posterior acoustic shadow. The dotted line represents the measured air-column width.

Additional confounding variables collected as part of this cohort study.
1. ETT cuff pressures: ETT cuff pressures may be associated with post-extubation complications. The ETT cuff pressures are recorded every four hours at all study hospitals by respiratory therapists and recorded into the medical record. We will classify patients by their average daily ETT cuff pressure.
2. Presence of naso or oral-gastric tube: classified as naso/gastric/none; and type of tube: Dobhoff vs. other.
3. Presence of esophageal temperature probe, esophageal balloon manometer to measure pleural pressures, performance of transesophageal echocardiogram, and other esophageal tubes when placed, such as a Blackmore tube for esophageal varices, and EGD examinations: each classified as Yes/no.
4. We will also examine other medically important variables such as malnutrition at the time of hospital admission using the Nutritional Risk Index, recent ICU admission in the prior 3 months, the duration of enteral feeds during the current ICU admission, COVID-19 status, and re-intubation.[109]

Primary Outcome Variable: Aspiration (PAS score of ≥6) on the FEES with any of the feeding consistencies. A PAS score of ≥ 6 includes patients with both silent and non-silent aspiration.[88]

Secondary Outcomes: 1. Aspiration subsets: We will stratify patients who aspirate into non-silent (PA = 6- 7) and silent (PAS=8) aspiration, and also determine maximum PAS scores across bolus and consistency types.
2. Post-extubation clinical laryngeal edema: We will define laryngeal edema as upper-airway obstruction within 24 hours after extubation. Minor laryngeal edema will be defined as stridor associated with a respiratory distress defined as a prolonged inspiratory phase and the presence of edema on FEES examination. Major laryngeal edema will defined as severe respiratory distress needing tracheal reintubation secondary to upper-airway obstruction that was visualized during the FEES examination.[62,110]
3. Other standard ICU outcomes: We will also collect the overall length of mechanical ventilation and the length of the liberation process from mechanical ventilation (both in days).

Statistical Analysis: The primary outcome (aspiration) will be modeled using a multivariable logistic regression with ETT size/tracheal diameter ratio as one independent variable, and the confounders mentioned in the section above included as other predictor variables. The endpoint of interest will then be estimated by the odds ratio for a one standard deviation increase in the ETT size/tracheal diameter ratio controlling for relevant confounders. Inference will be performed using likelihood ratio tests and profile likelihood confidence intervals. If insufficient variation is observed in the confounding variables, or if certain confounders are highly correlated creating partial or complete separation in the predictor space, we will pre-process these variables as needed prior to including them in the final model. This same modeling framework will be used to test the impact of ETT size/tracheal diameter ratio on non-silent and silent aspiration separately. Further, we will treat maximum PAS score across boluses and feeding consistencies as an ordinal outcome, modeled using a cumulative

link ordinal logistic regression model (CLM). The CLM tests a slightly different hypothesis than our primary analysis, estimating the effect of our covariate of interest on the odds of having a more severe aspiration outcome controlling for relevant confounders. A similar CLM will be used to model post-extubation clinical laryngeal edema (none, minor, and major), as an ordinal outcome with the same covariates. In these CLMs, the proportional odds assumption will be tested and relaxed if needed. Finally, we will model the overall length of mechanical ventilation and the length of the liberation process from mechanical ventilation using generalized linear models (GLMs), where we will select link functions that are best suited to the observed distributions of these variables. All analyses will be performed in the R software (version 4.0+).

Sample Size: Our data suggest that we can expect an aspiration prevalence of 30%. Assuming 30% aspiration, a 5% level of significance, and that the proportion of variance explained (R^2) in the primary covariate of interest by the confounders is no greater than 50%, our sample of 750 patients with complete outcome data will yield at least 80% power to detect an odds ratio of 1.4 or greater for a 1 SD increase in the ETT size/tracheal diameter ratio. If the R^2 for ETT size/tracheal diameter ratio is 25%, the detectible effect decreases to an odds ratio of 1.3, and if the R^2 is 0 (i.e. if the ETT size/tracheal diameter ratio is independent from the confounders), we will have 80% power to detect an odds ratio of 1.25 for our primary endpoint. These power calculations assume the ETT size/tracheal diameter ratio is approximately normally distributed.

Anticipated Results, Limitations, Additional Considerations, and Future Directions. We anticipate that a higher ETT tube/tracheal diameter ratio will be significantly associated with post-extubation aspiration and possibly with laryngeal edema. If we are correct, then tracheal ultrasound could be utilized prior to intubation to measure tracheal diameter and select the optimal sized ETT. We will also obtain serial tracheal ultrasound to see if tracheal diameter changes over time. We believe that this is unlikely as trachea is a cartilaginous structure. We will determine the effect of ETT cuff pressure and the placement of other esophageal devices on post-extubation aspiration. One limitation is we are measuring tracheal size, where measures of laryngeal size or diameter may be more relevant. However, tracheal diameter is related to laryngeal size. We will consider using ultrasound to measure laryngeal structures and examine the relationship between neck circumference or Mallampati scores at the time of intubation on the development of post-extubation aspiration.[111,112] *By utilizing tracheal ultrasound prior to intubation, these results would enhance care, reduce deleterious sequelae of intubation, and change the practice for all patients that require intubation for ARF.* We may also perform neuromuscular examinations to determine if peripheral weakness correlates with post-extubation aspiration. If so, then a measure of weakness such as dynamometry could screen for post-extubation aspiration.

This proposal meets the NIH requirements for rigorous and reproducible research. Based on our prior clinical trial experience, all four of our research groups maintain excellent protocol compliance and safety of our research subjects. Our biostatistician and data managers are integral members of our research team. Our ability to effectively perform the R21 award demonstrates that we conduct rigorous and reproducible research. In addition, we have developed a comprehensive training program in order to maintain excellent protocol fidelity that was implemented in our R21 grant, successfully. Due to the sex differences in ARF survivors, the majority of subjects (60%) will be male. We will analyze our data by sex separately and report sex differences observed. The proposal timeline is displayed in Table 8.

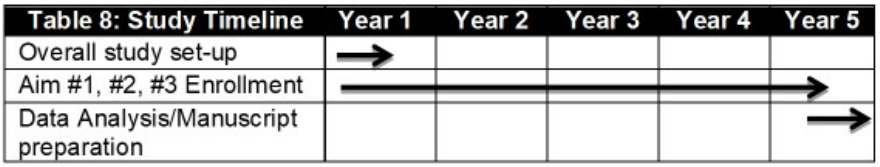


Table 8: Study Timeline	Year 1	Year 2	Year 3	Year 4	Year 5
Overall study set-up	→				
Aim #1, #2, #3 Enrollment	→	→	→	→	→
Data Analysis/Manuscript preparation					→

1. Screening and recruitment:

Patients meeting enrollment criteria will be approached for informed consent no later than 72 hours after extubation. Surrogate consent may be used if patients are unable to provide their own informed consent.

If patients meet an exclusion criterion, they can be re-evaluated to determine if the exclusion criteria no longer exists; up to 72 hours after extubation. The presence of delirium is the one exclusion criterion that is most likely to change over time and require repeated assessments. CAM-ICU Flow Sheet is attached as an appendix.

There is no minimal amount of time that is required after extubation to be enrolled into the study (as long as the patient meets the inclusion criteria and does not currently meet any of the exclusion criteria.

After enrollment, the research coordinator should complete the demographic information on the Case Report Forms. No fields on the Case Report Forms should be left blank. The research coordinator should also contact and the SLP who will perform the BSE screening tests, and the second SLP who will perform the FEES. The research coordinator should arrange a specific time that the BSE and FEES will be performed.

Screening and recruitment techniques:
Every new ICU admission receiving mechanical ventilation will be screened. This will include but not be limited to admissions from the ED, wards, and operating room. We will also assess patients transferred from outside hospitals. The enrollment window for these patients will include the time during admission at the outside hospital and during transfer.

The research coordinators or site PI will meet with the new incoming groups of ICU residents as part of their unit orientation. During this time, the residents will be alerted to each of the study inclusion and exclusion criteria. We would also recommend developing printed laminated cards with important study related and contact for the housestaff and other key members of the ICU teams. Each day, the research coordinator will identify each patient who is endotracheally intubated and receiving mechanical ventilation for at least 48 hours. Patients will then be followed until they are extubated.

At the time of extubation, the patient by definition meets inclusion criteria for the study. At this point the patient should be entered into the screening log in one of several ways
1. If they meet a permanent exclusion criteria, they should be entered as be excluded from the study
2. If they meet a potentially transient exclusion (like altered mental status), they should be followed for up to 72 hours after exclusion to determine if the exclusion criteria resolves. If it resolves they should approached for enrollment
3. If the patient meets no exclusion criteria, they should be approached about study participation.
4. If they agree to participate and sign the consent form then they are enrolled into the study.
5. If they decline to participate, then they should be entered as an excluded patient.

Inclusion Criteria:

1. Admission to an ICU.
2. Mechanical ventilation with an endotracheal tube for greater than 48 hours

Exclusion Criteria:

1. Contraindication to enteral nutrition administration.
2. Pre-existing history of dysphagia or aspiration.
3. Pre-existing or acute primary central or peripheral neuromuscular disorder.
4. Presence of a chronic tracheostomy (present prior to ICU admission).
5. Pre-existing head and neck cancer or surgery.
6. Coagulopathy resulting in uncontrolled nasal or pharyngeal bleeding.
7. Delirium for more than 72 hours after extubation as assessed by CAM-ICU.
8. Extubated for greater than 72 hours.
9. Inability to obtain informed consent from patient or an appropriate surrogate.
10. Age < 18 years.

Informed consent:
Obtaining informed consent is a process that is reviewed by the appropriate members of our research team on a monthly basis. All of the personnel involved in screening and patient identification have successfully completed the on-line course on the Responsible Conduct of Research. Informed consent will be obtained from each patient or legally authorized representative (LAR) prior to enrollment in the trial. No study procedures will be done prior to obtaining informed consent. Permission to approach patients and/or LARs will be requested from the attending physicians.

If possible, see if one of the patient's doctors can introduce you to the patient and/or their surrogate decision maker. In general our methods for obtaining informed consent include the following: 1. identification and contact of appropriate parties to perform informed consent, 2. arrangement of a mutually acceptable meeting time with this party in a private conference room or in the patient's room, and 3. a lengthy discussion between the study investigator and the interested party. The discussion includes an update of the patient's overall condition justifying the rationale for inclusion of the patient into the specific trial. The consent form is reviewed in detail including the background information and rationale regarding the specific intervention of the study, potential risks and options. Patients or their representatives are informed of their rights as a research subject and are informed of their ability to discontinue study participation at any time throughout the trial. Subjects or their representatives are given the opportunity to ask any questions regarding the verbally described consent form. Following this discussion, opportunity is given to privately read the consent form. If the patient or representative is illiterate, the consent form is read to them. After sufficient time, an additional question and answer session is performed if needed.

A few key points to the informed consent process.

1. Sit down when you are taking to the patient and/or surrogate.
2. Explain who you are and that you normally work with patients in the intensive care unit.
3. Explain that you are here to help determine if the patient is swallowing normally.
4. Explain that difficulty swallowing is common after being on a breathing machine
5. State that the standard tests to determine whether someone can swallow properly after being on a breathing machine are to have a nurse or speech therapist to observe a person swallow liquids and foods of different consistencies. However, these tests are not perfect. Sometimes it appears that the patient can eat normally, and they are actually swallowing things down the wrong tube (into their lungs), Other times, it appears that the patient is not swallowing properly when they actually are swallowing properly.
6. In addition to this normal swallowing exam, there is an additional simple test we can do that is above and beyond the normal swallowing exam. This additional technique will definitively identify if someone is swallowing normally, and allow us to identify the correct strategy for eating. Sometimes we do this test as part of the normal patient swallowing evaluation.
7. The test is simple and down right here in the patient's room. It takes 5-10 minutes and the patient can watch the test if they want. We will put a very small tube (like a very thin straw) down the back of the throat so we can see your vocal cords. We will then have you swallow liquids and foods of different consistencies and see if the material is actually going down the wrong tube.
8. Share these results with your doctors so they have the additional information and can use the information to potentially take better care of you in regard to your feeding and swallowing.

If the patient agrees to the study, then the coordinator should contact the SLP who will perform the bedside screening tests, and the second SLP who will perform the FEES.

STUDY PROCEDURES:

1. Baseline assessments:

This information will be collected by the study coordinator at the time of enrollment.

Patient Age
Patient Gender
Patient Race
Patient Height
Patient Weight
Primary Service
Hospital Admission Date
ICU Admission Date
Intubation Date and Time
Size of the Endotracheal Tube
Extubation Date and Time
Previous reintubation (y/n)
APACHE II score
Charlson Comorbidity Index

Next, a SLP will perform three screening tests on each ARF survivor, and a second blinded SLP will perform the FEES to determine whether aspiration is truly present. The order of the beside evaluations will be randomized. The reason for the random order of the tests is that after several swallows, a patient who has not eaten orally in several days or weeks will start to do better as the system "wakes up". If one screening test is always performed before the other screening tests, it might lead to a false result – it would show more aspiration on the BSE than the FEES. But it won't be because the BSE was showing a false positive; in fact it is just that the patient started to improve by the time he got the second screening test.

2. Bedside Evaluation:

Screening Test A. Our five-item decision tree algorithm: Three of the components (length of mechanical ventilation, APACHE II score, type of ICU) will be extracted from the medical record. The SLP will then assess the voice quality and

perform the 2-ounce water consistency assessment. The voice quality will be scored as (normal vs. abnormal defined as aphonic, hoarse, or wet). The 2-ounce water test will be administered via a straw controlled by the patient. The SLP may assist in holding the cup. The SLP will wait for 10 seconds following the completion of the trial before recording the results for that consistency. Five outcomes (cough, throat clearing, vocal quality change, change in breath sounds, or stridor) will be recorded.

Coughing: Dichotomized as a single cough within 10 seconds after diet administration (yes/no).

Throat Clearing: Dichotomized as a throat clearing sound within 10 seconds after diet administration (yes/no).

Change in vocal quality: Baseline vocal quality will be assessed initially and dichotomized as normal/abnormal. Transitions from normal to abnormal vocal quality during feeding will be recorded.

Change in breath sounds: Breath sounds will be assessed before and 10 seconds after the examination by auscultating over the larynx at the thyro-cricoid space during quiet breathing. Patients will be classified as "gurgling" or "non-gurgling." Gurgling is a low/medium-pitched rattling sound on inhalation or exhalation.[81]

Stridor: Dichotomized as present or absent in 10 seconds.

TABLE 4: Comparison of Three Screening Tools

Our Algorithm	3-WST	TOR-BSST
Our 2-oz. water test	3-oz. water test	The TOR-BSST 2-oz. water test
Length of ventilation		Tongue movement
APACHE II		Baseline voice
Voice quality		Post voice
Type of ICU		

Screening Test B. Three-Ounce Water Swallow Test (3-WST): Championed in ARF patients by our Yale colleagues, the 3-WST will be performed according to standard procedures. Patients will receive three ounces of water and will be instructed to drink the entire amount, via a cup or straw, completely and without interruption (the cup can be held to the patient's mouth by the SLP).[74;76;109] The 3-WST will be scored as pass/fail. Criteria for failure of the 3-WST are: the inability to drink the entire amount, coughing or choking up to 1 minute after completion, or the presence of a wet-hoarse vocal quality.

Screening Test C. Toronto Bedside Swallowing Screening Test (TOR-BSST): Though originally developed for stroke patients, the TOR-BSST has been used more broadly for other patient populations.[12,82,83] More recently, the TOR-BSST was studied in critically ill patients (manuscript currently under review). Designed to be administered by nurses, we will have our study SLPs complete the 4-hour TOR-BSST training program. Dr. Rosemary Martino (TOR-BSST developer) will provide our study SLPs access to the TOR-BSST educational videos and modules to enhance study fidelity (see Dr. Martino's letter of support). For consistency, we will have study SLPs assess each of the four components of the TOR-BSST; including assessment of baseline voice, tongue movement, ability to swallow water and post-voice quality. The ability to swallow water is assessed using the 2-ounce water swallow test according to the TOR-BSST protocol.

3. FEES examination: The SLP will review the subject's medical record and become knowledgeable with the patient's medical history. The FEES examination will be performed by a second SLP who is blinded to the results of the BSE. The FEES should be performed within approximately 4 hours of the BSE.

Similar to the BSE, the patient should be seated with the head of the bed as elevated as possible. At the discretion of the SLP/investigator, Afrin and Lidocaine spray can be administered into the nasal passage before the laryngoscope is inserted. The use of these medications will be noted in the case report form.
Part 1: First the SLP will perform and videotape the examination of the upper airway.

Velar closure, base of the tongue retraction, laryngeal elevation, right and left vocal cord/arytenoid mobility, right and left pharyngeal wall medialization, epiglottic retroflexion, granuloma formation, and upper airway edema will be assessed. Laryngeal sensation will be assessed by observing the laryngeal adductor reflex (LAR) or a patient response to a light touch/poke to the aeryepiglottic folds bilaterally with the tip of the laryngoscope, and scored dichotomously.

Part 2: Standardized consistency testing: The SLP will then administer five standard consistencies in two trials of each consistency with different amounts.[106]

Boluses will be administered from lowest to highest aspiration risk: 1) ½ tsp, then 1 tsp ice chips , 2) 1 tsp of nectar thick liquids, then 3 tsp of nectar thick liquids, 3) a 2 ounce patient controlled administration of nectar thick liquids, 4) 1 tsp of pureed solids (applesauce), then 10 mls of pureed solids (applesauce), 5) 5 mls of thin liquids (water or milk),15 mls of thin liquids (water or milk), and a 2 ounce patient controlled administration of thin liquids and 6) ¼ of a graham cracker.[107] The patient will be instructed to chew the graham cracker before swallowing. In order to limit the complexity and duration of our consistency testing, honey-thick liquids will be excluded from the protocol.

Table 3: PAS scoring system

Scale	Enters airway?	Relationship to vocal folds	Ejected from airway?	Effort made to eject?
1	No	--	--	--
2	Yes	Above	Yes	--
3	Yes	Above	No	--
4	Yes	Contacting	Yes	--
5	Yes	Contacting	No	--
6	Yes	Below	Yes	--
7	Yes	Below	No	Yes
8	Yes	Below	No	No

After the swallow, the laryngoscope will be advanced to closely view the partient's airway. The SLP will wait for 10 seconds following the completion of each individual trial before recording the results for that consistency. If necessary, patients will be allowed to drink water between consistency tests to clear any remaining residue from their upper airway

The entire FEES will be video recorded. The SLP will score each of the trials using the PAS score.

In addition for each of the trials of the consistencies, the SLP will record the following two physiological measures:

1) Swallowing onset time: The time from first bolus visualization until swallow onset.

2) Incomplete bolus clearance: leaving residue in the pharynx or laryngeal vestibule after a swallow.

Using the video recordings, the quantification of the swallowing onset time and incomplete bolus clearance will be determined by a single observer.

The results of the different components of the FEES assessment will be made available to the treating team if requested. The coordinator should make sure that the FEES CRF is completely filled out before the SLP who completed the test leaves the ICU. See Appendix for FEES evaluation form.

4. Outcome Assessments

All patients will be followed for the subsequent outcome assessments.
Date of ICU discharge
ICU length of stay
Date of hospital discharge
Hospital length of stay
Discharge location
Reintubation since enrollment
    If yes, date of reintubation
Died during ICU stay
Died during hospital stay
Surgical feeding tube placed?

Human Subjects

Each study participant or a legally authorized representative (LAR) must sign and date an informed consent form. Institutional review board approval will be required before any subject is entered into the study. PETAL will use a central IRB.

Selection of Subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The ICUs will be screened to determine if any patient meets inclusion and exclusion criteria. Data that have been collected as part of the routine management of the subject will be reviewed to determine eligibility. No protocol-specific tests nor procedures will be performed as part of

the screening process. If any subjects meet criteria for study enrollment, then the attending physician will be asked for permission to approach the patient or his/her LAR for informed consent. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals from participation in the research. Hence, the recruitment of subjects conforms to the principle of distributive justice.

Justification of Including Vulnerable Subjects

The present research aims to investigate the ability of a bedside evaluation to detect aspiration in acute respiratory failure survivors. Due to the nature of acute respiratory failure and its risk factors (eg, sepsis, trauma), some patients will have impaired decision-making capabilities. This study cannot be conducted if limited to enrolling only those subjects with retained decision-making capacity. Hence, subjects recruited for this trial are not being unfairly burdened with involvement in this research simply because they are easily available.

Informed Consent

Federal regulations 45 CFR 46.111(a)(5) require that informed consent will be sought from each prospective subject or the subject's legally authorized representative (LAR). As we will enroll patients recovering from acute respiratory failure, we anticipate initial informed consent will frequently be obtained from LARs. Consent will be obtained via face-to-face meeting. Patients who survive and regain decision-making capacity before hospital discharge will be approached for re-consent. At this point, subjects may choose to continue with study participation or withdraw from the study. Subjects who opt not to continue will be asked if their collected data to the point of withdrawal request, may be used in the primary analysis. If the subject does not agree, the data will be destroyed.

The investigator is responsible for ensuring that the LAR understands the risks and benefits of participating in the study, answering any questions the LAR may have throughout the study and sharing any new information in a timely manner that may be relevant to the LAR's willingness to continue the subject's participation in the trial.

The study team will make every effort to minimize coercion. All study participants, or their LARs, will be informed of the objectives of the study, all procedures, and voluntary nature of participation. The informed consent discussion will be used to explain study risks and benefits before the patient is entered into the study and documenting that the LAR is satisfied with his or her understanding of these risks and benefits, rights of a participant and consents to participate in the study.

Continuing Consent

For subjects for whom consent was initially obtained from a LAR, who subsequently regain decision-making capacity while in hospital, all sites will obtain written informed consent for continuing participation, inclusive of continuance of data acquisition. The initial consent form signed by the LAR will reflect that such consent will be obtained.

Withdrawal of Consent

Patients may withdraw or be withdrawn (by the LAR) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis, unless consent to use their data has also been withdrawn. If a patient or LAR requests termination of the trial during the study period, the study will be stopped but the patient will continue to be followed up as part of the trial. If a patient or LAR withdraws consent during trial treatment, the trial will be stopped but permission will be sought to access medical records for data related to the study. If a patient or LAR wishes to withdraw from the trial after completion of trial treatment, permission to access medical records for study data will be sought.

Identification of Legally Authorized Representatives

Many of the patients approached for participation in this research protocol may have limitations of decision-making abilities due to their critical illness. Hence, we anticipate most patients will not be able to provide informed consent at time of study eligibility. Accordingly, informed consent will be sought from the potential subject's legally authorized representative (LAR).

Regarding proxy consent, the existing federal research regulations ('the Common Rule') states at 45 CFR 46.116 that "no investigator may involve a human being as a subject in research…unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative"; and defines at 45 CFR 46 102 (c) a legally authorized representative (LAR) as "an individual or judicial or other body authorized under applicable law to

consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research." OHRP defined examples of "applicable law" as being state statutes, regulations, case law, or formal opinion of a State Attorney General that addresses the issue of surrogate consent to medical procedures. Such "applicable law" could then be considered as empowering the LAR to provide consent for subject participation in the research. Interpretation of "applicable law" may be state specific and will be addressed by the IRB.

According to a previous President's Bioethics Committee (National Bioethics Advisory Committee), an investigator should accept as an LAR,a relative or friend of the potential subject who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place (National Bioethics Advisory Commitee (NBAC), 1998). Finally, OHRP has stated in their determination letters that a surrogate could serve as a LAR for research decision making if such an individual is authorized under applicable state law to provide consent for the "procedures" involved in the research study (Office of Human Research Protections (OHRP), 2002).

Each participating site will defer to their institutional requirements for designation of LAR.

Justification of Surrogate Consent

According to the Belmont Report, respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that person with diminished autonomy are entitled to protection. One method that serves to protect subjects is restrictions on the participation of subjects in research that presents greater than minimal risks. Commentators and Research Ethics Commissions have held the view that it is permissible to include incapable subjects in greater than minimal risk research as long as there is the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits ***similar*** to that available in the clinical setting (Dresser, 1999). Several U.S. task forces have deemed it is permissible to include incapable subjects in research. For example, the American College of Physicians' document allows surrogates to consent to research involving incapable subjects only "if the net additional risks of participation are not substantially greater than the risks of standard treatment." (American College of Physicians, 1989). Finally, the National Bioethics Advisory Committee (NBAC) stated that an IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefits to the subject, provided that…the potential subject's LAR gives permission…" (National Bioethics Advisory Committee (NBAC), 1998)

Consistent with the above ethical sensibilities regarding the participation of decisionally incapable subjects in research and the previous assessment of risks and benefits in the previous section, the present study presents a balance of risks and potential direct benefits that is ***similar*** to that available in the clinical setting.

Additional Safeguards for Vulnerable Subjects

The present research will involve subjects who might be vulnerable to coercion or undue influence. As required in 45CFR46.111(b), we recommend that additional safeguards be included to protect the rights and welfare of these subjects. Such safeguards might include, but are not limited to: a) assessment of the potential subject's capacity to provide informed consent, b) the availability of the LAR to monitor the subject's subsequent participation and withdrawal from the study; c) augmented consent processes. The specific nature of the additional safeguards will be left to the discretion of the central IRB, in conjunction with the sites.

Confidentiality

Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. To maintain confidentiality, all laboratory specimens, evaluation forms, and reports will be identified only by a coded number. The coded number will be generated by a computer, and only the study team will have access to the codes. All records will be kept in a locked, password protected computer. All computer entry and networking programs will be done with coded numbers only. All paper case report forms will be maintained inside a locked office or electronically secured in a REDCap database. Study information will not be released without the written permission of the patient, except as necessary for monitoring by the National Heart, Lung, and Blood Institute, and the PETAL Clinical Coordinating Center.

Adverse Events

Safety Monitoring

Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his or her care. The Investigators will determine daily if any adverse events occur during the period from enrollment through **study day 2** or ICU discharge, whichever occurs first.

The following adverse events will be collected in the adverse event case report forms:

- Serious adverse events
- Nonserious adverse events that are considered by the investigator to be related to study procedures or of uncertain relationship

A clinical study adverse event is any untoward medical event associated with the study procedure in humans, whether or not it is considered related to a study procedure.

Adverse events related to protocol procedures must be evaluated by the investigator. If the adverse event is judged to be reportable, as outlined above, then the investigator will report to the medical monitor their assessment of the potential relatedness of each adverse event to protocol procedure. Investigators will assess if there is a reasonable possibility that the study procedure caused the event, based on standard criteria. Investigators will also consider if the event is unanticipated or unexplained given the patient's clinical course, previous medical conditions, and concomitant medications.

If a patient's participation in the study is discontinued as a result of an adverse event, study site personnel must report the circumstances and data leading to discontinuation of treatment in the adverse event case report forms.

Serious Adverse Events

Serious adverse event collection begins after the patient or surrogate has signed informed consent and has undergone study procedures. If a patient experiences a serious adverse event after consent, but prior to the start of the study, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

Study site personnel must alert the medical monitor of any **serious and study procedure related** adverse event within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on the adverse event case report form.

As per the FDA and NIH definitions, a serious adverse event is any adverse event that results in one of the following outcomes and is not classified as a clinical outcome of acute respiratory failure using the definitions noted above:

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Prolonged inpatient hospitalization or rehospitalization

  As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Persistent or significant disability/incapacity

  As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events will be collected during the first **2 study days** or until ICU discharge, whichever occurs first, regardless of the investigator's opinion of causation. Thereafter, serious adverse events are not required to be reported unless the investigator feels the events were related to either study drug or a protocol procedure.

APPENDIX: Case Report Forms

Refer to separate Appendix document: 21-3873 Moss Appendix CRF 07142021.pdf

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