Study:	***LOw Tidal volume Universal Support: Feasibility of RecrUitment for Interventional Trial***
Acronym:	***LOTUS FRUIT***
Version:	***II***
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1. ABBREVIATIONS & DEFINITIONS

1.1 Abbreviations

ABG = Arterial blood gas
ARDS = Acute Respiratory Distress Syndrome
ARMA = ARDSNet's Respiratory Management 6mL/kg vs 12mL/kg tidal volume study
ED = Emergency Department

FiO_2 = Fraction of Inspired Oxygen

ICU = Intensive Care Unit

IMV = Invasive Mechanical Ventilation

LOTUS = = LOw Tidal volume Universal Support

LOTUS FRUIT = LOw Tidal volume Universal Support: Feasibility of RecrUitment for Interventional Trial

LUNG-SAFE = Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE

NHLBI = National Heart Lung and Blood Institute

PETAL = Prevention and Early Treatment of Acute Lung Injury

OR = Operating room

P/F = PaO2/FiO2 ratio

$PaCO_2$ = Partial pressure of arterial carbon dioxide

PACU = Post anesthesia care unit

PaO_2 = Partial pressure of arterial oxygen

PBW = Predicted Body Weight

PEEP = Positive End-Expiratory Pressure

PS = Pressure Support Ventilation

S/F = SpO2/FiO2 ratio

SOFA = sequential organ failure assessment

SBP = Systolic Blood Pressure

SpO_2 = Oxygen Saturation via pulse oximetry

VFD = Ventilator-free Day

1.2 Definitions

Controlled Ventilation: Any mode with a backup rate and allows clinicians to either set tidal volume to a target or adjust pressures to target a tidal volume. Examples include volume assist control, pressure assist control, and pressure regulated volume control.

Extubation: Removal of an orotracheal tube, nasotracheal tube, or unassisted breathing with a tracheostomy

Home: Level of residence or health care facility where the patient was residing prior to hospital admission.

Invasive Mechanical Ventilation (IMV): Assisted positive pressure ventilation delivered by a nasotracheal, orotracheal, or tracheostomy tube

Mortality at hospital discharge: This includes deaths from all causes at the time of discharge from the hospital.

Funder: National Institutes of Health and the National Heart Lung and Blood Institute

Study Day: The day of intubation is study day zero. The next day is study day one etc.

Study hospital: Defined as the hospital where the patient was enrolled.

UAB (Unassisted Breathing): Spontaneously breathing with face mask, high flow, nasal prong oxygen, room air, T-tube breathing, tracheostomy mask breathing, CPAP ≤ 5 cm H_2O without pressure support (PS) or IMV assistance, or the use of noninvasive ventilation solely for sleep-disordered breathing.

2. PROTOCOL SUMMARY

Title: LOw Tidal volume Universal Support: Feasibility of RecrUitment for Interventional Trial (LOTUS FRUIT)

Objective: An assessment of hospital mechanical ventilation practices:

1. To inform the design and plan for a pragmatic interventional cluster randomized control trial of low tidal volume ventilation in the emergency department and intensive care unit.
2. To determine the feasibility of data collection for patients with acute respiratory failure in a pragmatic trial.

Hypothesis: Hospitals are not compliant with lung protective low tidal volume ventilation in acute respiratory failure.

Study Design: Multicenter, observational study to collect data on all consecutive patients who meet study criteria over a period of 30 days.

Inclusion Criteria: Patients must meet all inclusion criteria:

1. Age ≥ 18 years
2. Patients with acute respiratory failure requiring invasive mechanical ventilation via an endotracheal tube in the hospital
3. Patients who will receive care in the intensive care unit after intubation (ie: the patient was either intubated in the intensive care unit or will be admitted or transferred to an intensive care unit on mechanical ventilation, if intubation did not occur in the intensive care unit.)

Exclusion Criteria: Patients who meet one or more of the following criteria will be excluded from the cohort:

1. Patients undergoing chronic mechanical ventilation
2. Patients who are extubated prior to transfer to the ICU
3. Patients intubated outside of the study hospital and presented to the study hospital with more than 24 hours of invasive mechanical ventilation prior to presentation
4. Patients being cared for in an ICU that could not participate in a low tidal volume protocol under LOTUS
5. Patients admitted to an ICU after elective surgery

3. PROTOCOL DESCRIPTION

3.1 Background

Mechanical ventilation is necessary to assist critically ill and injured patients who cannot breathe on their own. However, mechanical ventilation may damage the lung, cause inflammation, and release cytokines into the systemic circulation.[1] Lung protective ventilation is an approach that limits tidal volume and distending pressure on the alveolus in order to prevent mechanical ventilation induced volutrauma (damage due to high tidal volume) and barotrauma (damage due to high pressures).

Lung protective ventilation for patients with the acute respiratory distress syndrome (ARDS) improves outcomes. In a prospective randomized clinical trial (ARMA) performed by the ARDS Network, mechanical ventilation with volume assist-control mode and a tidal volume goal of 6 ml/kg predicted body weight (PBW) improved mortality in patients with ARDS when compared to those ventilated with a tidal volume goal of 12 ml/kg PBW[2]. Consequently, mechanical ventilation with a low tidal volume of 6 ml/kg PBW is now recommended for the management of ARDS patients.[3-5] Furthermore, a subsequent prospective study of ARDS patients suggests that early intervention with low tidal volume ventilation on **initial** mechanical ventilation is important in ARDS. This study confirmed that low tidal volume ventilation was associated with lower mortality in ARDS. Moreover, there was a dose-dependent effect where for every 1 ml/kg PBW increase in *initial* tidal volume used, there was a 23% relative increase in mortality. There was a significant 2.7% absolute difference in mortality when the difference in tidal volumes was as small as 8 ml/kg PBW vs 6 ml/kg PBW.[3]

There is also increasing evidence to suggest that lung protective ventilation may also be beneficial in patients with acute respiratory failure without ARDS. A small randomized controlled trial comparing tidal volumes of 6 ml/kg PBW vs. 10 ml/kg in patients with acute respiratory failure but without ARDS found that patients ventilated with the higher tidal volumes developed ARDS more frequently with a relative risk of 5.1 (95% CI 1.2-22.6) compared to patients ventilated with tidal volumes of 6 ml/kg PBW.[6] The study was not powered to detect a difference in mortality. A more recent meta-analysis of mechanically ventilated patients without ARDS demonstrated that a mean tidal volume of 6.5 ml/kg as compared to 10.6 ml/kg resulted in a lower rate of development of acute lung injury or ARDS, fewer pulmonary infections, and lower mortality[7]. Of the 20 studies included in that meta-analysis, 15 studies set initial tidal volume in the intervention group at ≤6 ml/kg PBW. A more recent meta-analysis with individual patient-level data confirmed that in acute respiratory failure patients without ARDS, mechanical ventilation with lower tidal volume (≤ 7 ml/kg PBW) in the first 2 days of mechanical ventilation was associated with lower rates of subsequent development of ARDS and pneumonia.[8] A randomized controlled trial of intraoperative lung protective ventilation using 6-8 ml/kg versus 10-12 ml/kg PBW tidal volume in patients undergoing high-risk abdominal surgery resulted in significantly less pulmonary and non-pulmonary complications with the lower tidal volume strategy [9]. Taken together, these studies suggest that patients with acute respiratory failure requiring mechanical ventilation, but without ARDS, would benefit from low tidal volumes upon initiation of mechanical ventilation.

Low tidal volume ventilation is well tolerated by most patients with and without ARDS. The potential concerns for increased atelectasis and resultant ventilator associated pneumonia from low tidal volume ventilation have not been substantiated. A recent meta-analysis shows the opposite: low tidal volume ventilation was associated with less atelectasis and fewer pulmonary infections.[7] While some have raised the concern for increased requirements for sedation to keep

patients comfortable on low tidal volume ventilation, patients treated with low tidal volume ventilation (6mL/kg PBW) for ARDS did not require more sedation than patients receiving higher tidal volume.[10,11] Additionally, an individual patient-level data meta-analysis of low tidal volume ventilation in patients without ARDS showed no increase in the use of sedation or neuromuscular blockade with low tidal volume ventilation.[12]

Based upon the increasing evidence for benefit in acute respiratory failure patients without ARDS, and the high tolerance and safety profile of low tidal volume ventilation, there has been an increasing call to utilize low tidal volume ventilation for all patients with acute respiratory failure.[3,13,14] Indeed, several institutions have already adopted protocols for low tidal volume ventilation for patients with acute respiratory failure, regardless of ARDS.[15] At one institution, the adoption of low tidal volume ventilation in all patients with acute respiratory failure along with other quality improvement initiatives resulted in a significant reduction of initial tidal volume to 6.8 ml/kg PBW for all patients, a significant reduction in the development of hospital acquired ARDS from 81 to 38.3 cases per 100,000 person-years ($p<0.001$) and improvement in mortality from 20% to 16%.[16]

Currently, usual care practices in mechanical ventilation are not consistently compliant with low tidal volume ventilation in patients with acute respiratory failure.[17,18,19] In the International LUNG-SAFE (Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE) study that included more than 459 ICUs around the world, ARDS was recognized in only 34% of ARDS patients and the mean tidal volume in patients with ARDS was 7.6 ml/kg PBW (7.5-7.7).[19] Similarly, other prospective observational studies found that 40%-68% of ARDS patients had tidal volumes higher than recommended (> 6.5 cc/kg PBW)[20,21] In general, the initial tidal volume received by the patient on initiation of mechanical ventilation dictates the tidal volume used during the rest of the hospital stay.[22] This is especially important as nearly half of all patients with acute respiratory failure are intubated in the Emergency Department (ED), so tidal volume set in the ED will influence subsequent tidal volume throughout the hospital stay. Multiple studies have demonstrated great variability in tidal volume use in patients with acute respiratory failure, including those patients who had initiation of mechanical ventilation in the ED.[18,22,23] In one multicenter observational cohort of patients in the ED, the median tidal volume was 7.6 ml/kg PBW (IQR 6.9-8.9) and only 56% of patients had tidal volumes < 8 ml/kg PBW.[23] Similar results were found in another single center observational study done in the emergency department.[22] Notably in these studies, the tidal volume was never reduced to lung protective range for 41-68% of patients with initial high tidal volumes. The initial tidal volume set in the ED after intubation commonly determined the tidal volume for the duration of mechanical ventilation.

Overall, current evidence supports the potential benefit of low tidal volume ventilation in patients with and without ARDS with little evidence for harm. However, previous studies show inconsistent application of lung protective ventilation using 6 ml/kg PBW tidal volume in patients with acute respiratory failure. It is unclear whether mechanical ventilation at low tidal volume of 6 ml/kg PBW will further improve outcomes compared to the tidal volumes used in usual care for patients with acute respiratory failure. Given the current variability in the use of lung protective ventilation in patients with and without ARDS, a large randomized trial is needed to evaluate the effect of a systematic implementation of low tidal volume ventilation in patients with acute respiratory failure. The PETAL Network is planning a pragmatic, stepped wedged, cluster randomized controlled trial called LOTUS (LOw Tidal volume Universal Support). LOTUS proposes to study the implementation of a default initial low tidal volume (6 ml/kg PBW)

ventilation compared to usual care for patients with acute respiratory failure and to determine its effect on mortality, ventilator free days and development of ARDS.

Before the PETAL Network can proceed with LOTUS, we need data on current practices in the PETAL Network hospitals. This proposal is for the PETAL Network to perform a 30-day observational study to assess current practices among hospitals in the PETAL network (LOTUS FRUIT). The data from this cohort study will be used to do the following in preparation for the LOTUS trial:

1. Determine current compliance with low tidal volume ventilation in patients with and without ARDS in the PETAL Network sites. Sites with good compliance to existing low tidal volume ventilation protocols may not benefit from participating in the LOTUS trial and may dilute the ability to detect an effect.
2. Obtain preliminary data for planning the LOTUS trial. Data on number of potentially eligible patients at each hospital, their mortality, and ventilator free days will be used to design the size and composition of the cluster for the proposed LOTUS RCT, the length of the trial, and the power to detect a difference in mortality and ventilator free days.
3. Determine whether to proceed with the larger LOTUS trial ("Go or No Go") based upon the data from above
4. Evaluate the feasibility of and effort required for data collection in a pragmatic trial. Given the large number of patients in a pragmatic trial, data collection must be efficient but also informative enough for analysis.
5. Identify sites with high or low compliance to low tidal volume ventilation for evaluation of the implementation of their mechanical ventilation protocols to help plan the intervention in the cluster LOTUS trial.

3.2 Current practice in PETAL sites

To determine the current practice among the PETAL Network sites, we conducted a PETAL-wide survey in 2015. The survey asked PETAL investigators about existing ventilator practices at their site. All 12 clinical centers responded, covering 32 Emergency Departments and 28 ICUs. The survey of investigators found great variability in the number of patients with acute respiratory failure ranging from 60-1800 patients intubated in the ED per site per year and 300-4000 patients on mechanical ventilation in the hospital per year from each site. All respondents believe that a low tidal volume protocol could be implemented in their ED or ICU. When asked about the presence of a low tidal volume protocol at their site, 81% of ICU and 31% of ED respondents reported that a low tidal volume ventilation (<=6.5 ml/kg PBW) protocol already existed in their ICU or ED for patients with ARDS. Thirty-five percent of ICU and 22% of ED respondents reported that they have an existing low tidal volume ventilation protocol for patients *without ARDS*. Compliance to protocols could not be determined from that survey.

In 2015, we also conducted a more focused observational study to determine the tidal volumes used during usual clinical care in patients with and without ARDS. This study involved 10 PETAL hospitals from 7 clinical centers. There was great variability in the tidal volume used in acute respiratory failure (Table 1). In the observational cohort, 120/238 (50%) patients from 9 hospitals with acute respiratory failure were intubated in the ED. Among these 238 patients, 63 (28%) had ARDS on intubation and the initial tidal volume for these ARDS patients was 7.41 ml/kg PBW (SE 0.12). Only 35% of the ARDS patients had tidal volume $\leq$ 6.5 ml/kg PBW. Among the patients who were not placed initially on low tidal volume ventilation of $\leq$ 6.5 ml/kg PBW, only 1 (2%) had their tidal volume reduced at a later time. In patients acute respiratory

failure without ARDS, the average initial tidal volumes of patients intubated in the ED was 7.5 ml/kg PBW (SE 0.3) and only 23/120 (19%) had initial tidal volumes <=6.5 ml/kg. Among patients who were not on low tidal volume ventilation, few (5%) had their tidal volume lowered to <=6.5 ml/kg PBW over the next 3 days in the ICU. The above results are very similar to that found in LUNG-SAFE. All sites in the observational study reported that they had protocols for low tidal volume ventilation for patients with ARDS and only one site reported having a similar protocol for non-ARDS patients. In spite of the reported presence of existing protocols, compliance to low tidal volume ventilation was sub-optimal for most sites.

Table 1: Tidal Volume in Acute Respiratory Failure in PETAL

	Mean Tidal Volume per Predicted Body Weight (ml/kg) ± SD (# patients)		
Clinical Center	**Patients intubated in ED**	**Patients intubated outside of ED or operating room**	**Patients with ARDS**
#1 (2 hospitals)	7.8 ± 1.4 (N=40)	7.1 ± 1.1 (N=23)	7.9 ± 1.4 (N=21)
#2	6.5 ± 0.4 (N=9)	NA	NA
#3 (3 hospitals)	7.0 ± 1.3 (N=25)	7.3 ± 1.9 (N=60)	6.9 ± 2.1 (N=25)
#4	8.1 ± 1.4 (N=10)	9.4 ± 5.4 (N=3)	6.9 (N=1)
#5	8.0 ± 1.3 (N=10)	7.6 ± 1.3 (N=19)	7.1 ± 1.5 (N=4)
#6	7.4 ± 1.9 (N=5)	7.6 ± 1.9 (N=5)	5.7 ± 0.1 (N=3)
#7	8.2 ± 1.6 (N=21)	7.7 ± 0.7 (N=8)	8.5 ± 1.0 (N=9)

In contrast, one site (Hospital #2) reported that they use a low tidal volume ventilation protocol for all patients with acute respiratory failure on mechanical ventilation. Their compliance with ARDS and non-ARDS patients was good with an average initial tidal volume of 6.5 ± 0.4 cc/kg PBW that decreased to 5.68 ±0.5 cc/kg PBW by ICU day 3. This one site demonstrated that it is possible to have high compliance with low tidal volume ventilation for ARDS and non-ARDS patients with the implementation of a clinical protocol.

The variability demonstrated by this small preliminary study indicates the need for more comprehensive data from all sites to plan the proposed cluster LOTUS trial.

4. STUDY POPULATION

4.1 Inclusion criteria

Patients who meet all inclusion criteria during the 30 day study period are eligible for the cohort:

1. Age ≥ 18 years
2. Patients with acute respiratory failure requiring invasive mechanical ventilation via an endotracheal tube in the hospital
3. Patients who will receive care in the intensive care unit after intubation (i.e., the patient was either intubated in the intensive care unit or who will be admitted or transferred to an intensive care unit on mechanical ventilation, if intubation did not occur in the intensive care unit.)

4.2 Exclusion criteria

Patients who meet one of more of these exclusion criteria will be excluded from the cohort. See Table 2 for justification for exclusion criteria.

1. Patients receiving chronic invasive mechanical ventilation
2. Patients who are extubated prior to transfer to the ICU
3. Patients intubated outside of the study hospital and presented to the study hospital with more than 24 hours of invasive mechanical ventilation prior to presentation
4. Patients being cared for in an ICU that could not participate in a low tidal volume protocol under LOTUS
5. Patients admitted to an ICU after elective surgery

Table 2: Rationale for exclusion

Exclusion Criteria	Rationale
Chronic ventilation	Unable to control or determine what tidal volumes may be used because tidal volumes are set chronically, and duration of mechanical ventilation is unlikely to change with low tidal volume ventilation. Chronically ventilated patients will be excluded from LOTUS trial
Extubated prior to ICU	Unlikely to show benefit from such a short duration of low tidal volume ventilation
Mechanically ventilated > 24 hours before admission	Will be excluded from LOTUS trial as the tidal volumes in the initial period of mechanical ventilation will be determined outside of the study hospital. Will also be difficult to obtain and validate ventilator data outside of the study hospital.
Cared for in ICU that could not participate in low tidal volume protocol	These ICUs would not be included in the LOTUS cluster RCT
Elective surgery	Lower rates of ARDS and mortality with short duration of mechanical ventilation. Mechanical ventilation is not due to acute respiratory failure.

5. STUDY DESIGN

5.1 Observational study

This is a one month prospective observational study to be conducted at all PETAL Network hospitals. The data from the observational study will be used to inform the design of the LOTUS trial. To understand the feasibility of data collection for the subsequent larger LOTUS cluster RCT, research coordinators will be asked to provide the average time required to complete the case report form for patients enrolled in this study upon their discharge from the hospital. Additionally, there will be discussion with the site investigators from sites with either high and low compliance to low tidal volume to better understand their mechanical ventilation protocols and how they were implemented. The information from these interviews will be used to plan the implementation in the LOTUS trial.

6. DATA COLLECTION

At each site, consecutive patients up to a total of 50 patients per hospital who meet the study criteria within a 30 day period will be enrolled into the cohort for full data collection. Patients admitted during the study period will be followed until hospital discharge or 28 days. As LOTUS will be a pragmatic trial, we will focus on clinical data that can be easily collected from medical records. The data collection will include:

6.1 Background assessments

1. Demographic and Admission Data (including age, sex, race, ethnicity, hospital admission date and time)
2. Height recorded from medical record, if available and date of measurement of height
3. Location of endotracheal intubation
    - Pre-hospital
    - ED
    - OR
    - Hospital ward
    - ICU
    - Referring hospital
4. Type of ICU
    - Medical
    - Surgical
    - Trauma
    - Mixed
    - Other (e.g., Burn, Neuro)
5. Risk factors for ARDS (at time of intubation) [24]
    - Sepsis
    - Pneumonia
    - Aspiration
    - Smoke inhalational injury
    - Trauma
    - Near drowning
    - Pancreatitis
    - Burn
    - Non-cardiogenic shock
    - Drug overdose
    - Transfusions of blood products
    - Other
6. Azithromycin use in the 24 hours before and 24 hours after intubation

7. Use of non-invasive ventilation and high flow nasal cannula in the 12 hours before intubation

6.2 Baseline assessments after intubation

The following information will be recorded after intubation.

1. First ventilator parameters after intubation (Mode, set tidal volume, minute ventilation, actual rate, plateau pressure, if available).
    a. If patient was initially placed on volume controlled mode, was the set tidal volume on volume controlled mode changed at any time within the next 24 hours?
        i. If YES, indicate the date, time and the new set tidal volume for the first charted ventilator setting in which the set tidal volume is different from the initial ventilator settings after intubation.
2. Reason for intubation (acute hypoxemic, acute hypercapnic, mixed, airway protection, altered mental status, elective for surgery or procedure, unclear).
3. Worst PaO2 / FiO2 ratio after intubation on calendar day of intubation, if available
4. If no ABG available, worst imputed P/F (see Appendix A) and corresponding SpO2 and FiO2 after intubation on calendar day of intubation
5. SOFA score within first 24 hours after intubation
6. Level of consciousness and use of IV sedatives before ICU admission and in the 24 hours after ICU admission

6.3 Daily Assessments during Day 0-3 of study

The following data will be collected daily from Day 1 to day 3 unless the patient dies or is extubated. Day 0 is defined as the calendar day of intubation.

1. First Ventilator parameters in the ICU (Mode, set tidal volume, actual rate, plateau pressure, if available, total minute ventilation).
2. On day 1-3, Vent Mode, set tidal volume, actual rate, total minute ventilation, plateau pressure if available, recorded closest to 8AM
3. Worst PaO2 / FiO2 ratio on study days 1-3, if available
4. If no ABG available, worst imputed P/F (see Appendix A) and corresponding SpO2 and FiO2on study days 1-3
5. Level of consciousness closest to 8AM on Day 1-3 and use of IV sedatives on that calendar day

6.4 Study Assessments of Outcomes

1. Hospital admit and discharge date for hospital length of stay
2. ICU admit and discharge date for ICU length of stay
3. Patient status on hospital discharge or day 28-whichever comes first (alive or dead)

4. Discharged on mechanical ventilation via endotracheal tube or tracheostomy or still on mechanical ventilation on day 28 whichever comes first
5. Date of successful extubation to unassisted breathing to calculate duration of mechanical ventilation before day of discharge or day 28, whichever comes first
6. ARDS up to Study Day 3 (Site investigator or designee evaluates CXR (if available) for ARDS only when intubated and PAO_2/FiO_2 or equivalent SpO_2/FiO_2 is < 300)

6.5 Limited Data Collection for Additional Patients Beyond 50 Within the 30 Day Observational Period

For sites with more than 50 eligible patients within the 30 day observational period, either the full CRF or a limited dataset will be collected on additional patients beyond 50. The limited dataset will include only the following items:

Baseline Data:

1. Age
2. Gender
3. Height recorded from medical record, if available and date of measurement of height
4. Type of ICU

Intubation Data

5. Location of intubation
6. Date and time of intubation
7. Reason for intubation
8. Date and time of first documented vent parameters
9. First documented vent parameters after intubation

ICU Admission Data

10. First vent setting documented after ICU admission

Outcomes Data

11. Hospital admit and discharge date for hospital length of stay
12. ICU admit and discharge date for ICU length of stay
13. Patient status on discharge or at day 28, whichever comes first
14. Discharge on mechanical ventilation or not

6.6 Feasibility of Data Collection

A large number of patients are expected to be enrolled in a pragmatic trial like LOTUS. This style of trial (large numbers, lesser data collection) is novel to many of the PETAL network hospitals, and warrants a feasibility study to determine how well we can perform data collection on many patients. To determine the feasibility of data collection and to estimate the effort spent to collect the data, research coordinators at each site will be asked to provide the average time for data collection for patients at the end of their hospital stay.

6.7 Evaluation of Sites on Barriers and Implementation Strategies for Low Tidal Volume Ventilation Strategy in High Compliance Sites

The proposed LOTUS FRUIT will also identify sites that have high (mean tidal volume < 7 ml/kg PBW) or low compliance (mean tidal volume >8 ml/kg PBW) to low tidal volume ventilation strategy for ARDS and non-ARDS patients. These sites can be evaluated for barriers to low tidal volume and how high compliance sites were able to successfully implement and adhere to low tidal volume. Discussions will be held with the site investigators. We will collect the following data from high compliance and low compliance sites PETAL sites:

1. Does your site have an existing protocol or policies for low tidal volume ventilation (6 cc /kg PBW) for ARDS patients?
    - If YES, in which areas of the hospital does the protocol apply? (ED, MICU, SICU, MSICU, CCU, CSICU, NeuroICU)
2. Does your site have an existing protocol or policies for low tidal volume ventilation (6 cc /kg PBW) for all patients with acute respiratory failure (with and without ARDS)?
    - If YES, in which areas of the hospital does the protocol apply? (ED, MICU, SICU, MSICU, CCU, CSICU, NeuroICU)
3. Does your site have electronic order sets for ARDS patients?
    - If YES, in which areas of the hospital are these electronic order sets used? (ED, MICU, SICU, MSICU, CCU, CSICU, NeuroICU)
    - If NO, are there barriers to instituting such an electronic order sets? If yes, what are they?
4. Does your site have electronic order sets for initiation of mechanical ventilation?
    - If YES, in which areas of the hospital are these electronic order sets used? (ED, MICU, SICU, MSICU, CCU, CSICU, NeuroICU)
    - If NO, are there barriers to instituting such an electronic order sets. If yes, what are they?
5. Who usually sets up the ventilator for newly intubated patients in the ICU? In the ED? (respiratory therapist, intensivisit, emergency medicine attendings, housestaff (residents or fellows), nurses, other)
6. Who usually decides on the tidal volume setting on the ventilator for patients on mechanical ventilation in the ICU? In the ED? (respiratory therapist, intensivisit, emergency medicine attendings, housestaff (residents or fellows), nurses, other)
7. Who measures height for patients on mechanical ventilation? (RT, nurses, nurses aide or other, no one)
8. How often do respiratory therapists carry tape measures to determine height? (Never, sometimes, frequently, always)
9. How often do ED nurses have tape measures to determine height? (Never, sometimes, frequently, always)
10. How often do ICU nurses have tape measures to determine height? (Never, sometimes, frequently, always)
11. What were some of the barriers encountered when low tidal volume ventilation for acute respiratory failure was implemented at your site?

- Were there opposition or concerns from intensivists? What were they?
- Were there opposition or concerns from emergency medicine attendings? What were they?
- Were there opposition or concerns from respiratory therapists? What were they?
- Were there opposition or concerns from nurses? What were they?
- Were there opposition or concerns from housestaff or fellows in the ICU or ED? What were they?

For sites who report existing protocols or policies or existing electronic order sets, copies will be collected. Common themes and strategies among high and low compliance sites will be identified.

7. STATISTICAL ANALYSIS

7.1 Patient Level Data

After the conclusion of the LOTUS FRUIT study, data will be evaluated to determine the following:

- Baseline ventilator practice in PETAL and at each site. This includes:
  - % patients at each site on volume controlled ventilation on initial intubation
  - The average measured tidal volume per PBW for each hospital
  - % of time on controlled volume mechanical ventilation spent with tidal volume < 6.5 ml/kg PBW % of pts with tidal volumes decreased to <=6.5 ml/kg PBW at any time during the duration of mechanical ventilation
  - % of pts with height documented at each site
- Study population data in PETAL and at each site. This includes:
  - # patients with acute respiratory failure
  - Reasons for intubation in patients with acute respiratory failure
  - # patients intubated in the ED, ICU or elsewhere
  - # patients with ARDS on initial intubation and on subsequent days
- Hospital outcomes data in PETAL and at each site. This includes:
  - Hospital mortality rate
  - Ventilator free days and duration of mechanical ventilation
  - ARDS development within Day 0-3 of study

The data from the proposed 1 month prospective cohort will be used in the following manner to help plan the LOTUS trial:

1. Determination of the distribution of tidal volumes per kilogram of predicted body weight practices at each site. This will be used in the simulation models (described below) to determine how many and which sites may be eligible for the LOTUS trial
2. Determination of the number of patients with acute respiratory failure at each potential site and their outcomes. This data will be used in the simulation model below to determine the expected benefit and power to detect a change in outcome under different study scenarios. Additionally, this data will be used to help design the clusters, randomization scheme, the number of steps, and the duration of the trial. We expect the cluster sizes to vary in this trial, as hospitals will have different enrollment. Because the sizes of the clusters can be imbalanced, it will be important to balance groups by the choice of hospitals to be clustered together and the number of clusters and steps by which the intervention will be rolled out.

7.2 Simulation Models to Determine Feasibility and to Plan Cluster LOTUS Trial:

Statistical analysis of the above data will aim to determine if the stepped wedged cluster LOTUS trial is feasible and how best to design the inclusion criteria to determine which institutions should not participate in LOTUS because their usual care tidal volumes are close enough to 6 ml/kg PBW that their outcomes would not be expected to change during the trial. We will use simulation for this purpose. Using published data from Needham et. al and Neto AS et. al, we will estimate the expected change in mortality as tidal volume changes in patients with and without ARDS. [3,8,12] We will then calculate the expected mortality benefit for each institution

based on their current distribution of tidal volumes and their tidal volumes after implementation of a default initial low tidal volume ventilation protocol in LOTUS. We will assume a post-intervention distribution of tidal volumes similar to that seen in the last ARDSnet study. We will then be able to compute the power of the study for different choices of rules for including institutions based on their expected mortality benefit. In essence, using the data from this observational study, we will be able to use the simulation models to runs different trials in silico under different inclusion criteria for sites based upon their current tidal volume distribution and their expected mortality to find the set of criteria that can optimize power while minimizing sample size. For sensitivity analyses, we will consider the situation where we only achieve 50-90% compliance post implementation to help plan the target compliance goal for the cluster LOTUS RCT. We will repeat this analysis for other endpoints such as ventilator free days.

Using the simulation, we will determine the sample size, and minimal detectable difference in hospital mortality, ventilator free days, and duration of mechanical ventilation for a cluster stepped wedged randomized controlled trial conducted under different inclusion and exclusion criteria (for example, excluding sites with average tidal volumes < 7.0 ml/kg PBW vs a higher tidal volume).

We will proceed with the LOTUS trial if the simulation model demonstrates one or more study scenarios that can demonstrate:

1) *Expected absolute mortality difference of 3% or more on low tidal volume ventilation (6 cc/kg PBW)* ***OR****, in the absence of a mortality benefit, expected difference in ventilation-free days of 2 or more or duration of mechanical ventilation among survivors of 2 or more days after the intervention. This is considered to be clinically important enough to pursue a trial.*

AND

2) *Power and feasibility in that the trial to detect the above outcome difference can be accomplished with 90% power in a cluster stepped wedged randomized controlled trial lasting no more than 4 years and within the remaining allowable budget of PETAL.*

For the initial simulations, we will assume a four year study but if a shorter study is feasible we will consider this possibility. Note that there will be additional opportunities for early termination of the trial after the LOTUS trial begins. If the usual care tidal volumes in the pre-intervention phase drifts closer to 6 ml/kg PBW, a decision will be made to not proceed with the intervention phase.

8. RISK ASSESSMENT

As this is an observational study with no intervention, the only risk to the patient is that of breach of privacy. Participation of site investigators and others from sites with high compliance to low tidal volume ventilation will be voluntary.

8.1 Minimization of risks

Federal regulations at 45 CFR 46.111(a)(1) require that risks to subjects are minimized by using procedures which are consistent with sound research design. There are no study procedures, and there are no consent forms that pose a potential risk to privacy. All data will be sent to the clinical coordinating center in a secured fashion via an electronic data collection form. All data will be collected and stored securely, and the only information transmitted to the coordinating center will be devoid of personal health information. Performing this study under waiver of informed consent will minimize risk to privacy as there will be fewer paper records that have potential to cause a security breach.

8.2 Risks in relation to anticipated benefits

We do not anticipate any direct benefit to subjects for participation in this study but this is balanced against the minimal risk from limited data collection.

9. HUMAN SUBJECTS

9.1 Selection of subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The EDs, ICUs, and other acute care areas of PETAL sites 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. 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.

9.2 Minorities and women

Sex and racial patient subsets were considered by the NHLBI in selecting the PETAL Network Centers. The demographic profiles of the Centers selected for the Network show that the aggregate patient population contains representative proportions of minorities and women that reflects the US census. Recruitment of minorities and women will be monitored by the PETAL Network Coordinating Center. If necessary, additional recruitment efforts will be made at specific centers to ensure that the aggregate patient sample contains appropriate gender and minority subsets. With regard to pregnant women, they will not be specifically excluded.

9.3 Justification of including vulnerable subjects

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."[25] Research Ethics Commission have held the view that it is permissible to include incapable subjects in research as long as there are 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 or "if the net additional risks of participation are not substantially greater than the risks of standard treatment."[25,26]

9.4 Waiver of informed consent

We are applying for waiver of informed consent to collect clinically obtained data for the proposed one month observational cohort. As per 45 CFR 46.116d, LOTUS FRUIT would meet the required four criteria for a waiver of informed consent:

1. <u>The research involves no more than minimal risk to the subjects:</u> This is an observational study and no personal health information will be transmitted outside the study hospital. Obtaining written consent would actually pose greater risk to the subject due to the requirements to maintain these paper records.
2. <u>The waiver will not adversely affect the rights and welfare of the subjects:</u> This study has no intervention, and all data collected are typical data obtained from inpatients.
3. <u>The research could not be practically carried out without a waiver:</u> LOTUS FRUIT studies patients when they are first intubated. It is neither practical nor possible to

consent patients or to find family for consent for data collection and may risk consent bias as only patients who are well enough or who have family readily available could be consented for this study.

4. When appropriate, the subject will be provided with additional pertinent information after participation. There is no intervention planned and no data generated that would not already be part of the medical record of the patients. Thus, no additional pertinent information will be shared with the subject after participation.

APPENDIX A

S/F ratio

Table 2 displays an equivalence table that determines the estimated P/F ratio from the FiO2 and SpO2. This data was generated by investigators at the University of Utah, on a cohort of critically ill patients with pneumonia.[72-78].

Table 2: Imputed PaO2/FiO2 for combination of SpO2 (rows) and FiO2 (columns)

SPO2	FiO2														
	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1
80%	148	127	111	98	89	81	74	68	63	59	55	52	49	47	44
81%	151	129	113	101	91	82	76	70	65	60	57	53	50	48	45
82%	155	132	116	103	93	84	77	71	66	62	58	55	52	49	46
83%	158	136	119	106	95	86	79	73	68	63	59	56	53	50	47
84%	162	139	122	108	97	89	81	75	70	65	61	57	54	51	49
85%	167	143	125	111	100	91	83	77	71	67	63	59	56	53	50
86%	171	147	129	114	103	94	86	79	73	69	64	61	57	54	51
87%	177	151	132	118	106	96	88	81	76	71	66	62	59	56	53
88%	182	156	137	121	109	99	91	84	78	73	68	64	61	58	55
89%	189	162	141	126	113	103	94	87	81	75	71	67	63	60	57
90%	196	168	147	130	117	107	98	90	84	78	73	69	65	62	59
91%	203	174	153	136	122	111	102	94	87	81	76	72	68	64	61
92%	213	182	159	142	128	116	106	98	91	85	80	75	71	67	64
93%	223	191	168	149	134	122	112	103	96	89	84	79	74	71	67
94%	236	202	177	157	142	129	118	109	101	94	89	83	79	75	71
95%	252	216	189	168	151	138	126	116	108	101	95	89	84	80	76
96%	273	234	205	182	164	149	136	126	117	109	102	96	91	86	82

For altitude adjustment, we would recommend the practice from ARDS Network studies of multiplying the qualification threshold P/F by the ratio of average ambient to sea level barometric pressure (for Utah, it is 0.86*150 = 129; for Denver it is 0.84*150 = 126).

Additional requirements for the use of the S/F ratio include:

1. SpO_2 between 80-96%
2. SpO_2 should be measured at least 10 minutes after any change in FiO_2.
3. PEEP ≥ 8 cm H20
4. An adequate pulse oximeter waveform tracing

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