Supplementary Appendix:
Study Protocol and Statistical Analysis Plan

Trial: Pragmatic Investigation of optimaL Oxygen Targets (PILOT) trial

Manuscript: Lower, intermediate, and higher oxygen saturation targets for mechanically ventilated critically ill adults

ClinicalTrials.gov: NCT03026322

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This Supplementary Appendix contains the following items:

1) Original Trial Protocol [dated 5/1/2018]
2) Final Trial Protocol [dated 4/7/2021]
3) Summary of changes to Trial Protocol
4) Original Statistical Analysis Plan [dated 4/2/2021]
5) Final Statistical Analysis Plan [dated 10/28/2021]
6) Summary of changes to Statistical Analysis Plan

Preliminary Investigation of optimaL Oxygen Targets (PILOT) trial

Version 1.0

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1.0 Study Summary

Title: Preliminary Investigation of optimaL Oxygen Targets (PILOT) trial

Background: Mechanical ventilation of ICU patients universally involves titration of the fraction of inspired oxygen (FiO_2) to maintain arterial oxygen saturation (SpO_2). Despite decades of ICU practice, however, the optimal SpO_2 target remains unknown. Higher SpO_2 targets (96-100%) provide a margin of safety against hypoxia but increase exposure to hyperoxia. Lower SpO_2 targets (88-92%) minimize hyperoxia, but may increase the risk of hypoxia. An intermediate SpO_2 target (92-96%) may avoid the risks of both hyperoxia and hypoxia, or may expose patients intermittently to both sets of risks. Current guidelines offer divergent recommendations as to the optimal SpO_2 target and clinical safety and efficacy data are lacking. Therefore, we propose a 2,250-patient cluster-randomized cluster-crossover trial comparing a lower SpO_2 target (90%), an intermediate SpO_2 target (94%), and a higher SpO_2 target (98%) with regard to the outcome of days alive and free of invasive mechanical ventilation.

Primary Aim:

- To compare the effect of higher, intermediate, and lower SpO_2 targets on days alive and free of invasive mechanical ventilation among mechanically ventilated critically ill adults.

Primary Hypotheses:

- Use of a lower SpO_2 target (90%) for mechanically ventilated ICU patients will result in more days alive and free of invasive mechanical ventilation than use of an intermediate SpO_2 target (94%) or a higher SpO_2 target (98%).

Inclusion Criteria:

- We will include adults (≥ 18 years old) receiving mechanical ventilation through an endotracheal tube or tracheostomy who are admitted to the study ICU or for whom admission to the study ICU from the emergency department is planned.

Exclusion Criteria:

- We will exclude patients who are pregnant or who are prisoners.

Consent: Because [1] the study enrolls only patients who would have been exposed to oxygen therapy as a part of clinical care outside of the study, [2] all SpO_2 targets examined are currently used in routine care in the study ICU, [3] no high-quality data suggest that the choice of SpO_2 target affects clinical outcomes, and [4] during the trial treating clinicians retain discretion to control the SpO_2 target when felt to be required for the safe treatment a specific patient, we feel the study qualifies as minimal risk.

Given the minimal risk, the implementation of SpO_2 targets at an ICU level, and the impracticability of consenting each patient during initiation of mechanical ventilation in the ICU or emergency department, we will request a waiver of informed consent.

Randomization: In the PILOT trial, the entire study ICU will be assigned to a single SpO_2 target (cluster-randomized) and the ICU will switch between lower, intermediate, and higher SpO_2 targets every two months in a randomly generated sequence (cluster-crossover).

Study Interventions:

- **Lower SpO_2 Target** – FiO_2 will be titrated according to an oxygen therapy protocol to a target SpO_2 of 90% with a range considered compliant of 88-92%.
- **Intermediate SpO_2 Target** – FiO_2 will be titrated according to an oxygen therapy protocol to a target SpO_2 of 94% with a range considered compliant of 92-96%.
- **Higher SpO_2 Target** – FiO_2 will be titrated according to an oxygen therapy protocol to a target SpO_2 of 98% with a range considered compliant of 96-100%.

Primary Outcome:

- Ventilator-free days (VFDs) to study day 28, defined as the number of days from liberation from invasive mechanical ventilation to day 28 after enrollment.

Secondary Outcomes:

- *Secondary Clinical Outcomes*: ICU mortality, in-hospital mortality, vasopressor-free days, duration of vasopressor receipt, renal replacement therapy-free days, duration of renal replacement therapy receipt, ICU-free days, ICU-length of stay, hospital length of stay.
- *Secondary Organ Function Outcomes*: daily SOFA score, creatinine, lactate, presence of acute respiratory distress syndrome, Stage II or greater AKI by KDIGO criteria.
- *Secondary Safety Outcomes*: Atrial arrhythmia, ventricular arrhythmia, cardiac arrest, pneumothorax.
- *Secondary Feasibility Outcomes*: SpO_2, SaO_2, FiO_2, PaO_2, percentage of SpO_2 values outside target range, <88% with FiO_2 <1.0, PaO_2 < 55 with FiO_2 <1.0, SpO_2 >98% with FiO_2 > 0.21, PaO_2 >120 with FiO_2 >0.21, episodes of $SpO_2 \leq 85\%$ lasting > 5 minutes, PaO_2/FiO_2 ratio.
- *Secondary Process of Care Outcomes*: Tidal volume, positive end expiratory pressure, peak airway pressure, net fluid balance, receipt of mandatory ventilator mode, number of arterial blood gasses, hemoglobin, red cell transfusion.

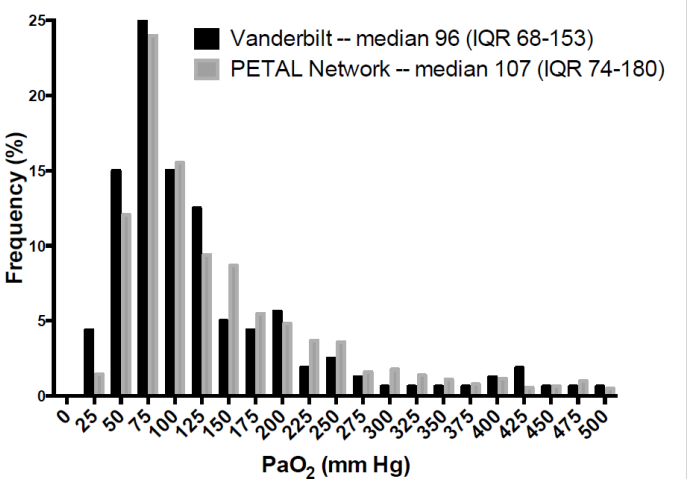
2.0 Background

Each year 2-3 million intensive care unit (ICU) patients receive invasive mechanical ventilation,[1–3] at a cost of more than $20 billion dollars.[4,5] Despite recent advances,[6] in-hospital mortality among mechanically ventilated ICU patients remains 25-35%,[7] and survivors often face cognitive, psychiatric, and physical dysfunction.[8–11]

Mechanical ventilation of ICU patients universally involves titration of the fraction of inspired oxygen (FiO_2) to maintain arterial oxygen saturation (SpO_2). Despite decades of ICU practice, however, the optimal SpO_2 target remains unknown. Higher SpO_2 targets (96-100%) provide a margin of safety against hypoxemia, but may increase exposure to excess FiO_2, hyperoxemia, and tissue hyperoxia, causing oxidative damage, [12–14] inflammation,[15,16] and increased alveolar-capillary permeability.[17] Lower SpO_2 targets (88-92%) minimize hyperoxia,[6,18,19] but may increase the risk of hypoxemia, tissue hypoxia, and organ dysfunction.[20,21] An intermediate SpO_2 target (92-96%) may avoid the risks of both hyperoxia and hypoxia, or, conversely, may expose patients intermittently to both sets of risks.

Current guidelines offer divergent recommendations – ranging from tolerating SpO_2 values as low as 88% (ARDS Network)[22,23] to pursuing SpO_2 values as high as 98% (British Thoracic Society)[24]. The relative risks and benefits of different SpO_2 targets have been extensively examined in the setting of the neonatal ICU,[25–28] but have only been investigated in adult ICU patients in three small trials.[29–31] Targeting lower SpO_2 resulted in improved survival in one trial and trends toward improved survival in the other two.

In clinical practice, however, hyperoxemia remains common.[32,33] In our recent observational study of 2,200 mechanically ventilated ICU patients at 50 centers across the United States (see Figure), the majority of patients had a lowest PaO_2 value on the first study day > 100 mm Hg (~SpO_2 > 97%). The wide variation in current practice (frequently favoring higher SpO_2 targets), conflicting guidelines, and pilot trial data favoring lower SpO_2 targets have led to calls for a large, randomized trial to determine the effect of SpO_2 target on patient outcomes.[18]



3.0 Rationale, Aims, and Hypotheses

In order to determine the effect of SpO_2 targets during mechanical ventilation of critically ill adults on clinical outcomes, a randomized trial is needed.

Study Aims:

- **Primary:** To compare the effect of higher, intermediate, and lower SpO_2 targets on days alive and free of invasive mechanical ventilation among mechanically ventilated critically ill adults.
- **Secondary:**
    - To evaluate the effect of the same intervention in the same population on pre-specified *Secondary Clinical Outcomes*, *Secondary Organ Function Outcomes*, *Secondary Safety Outcomes*, *Secondary Feasibility Outcomes*, and *Secondary Process of Care Outcomes*.
    - To evaluate the effect of the same intervention on days alive and free of invasive mechanical ventilation in clinically relevant pre-specified patient subgroups.

Study Hypotheses:

- **Primary:** Use of a lower SpO_2 target (90%) for mechanically ventilated ICU patients will result in more days alive and free of invasive mechanical ventilation than use of an intermediate SpO_2 target (94%) or a higher SpO_2 target (98%).

- **Secondary:**
    - Compared with use of an intermediate SpO_2 target (94%) or higher SpO_2 target (98%), use of a lower SpO_2 target (90%) for mechanically ventilated ICU patients will result in:
        - Lower ICU and in-hospital mortality
        - No difference between in other *Secondary Clinical Outcomes*
        - Lower daily SOFA score
        - Lower incidence of acute respiratory distress syndrome
        - No difference in other *Secondary Organ Function Outcomes*
        - No difference in *Secondary Safety Outcomes*
        - Lower SpO_2, SaO_2, FiO_2, PaO_2, and incidence of SpO_2 >98% with FiO_2 > 0.21 or PaO_2 >120 with FiO_2 >0.21
        - Higher PaO_2/FiO_2 ratio and incidence of SpO_2 <88% with FiO_2 <1.0 or PaO_2 < 55 with FiO_2 <1.0
        - No difference in episodes of $SpO_2 \leq 85\%$ lasting > 5 minutes
        - No difference in *Secondary Process of Care Outcomes*

4.0 Study Description

In order to address the aims outlined above, we propose the Preliminary Investigation of optimaL Oxygen Targets (PILOT) trial. The PILOT trial will be a prospective, un-blinded, cluster-randomized, cluster-crossover trial conducted between July 1, 2018 and June 30, 2021 in the medical ICU at Vanderbilt University Medical Center examining the effect of SpO_2 targets on days alive and free of mechanical ventilation among mechanically ventilated ICU patients. For the 36 months of the PILOT trial, the entire medical ICU will be assigned to a single SpO_2 target and the ICU will switch between lower, intermediate, and higher SpO_2 targets every two months in a randomly generated sequence (Figure below). Patients who fulfill inclusion criteria without meeting exclusion criteria will be enrolled at the initiation of mechanical ventilation in the study ICU or in the emergency department when admission to the study ICU is planned. The PILOT trial will control only the SpO_2 target and all other aspects of patients clinical care will remain at the discretion of the treating clinicians.

Study Year 1						Study Year 2						Study Year 3					
Jul-Aug	Sep-Oct	Nov-Dec	Jan-Feb	Mar-Apr	May-Jun	Jul-Aug	Sep-Oct	Nov-Dec	Jan-Feb	Mar-Apr	May-Jun	Jul-Aug	Sept-Oct	Nov-Dec	Jan-Feb	Mar-Apr	May-Jun
2018			2019						2020						2021		
High	Mid.	Low	Mid.	Low	High	Low	Mid.	High	High	Mid.	Low	Mid.	High	Low	Mid.	High	Low

The study ICU was randomly assigned to an SpO_2 target for each two-month block.
High = SpO_2 target 98% (range 96-100%); Mid. = SpO_2 target 94% (range 92-96%); Low = SpO_2 target 90% (range 88-92%)

5.0 Inclusion and Exclusion Criteria

5.1 Inclusion Criteria:

1. Age ≥ 18 years
2. Receiving mechanical ventilation through an endotracheal tube or tracheostomy
3. Admitted to the study ICU or admission to the study ICU from the emergency department is planned

5.2 Exclusion Criteria:

1. Known pregnancy or beta hCG level greater than the laboratory upper limit of normal in a patient capable of becoming pregnant
2. Known to be a prisoner

6.0 Enrollment/Randomization

6.1 Study Sites:

- Medical Intensive Care Unit at Vanderbilt University Medical Center
- Emergency Department at Vanderbilt University Medical Center

6.2 Study Population: All adults located in the study ICU (or for whom admission to the study ICU from the emergency department is planned) for whom the treating clinicians have decided invasive mechanical ventilation is required will be enrolled unless meeting exclusion criteria. Patients will be included regardless of age, gender, race, weight or body mass index, initial oxygen saturation, or other clinical factors.

6.3 Enrollment: All adult patients who do not meet exclusion criteria will be enrolled immediately upon receipt of invasive mechanical ventilation in the study ICU or in the emergency department when admission to the study ICU is planned.

6.4 Consent:

All patients receiving invasive mechanical ventilation in an intensive care unit receive oxygen therapy titrated to maintain SpO_2 as a part of routine care. In clinical practice, 98% of SpO_2 values experienced by mechanically ventilated adults fall between 88-100%.[32,33] Within this range, current guidelines for oxygen therapy in mechanically ventilated adults outline three contrasting approaches: [1] tolerating SpO_2 values as low as 88% (NIH/NHLBI ARDS Network),[22] [2] titrating within the range 92-96% (Thoracic Society of Australia and New Zealand),[34] or [3] pursuing SpO_2 values as high as 98% (British Thoracic Society).[24] The lower SpO_2 target (90%), intermediate SpO_2 target (94%), and higher SpO_2 target (98%) examined in this study are all intermittently used in routine care in the study ICU and recommended by at least one international guideline. There are currently no high-quality data to suggest that one SpO_2 target is better than the others with regard to clinical outcomes. Although there are no clear data to support the choice of SpO_2 target, during the PILOT trial, treating clinicians in the study ICU will be allowed to change the SpO_2 target at any point if it is felt to be required for the safe treatment a specific patient.

Because the interventions studied [1] are used as part of routine care in the study ICU, [2] are interventions o which the patient would be expected even if not participating in the study, [3] have no prior data to suggest the superiority of one approach over the other, and [4] are equivalent options from the perspective of the treating clinicians (otherwise the treating clinician retains control of SpO_2 target), we feel the study presents minimal risk.

Additionally, obtaining informed consent prior to participation in the study would be impractical. Endotracheal intubation and initiation of mechanical ventilation for critically ill patients is frequently a time-sensitive procedure. Despite the availability of a formal informed consent document for the endotracheal intubation and initiation of mechanical ventilation, time allows discussion of risks and benefits in less than 10% of airway management events in the study ICU. The oxygen titration protocol used to target SpO2 in this trial begins immediately at the initiation of mechanical ventilation to capture the period of mechanical ventilation with the highest risk for hyperoxia and hypoxia. Moreover, in this cluster-randomized trial, the entire ICU is assigned to a single SpO_2 target delivered by the unit's respiratory therapist through a unit-wide oxygen

titration protocol. Obtaining informed consent from every eligible patient in the ICU each day would be logistically infeasible and patients who declined to participate would need to be transferred between ICUs which might adversely impact their care.

Because the study presents minimal risk, would not adversely affect the welfare or privacy rights of the participant, and consent would be impracticable, we will request a waiver of informed consent.

6.5 Randomization:

During each two-month block of the study, the ICU will be assigned to either a higher SpO_2 target (98%), an intermediate SpO_2 target (94%), or a lower SpO_2 target (90%). The order of study group assignments will be generated by computerized randomization using permuted blocks of 3 to minimize the impact of seasonal variation. The last 7 days of each two-month block will be a washout period during which the ICU will continue to target the assigned SpO_2 but new patients will not be enrolled. Assuming a duration of mechanical ventilation similar to that observed for mechanically ventilated patients admitted to the study ICU in a prior year (median 3 [IQR 3-5] days), a 7-day washout period will ensure that 98% patients do not experience a "crossover" from one assigned SpO_2 target to another.

7.0 Study Procedures

7.1 Study Interventions

Choice of SpO_2 targets: In clinical practice, 98% of SpO_2 values experienced by mechanically ventilated adults fall between 88-100%.[32,33] Within this range, current guidelines for oxygen therapy in mechanically ventilated adults outline three contrasting approaches: [1] tolerating SpO_2 values as low as 88% (NIH/NHLBI ARDS Network),[22] [2] titrating within the range 92-96% (Thoracic Society of Australia and New Zealand),[34] or [3] pursuing SpO_2 values as high as 98% (British Thoracic Society).[24] The PILOT trial will have three study groups, each emulating an approach to SpO_2 targets represented in guidelines and clinical practice (Table).

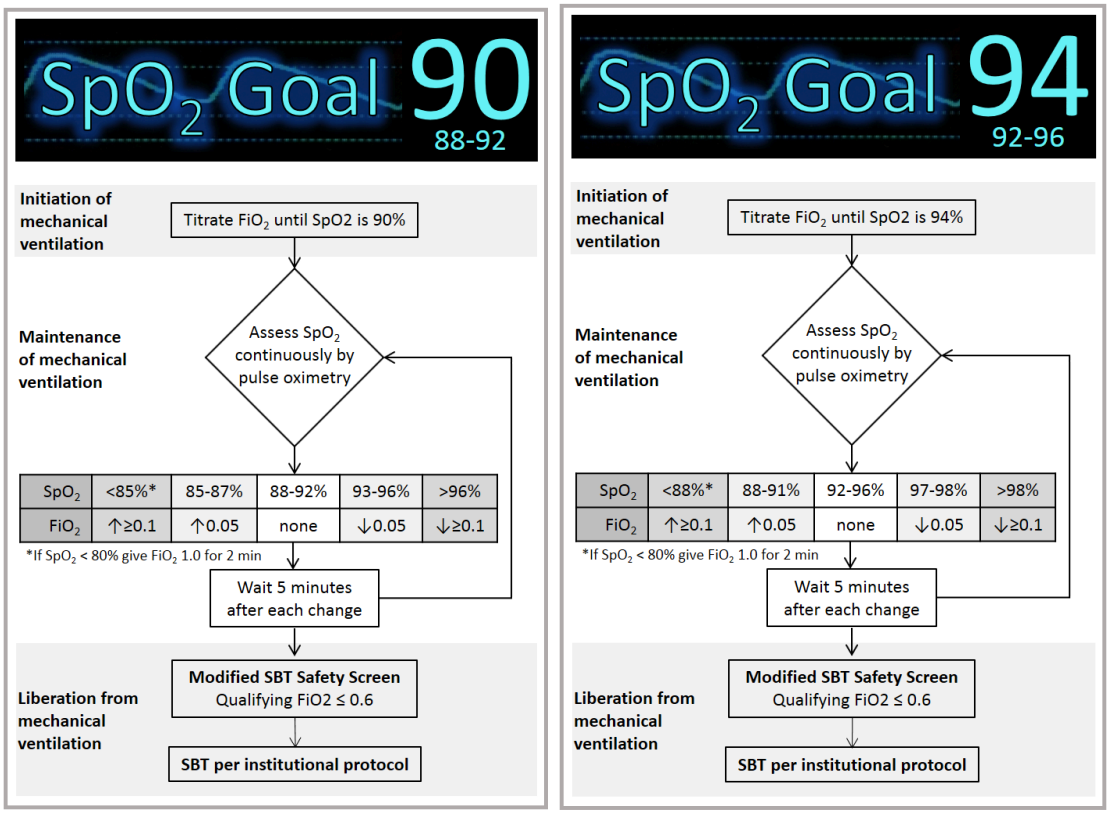
Study Group	SpO_2 target	SpO_2 range	PaO_2 target	PaO_2 range
Lower SpO_2 target	90%	88-92%	60 mm Hg	55-65 mm Hg
Intermediate SpO_2 target	94%	92-96%	70 mm Hg	65-80 mm Hg
Higher SpO_2target	98%	96-100%	110 mm Hg	> 80 mm Hg

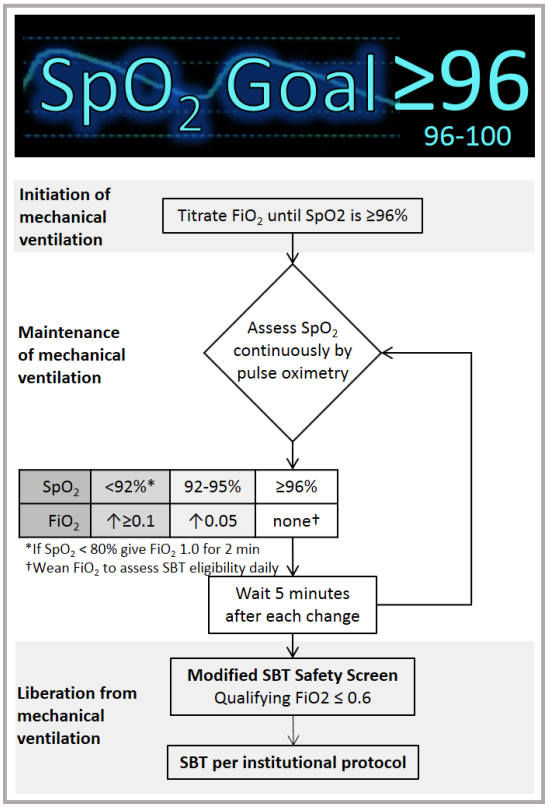
The SpO_2 target and range of SpO_2 values considered to be compliant are displayed for each study group. PaO_2 will be used to guide oxygen titration for participants without functioning pulse oximetry monitoring.

SpO_2 versus PaO_2: SpO_2 is measured continuously via non-invasive pulse oximetry for nearly all mechanically ventilated ICU patients. In contrast, PaO_2 is assessed via arterial puncture intermittently and selectively, particularly among more severely ill patients

earlier in their clinical course. Similar to prior studies of oxygen therapy during mechanical ventilation[29], the PILOT trial will target ranges of SpO_2 for all patients with functioning non-invasive pulse oximetry monitoring. For patients in the PILOT trial for whom non-invasive pulse oximetry monitoring is unavailable (e.g., inadequate plethysmography signal due to hypoperfusion), PaO_2 values corresponding to the assigned SpO_2 target will be used to guide oxygen therapy (see above Table).[35]

Oxygen Titration Protocol: In current usual care in the study ICU, titration of FiO_2 to maintain SpO_2 for mechanically ventilated adults is performed by respiratory therapists, with input from nurses and physicians. Other aspects of mechanical ventilation (selection of tidal volume, titration of positive end-expiratory pressure, screening for spontaneous breathing trials) are governed by respiratory therapy protocols jointly developed by respiratory therapy and physician leaders. In preparation for the PILOT trial, we have collaborated with respiratory therapy leaders in the study ICU to develop an oxygen titration protocol for each SpO_2 target group (see Figure below). Each block of the study, the mechanical ventilators in the study ICU will be outfitted by study personnel with paper copies of the oxygen titration protocol targeting the assigned SpO_2. The oxygen titration protocol will also be available to respiratory therapists, nurses, and physicians through the electronic order entry system.





Initiation of Mechanical Ventilation: The oxygen titration protocol guides respiratory therapists and treating clinicians to begin titrating FiO2 to the target SpO2 value within 15 minutes of the initiation of mechanical ventilation in the participating ED or ICU. This initial 15-minute window is intended to give the treating clinicians adequate time after emergent tracheal intubation to stabilize the patient's hemodynamics and initiate basic ventilator settings, but also to intervene early enough to control the FiO2 and SpO2 during the critical early period of mechanical ventilation when exposure to excess FiO2 and hyperoxemia is most common.

Oxygen Titration during Mechanical Ventilation: SpO_2 will be assessed by continuous pulse oximetry. The respiratory therapist managing the patient's ventilator will target an SpO_2 value of 98% in the higher SpO2 group, 94% in the intermediate SpO_2 group, and 90% in the lower SpO_2 group. The respiratory therapist will titrate FiO_2 as directed by the oxygen titration protocol when SpO_2 values are outside of the range 96-98% in the higher SpO_2 group, 92-96% in the intermediate SpO_2 group, and 88-92% in the lower SpO_2 group. SpO_2 will be reassessed 5 minutes after each change in FiO_2.

Liberation from Mechanical Ventilation: Each day of mechanical ventilation, all patients in the study ICU are assessed for safety of a spontaneous awakening trial (SAT) and spontaneous breathing trial (SBT)[36] using the SAT and SBT safety criteria from the

Awakening and Breathing Controlled trial.[37] To prevent patients in the higher SpO_2 target group from experiencing delays in qualifying for an SBT based on receipt of higher FiO_2 to achieve the higher SpO_2 target, during the PILOT trial we will allow patients in all groups to qualify for an SBT with an FiO2 ≤ 0.6. Definitions of SAT and SBT failure and the ventilator settings and duration of the SBT will not be changed from those used in the ABC trial and during usual care in the study ICU. For patients who have passed an SBT and SAT, the decision to discontinue invasive mechanical ventilation will be made by the treating clinicians.

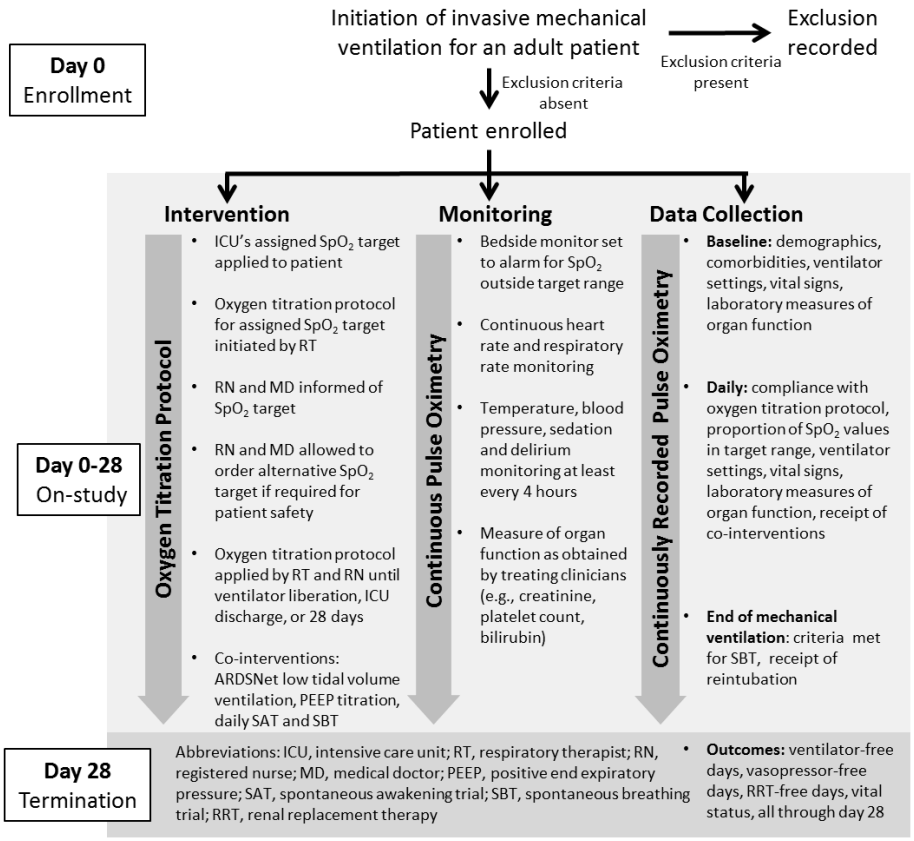
Modification of SpO_2 Targets: At any time during the course of the study, if a treating clinician feels an SpO_2 target other than that assigned by the study is required for the safe treatment of a specific patient, the SpO_2 target for that patient may be modified. To modify the target, the supervising physician will complete a one-page SpO_2 target modification sheet documenting the rationale for modifying the target and prompting reassessment of the need for modification every twelve hours. Details of each SpO_2 target modification will be collected and monitored. In our prior cluster-crossover trial using the same approach to modification of therapy assignment, treating clinicians exercised the ability to modify the assigned therapy for < 5% of patients.[38]

Anticipated examples of conditions for which treating clinicians may elect to override the assigned SpO2 target include:

- pneumothorax,
- pneumomediastinum,
- carbon monoxide poisoning,
- decompression sickness,
- bleomycin toxicity,
- paraquat toxicity

SpO_2 Monitoring: For all mechanically ventilated patients in the study ICU, SpO_2 is continuously monitored using Nellcor™ SpO_2 Adhesive Sensors (Medtronic, Minneapolis, MN), which measure changes in red and infrared light absorption in an arteriolar bed throughout the pulse cycle to report a non-normalized real-time plethysmographic waveform and arterial hemoglobin saturation values averaged over the prior 6 seconds with a mean difference between SpO_2 and SaO_2 < 2% for SpO_2 values 80-100%.[39] Plethysmography and SpO_2 values are displayed [1] on IntelliVue MP90 bedside patient monitors (PHILIPS, Amsterdam, Netherlands) in each ICU room, [2] on telemetry monitors located at ICU nursing stations and adjacent to the respiratory therapy office, and [3] in real-time in the institutional EHR, available from any physical location. SpO_2 values are archived every 60 seconds into an intuitional data warehouse.[40,41] **Collecting SpO_2 values every 60 seconds will allow the PILOT trial report with far greater accuracy the incidence, severity, and duration of desaturation than prior trials in which SpO_2 values were collected every 4-24 hours.**[29,30]

Feedback on SpO_2 Target Adherence: [1] During the study, the IntelliVue MP90 bedside patient monitors in each room will be set to generate a low priority alarm for SpO_2 values 1-3% outside the assigned target range and a high priority alarm for SpO_2 values ≥ 4% outside the assigned target range (see Figure below). For example, for patients in the lower SpO_2 target group, SpO_2 values 88-92% will generate no alarm, SpO_2 values 85-87% or 93-95% will generate a low priority alarm, and SpO2 values ≤ 84% or ≥ 96% will generate a high-priority alarm. [2] For the first 6 months of the PILOT trial, study personnel will remotely monitor SpO_2 values in real-time 8am-5pm Monday through Friday and during a 10% sample of night and weekend hours to identify instances of lag between out of range SpO_2 values and FiO_2 titration, provide feedback and reinforcement to bedside nurses and respiratory therapists, and identify any barriers to SpO_2 target compliance. [3] For the entire period of the PILOT trial, study personnel will attend quarterly respiratory therapy group meetings, monthly nursing unit board meetings, and monthly ICU physician leadership meetings to educate staff about the study, solicit safety concerns and adverse events, and identify and address barriers to SpO_2 target compliance. **This approach to daily monitoring and intermittent feedback to clinical personnel successfully achieved 95% compliance with the assigned intervention in a prior cluster-crossover trial in the same ICU.**[38]



Co-interventions: Institutional protocols in the study setting will ensure that mechanically ventilated patients in PILOT receive: [1] ventilation targeting 6 mL/kg of predicted body weight and plateau pressure ≤ 30 cm H_2O,[6] [2] PEEP titration according to the ARDSNet Lower PEEP/higher FiO_2 table (except for patients with severe ARDS, for

whom the Higher PEEP/lower FiO_2 table is applied),[42,43] [3] management of pain, agitation, and delirium[44] targeting Critical Care Pain Observation Tool (CPOT),[45] Richmond Agitation-Sedation Scale (RASS),[46,47] and Confusion Assessment Method for the ICU (CAM-ICU) scores,[48,49] and [4] daily spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT).[36,37]

7.2 Blinding: Similar to prior SpO_2 target studies among critically ill adults[29,30], patients and clinicians will not be blinded to study group assignment. Observer bias will be minimized by use of objective endpoints collected *in duplicate* by [1] study personnel blinded to group assignment and [2] automated data extraction from the EHR (see *Data Collection* below).

7.3 Data Collection: The PILOT trial will primarily use structured data collected in routine clinical care, exported daily from the institution's EHR into an Enterprise Data Warehouse, along with data from the patient registration, billing, and laboratory clinical information systems. We have previously validated the quality of this method of data collection against the reference standard of two-physician manual chart review,[50] and the planned approach to electronic dataset generation for the PILOT trial has already been successfully employed for the conduct of three prior pragmatic trials.[38,38,51]

Electronically extracted data elements will include:
Enrollment (Day 0): age; sex; race; ethnicity; height, weight; APACHE II score;[52] SOFA score;[53] Glasgow Coma Scale score;[54] Elixhauser Comorbidity Index;[55] vital signs (temperature, heart rate, systolic blood pressure, diastolic blood pressure, SpO_2); mechanical ventilator settings (mode, set and exhaled tidal volume, set and actual respiratory rate, positive end-expiratory pressure, peak pressure, FiO_2); serum laboratory values (white blood cell count, hemoglobin, platelet count, sodium, potassium, bicarbonate, creatinine, bilirubin, alanine aminotransferase, aspartate aminotransferase, lactate, arterial pH, PaO_2, SaO_2).

Daily On-Study (Days 0-28): Vital signs, ventilator settings, and serum laboratory values (as above); net fluid balance; receipt of red cell transfusion; number of arterial blood gases; SOFA score; ARDS by Berlin criteria;[56] Stage II or greater AKI by KDIGO criteria;[57] atrial arrhythmia, ventricular arrhythmia, cardiac arrest, or pneumothorax.

Termination (Days 0-28): Vital status at 28 days; time of liberation from invasive mechanical ventilation; receipt and duration of vasopressors; receipt and duration of renal replacement therapy; duration of ICU and hospital admission.

Data elements collected manually by study personnel will include: [1] all data elements for a randomly selected 10% of participants to ensure the quality of electronically extracted data, [2] all primary and secondary outcomes collected at study termination for 100% of participants to ensure duplicate data collection of key study outcomes, and [3] any data elements for which electronic data extraction has not been developed and validated, including etiology of respiratory failure, indication for mechanical ventilation, protocol violations, and adverse events. Data will be stored, curated, and secured in the online database, REDCap.[58]

7.4 Outcome Measures

Primary Outcome: Ventilator-free days (VFDs) to study day 28, defined as the number of days from liberation from invasive mechanical ventilation to day 28 after enrollment. Patients who continue to receive invasive mechanical ventilation at day 28 or have died prior to day 28 will receive zero VFDs. For patients who return to invasive mechanical ventilation and are subsequently liberated from invasive mechanical ventilation prior to day 28, VFDs will be counted from final liberation from mechanical ventilation. We chose VFDs as the primary outcome for the PILOT trial as choice of SpO_2 target may simultaneously affect both mortality and duration of invasive mechanical ventilation.

Secondary Clinical Outcomes:

1. ICU mortality
2. In-hospital mortality
3. Vasopressor-free days
4. Duration of vasopressor receipt
5. Renal replacement therapy-free days
6. Duration of renal replacement therapy receipt
7. ICU-free days
8. ICU-length of stay
9. Hospital length of stay.

Secondary Organ Function Outcomes: (All secondary organ function outcomes will employ only laboratory values and imaging obtained as a part of routine clinical care)

1. Daily SOFA score
2. Daily creatinine
3. Daily lactate
4. Presence of acute respiratory distress syndrome
5. Stage II or greater AKI by KDIGO criteria

Secondary Safety Outcomes:

1. Atrial arrhythmia
2. Ventricular arrhythmia

3. Cardiac arrest
4. Pneumothorax.

Secondary Feasibility Outcomes:

1. SpO_2
2. SaO_2
3. FiO_2
4. PaO_2
5. Percentage of SpO_2 values outside target range
6. <88% with FiO_2 <1.0
7. PaO_2 < 55 with FiO_2 <1.0
8. SpO_2 >98% with FiO_2 > 0.21
9. PaO_2 >120 with FiO_2 >0.21
10. Episodes of SpO_2 ≤ 85% lasting > 5 minutes
11. PaO_2/FiO_2 ratio

Secondary Process of Care Outcomes:

1. Tidal volume
2. Positive end expiratory pressure
3. Peak airway pressure
4. Net fluid balance
5. Receipt of mandatory ventilator mode
6. Number of arterial blood gasses
7. Hemoglobin
8. Red cell transfusion

8.0 Risks and Benefits:

Among adult patients for whom the treating clinicians have decided invasive mechanical ventilation is required, there are currently no established risks or benefits to targeting a higher, intermediate, or lower SpO_2. At this time, there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by critically ill patients receiving invasive mechanical ventilation as a part of routine care. The greater benefit of the study would be to society in the form of improved understanding of safe and effective provision of oxygen therapy during mechanical ventilation for critically ill patients.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. After publication, a de-identified database will be generated to protect participant privacy.

9.0 Safety Monitoring and Adverse Events:

9.1 Safety Monitoring

The PILOT trial will take place in a high-acuity clinical care environment during delivery of a high-acuity procedure required for routine clinical care. During the time of the study intervention, the patient will have a critical care or emergency medicine nurse with a low patient-to-nurse staffing ratio, immediate access to a respiratory therapist, and a team of critical care physicians physically located on the study unit twenty-four hours a day. As a part of routine care all patients will be receiving continuous invasive or non-invasive monitoring of heart rate, blood pressure, respiratory rate, and oxygen saturation.

Study personnel will monitor compliance with the study inclusion and exclusion criteria, study protocol, and study safety measures daily. Study personnel will be readily available to answer questions at any time from patients, legally authorized representatives, or treating clinicians. If, at any point in a patient's clinical course, the treating clinicians believe an SpO2 target different from the assigned target is required for the safe treatment of the patient, the SpO2 target will be modified to the target the treating clinicians judge to be safest.

A structured plan for prospective collection of study outcomes has been specified, in addition to a process by which Adverse Events and Serious Adverse Events will be managed and reported as required to regulatory bodies.

A Data and Safety Monitoring Board (DSMB) will be appointed to oversee the study. The DSMB will be available throughout the trial to monitor enrollment, protocol compliance, safety, and adverse events. Additionally the DSMB will perform an interim analysis for safety and efficacy.

9.2 Adverse Event Reporting

A system has been established to report and track clinical outcomes and adverse events (AEs). Study personnel will monitor the safety of subjects and follow AEs until the event resolves or is explained.

Clinical Outcomes (not considered Adverse Events). In this study of critically ill patients who are at high risk for death or other adverse outcomes due to their underlying critical illness, clinical outcomes, including death and organ dysfunction, will be systematically tracked (collected in the case report form) and will be included as part of the analyses for this study. For the purposes of reporting, death and organ dysfunction will not be recorded as AEs unless the investigator believes the event may have been caused by the study or is more severe or prolonged than expected given the underlying critical illness. This approach—considering death and organ dysfunction as outcomes rather than AEs

and systemically tracking expected outcomes for analysis rather than solely recording individual AEs—is common in ICU trials because these outcomes/events occur commonly in the ICU and this system mandates that data regarding death, organ dysfunction, and expected outcomes be tracked systematically for all patients and analyzed appropriately. Clinical outcomes will be systemically tracked throughout the study period. Listed below are events that will be tracked as primary or secondary clinical outcomes and will not therefore be reported as AEs during this study (unless believed to be study related and more severe or prolonged than expected given the underlying critical illness):

1. Death (all deaths occurring prior to hospital discharge will be reported on the CRF in the vital status at hospital discharge section);
2. Recurrence of respiratory failure, including need for re-intubation or non-invasive mechanical ventilation, presence of acute respiratory distress syndrome, or presence of pneumothorax;
3. Circulatory failure, including cardiac arrest or shock with or without receipt of vasopressors;
4. Incidence of sustained atrial and ventricular arrhythmias;
5. Acute kidney injury, including leading to increased creatinine or receipt of renal replacement therapy;
6. Hepatic injury or failure leading to increased bilirubin, AST, or ALT;
7. Coagulation derangements leading to elevated PT/INR or PTT, DIC, thrombocytopenia, or thrombocytosis;
8. Lactic acidosis;
9. Delirium, disability, and physical or cognitive impairment believed to be newly acquired;
10. All values for SpO_2, SaO_2, FiO_2, PaO_2, or PaO2/FiO2 ratio;
11. All values for vital signs (e.g., temperature, respiratory rate, SpO2);
12. Receipt of co-interventions (e.g., net fluid balance, number of arterial blood gasses, red cell transfusion)
13. Duration of ICU admission, ICU readmission;
14. Duration of hospitalization, hospital readmission;
15. Alterations in routine labs, including chemistries, complete blood counts, liver function tests, and hemostasis profiles.

Adverse Event Classifications. An Adverse Event (AE) will be any untoward medical occurrence for a patient enrolled in the trial that is not tracked as a clinical outcome, regardless of whether the event is considered study related or not. All AEs occurring during the observational study period will be recorded on the CRF. All AEs will then be assessed as to whether they are (1) related to study procedures, (2) serious, and/or (3) unexpected according to the following definitions:

I. Related to study procedures. AEs that the investigator suspects are related to the study will be classified as study related. Certainty of relatedness is not required as long as a reasonable possibility exists that the AE is related to a study procedure.

II. Serious. AEs that meet any of the criteria below will be considered Serious Adverse Events (SAEs):
   a. Results in death
   b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
   c. Prolongs an existing hospitalization
   d. Results in persistent or significant disability or incapacity
   e. Results in a congenital anomaly or birth defect
   f. Important medical event that requires an intervention to prevent any of a-e above.

III. Unexpected. AEs that are more severe or prolonged than expected based on the investigator's discretion will be considered Unexpected.

The PILOT trial will monitor, track, and report all Clinical Outcomes and AEs as required by regulatory bodies.

Communication and Reporting of Adverse Events. In order to ensure proper and timely reporting of all adverse events, there will be a clear communication plan for all study personnel to follow. AEs will be recorded in the AE CRF in the electronic database and reported to the PI within 5 days of occurrence. The PI will provide a report of all AEs annually to the IRB and DSMB as part of the annual review process as required. All SAEs will be reported to the PI within 72 hours of occurrence. The PI will, in turn, report all SAEs to the IRB, DSMB, and funding body within 7 calendar days of occurrence.

9.3 Frequency of Monitoring and Interim Analysis.

Study personnel will continuously monitor enrollment, protocol compliance, and AEs and SAEs throughout the course of the trial. Annually, the DSMB will formally review enrollment, protocol compliance, and AEs and SAEs as part of a formal DSMB meeting. Additionally, the DSMB will be available to convene a meeting at any point in the course of the trial to review urgent issues related to AEs, protocol compliance, or unexpected adverse events. Study personnel and DSMB members will adhere to the expectations for reporting and managing AEs and unexpected adverse events outlined in the DSMB charter.

Interim Analysis. In addition to ongoing monitoring of safety throughout the trial, the DSMB will conduct a single interim analysis for efficacy and safety at the

anticipated halfway point of the PILOT trial. The interim analysis will include patients enrolled during the first 18 months of the trial. The stopping boundary for efficacy will be met if the P value for the difference between groups is <0.001. Use of the conservative Haybittle-Peto boundary (P < 0.001) will allow the final analysis to be performed using an unchanged level of significance (P = 0.05). Given the minimal risk nature of the study and current use of all SpO_2 target as a part of usual care, there will be no stopping boundary for futility. The DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

9.4 Data and Safety Monitoring Board (DSMB). A formal independent DSMB will oversee the conduct of the trial and the planned interim analysis. The DSMB will be composed of at least one physician outside the study institution experienced in the conduct of critical care clinical trials and one biostatistical expert who will assist with study monitoring and performance of the interim analysis.

9.5 Data Monitoring Plan. To ensure data are accurately and completely collected during the PILOT trial, the study team will follow a specific Data Monitoring Plan. All clinical outcomes will be collected in duplicate by both electronic data collection and by the study nurse. All study data from random sample of 10% of study records will be collected in duplicate by electronic data collection and by the study nurse. Each of these records will also be reviewed annually by the primary investigator to ensure data collection is accurate, complete, and current. The study biostatistician will run periodic data cleans throughout the study looking for outliers or overtly erroneous data. This Monitoring Plan will serve as a method for identifying and resolving systematic problems and therefore increase data quality. We will submit progress reports to the local IRB annually, or more frequently if requested.

10.0 Study Withdrawal/Discontinuation

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI.

The reason and date of every withdrawal will be recorded in the patient study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or other safety parameter that could have led to discontinuation. Follow-up will be conducted until the condition has resolved, until diagnosis of the adverse event or

safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well.

11.0 Statistical Considerations

Power calculation. In a prior cluster-randomized cluster-crossover trial in the same ICU,[51] 880 mechanically ventilated adults were enrolled per year (73.3 per month), with a median of 22 VFDs [IQR 0-25 VFDs] and an intra-cluster intra-period correlation of 0.01. During the planned 36 month PILOT trial, we estimate 2,640 mechanically ventilated adults will be admitted to the study ICU, of whom 390 will be excluded during washout periods and 2,250 will be enrolled. With a total enrollment of 2,250 patients, a standard deviation in the primary outcome of VFDs of 11.4 days, and a two-sided alpha of 0.05, ***the PILOT trial will have 92 percent statistical power to detect an absolute reduction in VFDs of 2.0 days*** (similar to the numerical difference in VFDs between SpO_2 target groups reported in prior studies[29,30]).

Proposed effect modifiers to be included in model		
	Lower SpO_2 target better	**Higher SpO_2 target better**
Demographic	--	↑Age
Comorbidities	Supplemental O_2, COPD	↑NYHA stage of CHF, Coronary disease
Acute illnesses	Cardiac arrest, Myocardial infarction, ARDS, Pneumonia, Sepsis	Ischemic stroke, Status epilepticus, Acute kidney injury
Severity of illness	↑SOFA score	--
Vent Settings	↑static compliance, ↓PaO_2/FiO_2	--
Lab values	↑WBC, ↓Platelets, ↓Albumin	↓Hemoglobin, ↓Bicarbonate
Possible effect modifiers not included in model due to low representation in study ICU: Traumatic brain injury, Post-operative admission after organ transplant or surgical anastomosis		
Additional co-variates included in the model: Sex, Race, End-stage renal disease, Pre-enrollment duration of mechanical ventilation		

NYHA = New York Heart Association; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; ARDS = acute respiratory distress syndrome; SOFA = sequential organ failure assessment; WBC = white blood cell count

Primary analysis. The primary analysis will be an intention-to-treat comparison of the number of VFDs experienced by patients in each study group using the Kruskal–Wallis test. Secondary analyses will include [1] intention-to-treat comparisons of the pre-specified secondary outcomes between study groups; [2] intention-to-treat comparison of the SpO_2 target groups with regard to ventilator free days using a generalized linear mixed-effects model adjusting for fixed effects (age, sex, race, source of admission, vasopressor receipt, acute diagnosis) and random effects (study period) to account for intra-period correlation, and [3] examination of the differential effects of the intervention for patients with different baseline characteristics (heterogeneity of treatment effect) (see Figure below).

All of secondary analyses will be considered hypothesis-generating, and no corrections for multiple comparisons will be performed. No imputations will be made for missing baseline or on-study laboratory or physiologic data. Continuous variables will be described as mean and standard deviation or median and 25th percentile – 75th percentile or bootstrapped 95% confidence intervals as appropriate. Categorical variables will be given as number and percentage. All between-group comparisons with continuous variables will be performed using Kruskal–Wallis tests; categorical variables will be compared with chi-square testing or Fisher's exact test as appropriate. A complete pre-specified statistical analysis plan will be published prior to the completion of enrollment.

Interim Analysis

We will plan for the DSMB to conduct a single interim analysis for efficacy and safety at the anticipated halfway point of the trial. The interim analysis will include patients enrolled during the first 18 months of the trial. The stopping boundary for efficacy will be met if the P value for the difference between groups is <0.001. Use of the conservative Haybittle-Peto boundary ($P < 0.001$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$). Given the minimal risk nature of the study and current use of all SpO_2 target as a part of usual care, there will be no stopping boundary for futility. The DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

12.0 Privacy/Confidentiality Issues

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the treating clinician

modification of SpO_2 target sheet will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

13.0 Follow-up and Record Retention

Patients will be followed after enrollment for 28 days or until hospital discharge, whichever occurs first. Data collected from the medical record will be entered into the secure online database REDCap. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

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Pragmatic Investigation of optimaL Oxygen Targets (PILOT) trial

Version 1.5

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Study Schema

1.0 Study Summary

Title: Pragmatic Investigation of optimaL Oxygen Targets (PILOT) trial

Background: Mechanical ventilation of ICU patients universally involves titration of the fraction of inspired oxygen (FiO_2) to maintain arterial oxygen saturation (SpO_2). Despite decades of ICU practice, however, the optimal SpO_2 target remains unknown. Higher SpO_2 targets (96-100%) provide a margin of safety against hypoxia but increase exposure to hyperoxia. Lower SpO_2 targets (88-92%) minimize hyperoxia, but may increase the risk of hypoxia. An intermediate SpO_2 target (92-96%) may avoid the risks of both hyperoxia and hypoxia, or may expose patients intermittently to both sets of risks. Current guidelines offer divergent recommendations as to the optimal SpO_2 target and clinical safety and efficacy data are lacking. Therefore, we propose a 2,250-patient cluster-randomized cluster-crossover trial comparing a lower SpO_2 target (target 90% and goal range 88-92%), an intermediate SpO_2 target (target 94% and goal range 92-96%), and a higher SpO_2 target (target 98% and goal range 96-100%) with regard to the outcome of days alive and free of invasive mechanical ventilation.

Primary Aim:

- To compare the effect of higher, intermediate, and lower SpO_2 targets on days alive and free of invasive mechanical ventilation among mechanically ventilated critically ill adults.

Primary Hypothesis:

- Use of a lower SpO_2 target (target 90% and goal range 88-92%) for mechanically ventilated ICU patients will result in more days alive and free of invasive mechanical ventilation than use of an intermediate SpO_2 target (target 94% and goal range 92-96%) or a higher SpO_2 target (target 98% and goal range 96-100%).

Inclusion Criteria:

- We will include adults (≥ 18 years old) receiving mechanical ventilation through an endotracheal tube or tracheostomy who are admitted to the study ICU or for whom admission to the study ICU from the emergency department is planned.

Exclusion Criteria:

- We will exclude patients who are pregnant or who are prisoners.

Consent: Because [1] the study enrolls only patients who would have been exposed to oxygen therapy as a part of clinical care outside of the study, [2] all SpO_2 targets examined are currently used in routine care in the study ICU, [3] no high-quality data suggest that the choice of SpO_2 target affects clinical outcomes, and [4] during the trial

treating clinicians retain discretion to control the SpO_2 target when felt to be required for the safe treatment a specific patient, we feel the study qualifies as minimal risk. Given the minimal risk, the implementation of SpO_2 targets at an ICU level, and the impracticability of consenting each patient during initiation of mechanical ventilation in the ICU or emergency department, we will request a waiver of informed consent.

Randomization: In the PILOT trial, the entire study ICU will be assigned to a single SpO_2 target (cluster-randomized) and the ICU will switch between lower, intermediate, and higher SpO_2 targets every two months in a randomly generated sequence (cluster-crossover).

Study Interventions:

- **Lower SpO_2 Target** – FiO_2 will be titrated to a target SpO_2 of 90% with a goal range of 88-92%.
- **Intermediate SpO_2 Target** – FiO_2 will be titrated to a target SpO_2 of 94% with a goal range of 92-96%.
- **Higher SpO_2 Target** – FiO_2 will be titrated accord to a target SpO_2 of 98% with a goal range of 96-100%.

Primary Outcome:

- Ventilator-free days (VFDs) to study day 28, defined as the number of calendar days alive and free of invasive mechanical ventilation from the final receipt of invasive mechanical ventilation through 28 days after enrollment.

Secondary Outcome:

- 28-day in-hospital mortality, defined as death from any cause between enrollment and the first of hospital discharge or 28 days after enrollment.

Exploratory Outcomes:

- *Exploratory Clinical Outcomes*: ICU mortality, vasopressor-free days, renal replacement therapy-free days, ICU-free days, hospital-free days.
- *Exploratory Organ Function Outcomes*: daily non-respiratory SOFA score, creatinine, lactate, presence of acute respiratory distress syndrome, Stage II or greater AKI by KDIGO criteria.
- *Exploratory Safety Outcomes*: Atrial arrhythmia, ventricular arrhythmia, cardiac arrest with return of spontaneous circulation, pneumothorax or pneumomediastinum, ischemic stroke, myocardial infarction

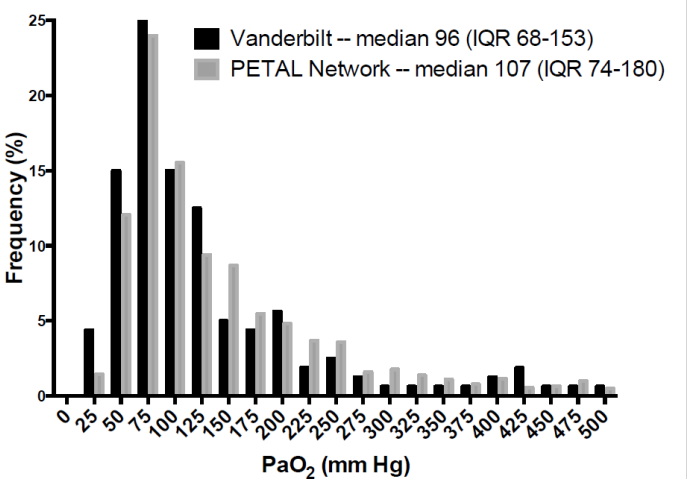
2.0 Background

Each year 2-3 million intensive care unit (ICU) patients receive invasive mechanical ventilation,[1–3] at a cost of more than $20 billion dollars.[4,5] Despite recent advances,[6] in-hospital mortality among mechanically ventilated ICU patients remains 25-35%,[7] and survivors often face cognitive, psychiatric, and physical dysfunction.[8–11]

Mechanical ventilation of ICU patients universally involves titration of the fraction of inspired oxygen (FiO_2) to maintain arterial oxygen saturation (SpO_2). Despite decades of ICU practice, however, the optimal SpO_2 target remains unknown. Higher SpO_2 targets (96-100%) provide a margin of safety against hypoxemia, but may increase exposure to excess FiO_2, hyperoxemia, and tissue hyperoxia, causing oxidative damage, [12–14] inflammation,[15,16] and increased alveolar-capillary permeability.[17] Lower SpO_2 targets (88-92%) minimize hyperoxia,[6,18,19] but may increase the risk of hypoxemia, tissue hypoxia, and organ dysfunction.[20,21] An intermediate SpO_2 target (92-96%) may avoid the risks of both hyperoxia and hypoxia, or, conversely, may expose patients intermittently to both sets of risks.

Current guidelines offer divergent recommendations – ranging from tolerating SpO_2 values as low as 88% (ARDS Network)[22,23] to pursuing SpO_2 values as high as 98% (British Thoracic Society)[24]. The relative risks and benefits of different SpO_2 targets have been extensively examined in the setting of the neonatal ICU,[25–28] but have only been investigated in adult ICU patients in three small trials.[29–31] Targeting lower SpO_2 resulted in improved survival in one trial and trends toward improved survival in the other two.

In clinical practice, however, hyperoxemia remains common.[32,33] In our recent observational study of 2,200 mechanically ventilated ICU patients at 50 centers across the United States (see Figure), the majority of patients had a lowest PaO_2 value on the first study day > 100 mm Hg (~SpO_2 > 97%). The wide variation in current practice (frequently favoring higher SpO_2 targets), conflicting guidelines, and pilot trial data favoring lower SpO_2 targets have led to calls for a large, randomized trial to determine the effect of SpO_2 target on patient outcomes.[18]



3.0 Rationale, Aims, and Hypotheses

In order to determine the effect of SpO_2 targets during mechanical ventilation of critically ill adults on clinical outcomes, a randomized trial is needed.

Study Aims:

- **Primary:** To compare the effect of higher, intermediate, and lower SpO_2 targets on days alive and free of invasive mechanical ventilation among mechanically ventilated critically ill adults.

- **Secondary:**
    - To evaluate the effect of the same intervention in the same population on the pre-specified *Secondary Outcome* and on pre-specified *Exploratory Clinical Outcomes*, *Exploratory Organ Function Outcomes*, and *Exploratory Safety Outcomes*.
    - To evaluate the effect of the same intervention on days alive and free of invasive mechanical ventilation in clinically relevant pre-specified patient subgroups.

Study Hypotheses:

- **Primary:** Use of a lower SpO_2 target (target 90% and goal range 88-92%) for mechanically ventilated ICU patients will result in more days alive and free of invasive mechanical ventilation (*Primary Outcome*) than use of an intermediate SpO_2 target (target 94% and goal range 92-96%) or a higher SpO_2 target (target 98% and goal range 96-100%).

- **Secondary:** Use of a lower SpO_2 target (target 90% and goal range 88-92%) for mechanically ventilated ICU patients will result in lower 28-day in-hospital mortality (*Secondary Outcome*) than use of an intermediate SpO_2 target (target 94% and goal range 92-96%) or a higher SpO_2 target (target 98% and goal range 96-100%).

4.0 Study Description

In order to address the aims outlined above, we propose the Pragmatic Investigation of optimaL Oxygen Targets (PILOT) trial. The PILOT trial will be a prospective, un-blinded, cluster-randomized, cluster-crossover trial conducted between July 1, 2018 and August 31, 2021 in the medical ICU at Vanderbilt University Medical Center examining the effect of SpO_2 targets on days alive and free of mechanical ventilation among mechanically ventilated ICU patients. For the 36 months of enrollment in the PILOT trial, the entire medical ICU will be assigned to a single SpO_2 target and the ICU will switch between lower, intermediate, and higher SpO_2 targets every two months in a

randomly generated sequence (Figure below). Patients who fulfill inclusion criteria without meeting exclusion criteria will be enrolled at the initiation of mechanical ventilation in the study ICU or in the emergency department when admission to the study ICU is planned. The PILOT trial will control only the SpO_2 target and all other aspects of patients' clinical care will remain at the discretion of the treating clinicians.

Study Year 1						Study Year 2						Study Year 3					
Jul-Aug	Sep-Oct	Nov-Dec	Jan-Feb	Mar-Apr	May-Jun	Jul-Aug	Sep-Oct	Nov-Dec	Jan-Feb	*Mar & Jun*	Jul-Aug	Sept-Oct	Nov-Dec	Jan-Feb	Mar-Apr	May-Jun	Jul-Aug
2018			2019						2020			2021					
High	Mid.	Low	Mid	Low	High	Low	Mid.	High	High	Mid.	Low	Mid.	High	Low	Mid.	High	Low

The study ICU was randomly assigned to an SpO2 target for each two-month block. The study did not enroll in April and May of 2020 secondary to the COVID-19 pandemic. High = SpO2 target 98% (range 96-100%), Mid. = SpO2 target 94% (range 92-96%), Low = SpO2 target 90% (range 88-92%)

5.0 Inclusion and Exclusion Criteria

5.1 Inclusion Criteria:

1. Age ≥ 18 years
2. Receiving mechanical ventilation through an endotracheal tube or tracheostomy
3. Admitted to the study ICU or admission to the study ICU from the emergency department is planned

5.2 Exclusion Criteria:

1. Known pregnancy or beta hCG level greater than the laboratory upper limit of normal in a patient capable of becoming pregnant
2. Known to be a prisoner

6.0 Enrollment/Randomization

6.1 Study Sites:

- Medical Intensive Care Unit at Vanderbilt University Medical Center
- Emergency Department at Vanderbilt University Medical Center

6.2 Study Population: All adults located in the study ICU (or for whom admission to the study ICU from the emergency department is planned) for whom the treating clinicians have decided invasive mechanical ventilation is required will be enrolled unless meeting exclusion criteria. Patients will be included regardless of age, gender, race, weight or body mass index, initial oxygen saturation, or other clinical factors.

6.3 Enrollment: All adult patients who do not meet exclusion criteria will be enrolled immediately upon receipt of invasive mechanical ventilation in the study ICU or in the emergency department when admission to the study ICU is planned.

6.4 Consent:

All patients receiving invasive mechanical ventilation in an intensive care unit receive oxygen therapy titrated to maintain SpO_2 as a part of routine care. In clinical practice, 98% of SpO_2 values experienced by mechanically ventilated adults fall between 88-100%.[32,33] Within this range, current guidelines for oxygen therapy in mechanically ventilated adults outline three contrasting approaches: [1] tolerating SpO_2 values as low as 88% (NIH/NHLBI ARDS Network),[22] [2] titrating within the range 92-96% (Thoracic Society of Australia and New Zealand),[34] or [3] pursuing SpO_2 values as high as 98% (British Thoracic Society).[24] The lower SpO_2 target (target 90% and goal range 88-92%), intermediate SpO_2 target (target 94% and goal range 92-96%), and higher SpO_2 target (target 98% and goal range 96-100%) examined in this study are all intermittently used in routine care in the study ICU and within the range recommended by at least one international guideline. There are currently no high-quality data to suggest that one SpO_2 target is better than the others with regard to clinical outcomes. Although there are no clear data to support the choice of SpO_2 target, during the PILOT trial, treating clinicians in the study ICU will be allowed to change the SpO_2 target at any point if it is felt to be required for the safe treatment a specific patient.

Because the interventions studied [1] are used as part of routine care in the study ICU, [2] are interventions to which the patient would be exposed even if not participating in the study, [3] have no prior data to suggest the superiority of one approach over the other, and [4] are equivalent options from the perspective of the treating clinicians (otherwise the treating clinician retains control of SpO_2 target), we feel the study presents minimal risk.

Additionally, obtaining informed consent prior to participation in the study would be impractical. Endotracheal intubation and initiation of mechanical ventilation for critically ill patients is frequently a time-sensitive procedure. Despite the availability of a formal informed consent document for the endotracheal intubation and initiation of mechanical ventilation, time allows discussion of risks and benefits in less than 10% of airway management events in the study ICU. The oxygen titration protocol used to target SpO_2 in this trial begins immediately at the initiation of mechanical ventilation to capture the period of mechanical ventilation with the highest risk for hyperoxia and hypoxia. Moreover, in this cluster-randomized trial, the entire ICU is assigned to a single SpO_2 target delivered by the unit's respiratory therapists through a unit-wide oxygen titration protocol. Obtaining informed consent from every eligible patient in the ICU each day would be logistically infeasible and patients who declined to participate would need to be transferred between ICUs which might adversely impact their care.

Because the study presents minimal risk, would not adversely affect the welfare or privacy rights of the participant, and consent would be impracticable, we will request a waiver of informed consent.

6.5 Information for Patients, Families, or Surrogates about the Study:

Although the study will be conducted with waiver of informed consent, we will implement a process by which patients, families, or surrogates may be made aware of the study and receive investigators' contact information in order to solicit additional information about the study, ask questions, or express concerns. An information sheet providing an IRB-approved lay language summary of the study activities and containing the contact information for investigators (who will remain available throughout the study period to provide additional information to patients and families upon request) will be made available in the following manner:

1. Throughout the study period, the information sheet will be posted in at least two glass display cases, one near the public entrance to the medical ICU and one near the mid-point of the medical ICU.
2. Throughout the study period, the information sheet will be included in the welcome packet of information about the medical ICU, which is distributed at the time of ICU admission to available families or surrogates by the medical receptionist or charge nurse as a part of routine clinical care.
3. Throughout the study period, copies of the information sheet will be available in a brochure holder on the display table in the medical ICU family waiting room.
4. Throughout the study period, additional copies of the information sheet will be available in the physician and respiratory therapy offices to be provided to patients, families, or surrogates with questions or concerns about the study.

Unlike an informed consent document, the information sheet will not be distributed by research personnel directly to participants but will be made generally available in the study setting to patients, families, and surrogates. There may be patients in the study who do not receive information about the study (e.g., a patient without family or surrogate who is admitted to the ICU with coma). There may be patients who are not in the study who do receive information about the study (e.g., a patient admitted to the medical ICU on high-flow nasal cannula who does not require invasive mechanical ventilation).

In order to ensure and record the execution of the above approach to providing information about the study, the primary investigator will:

1. Throughout the study period, audit in-person at least every fourteen (14) days to confirm that the most recent IRB-approved information sheet is posted in at least two glass display cases in the medical ICU. At least twice a year take a photograph of the most recent IRB-approved information sheet in one of the glass display cases in the medical ICU. Store the photographs with the date and time that they were taken electronically in the study files and in hard copy in the study binder.

2. Throughout the study period, audit in-person at least every fourteen (14) days to confirm that copies of the most recent IRB-approved information sheet are available in a brochure holder on the display table in the medical ICU family waiting room. At least twice a year, take a photograph of the most recent IRB-approved information sheets in a brochure holder on the display table in the medical ICU family waiting room. Store the photographs with the date and time that they were taken electronically in the study files and in hard copy in the study binder.
3. Throughout the study period, audit in-person at least every fourteen (14) days to confirm that additional copies of the information sheet are available in the physician and respiratory therapy offices to be provided to patients, families, or surrogates with questions or concerns about the study.
4. Record and complete a case report form in the study database detailing contact about the study between patients, families, and surrogates and study personnel.

6.6 Randomization:

During each two-month block of the study, the ICU will be assigned to either a higher SpO_2 target (target 98% and goal range 96-100%), an intermediate SpO_2 target (target 94% and goal range 92-96%), or a lower SpO_2 target (target 90% and goal range 88-92%). The order of study group assignments will be generated by computerized randomization using permuted blocks of 3 to minimize the impact of seasonal variation. The last 7 days of each two-month block will be a washout period during which the ICU will continue to target the assigned SpO_2 but new patients will not be included in the primary analysis. Assuming a duration of mechanical ventilation similar to that observed for mechanically ventilated patients admitted to the study ICU in a prior year (median 3 [IQR 3-5] days), a 7-day washout period will ensure that 98% patients do not experience a "crossover" from one assigned SpO_2 target to another.

7.0 Study Procedures

7.1 Study Interventions

Choice of SpO_2 targets: In clinical practice, 98% of SpO_2 values experienced by mechanically ventilated adults fall between 88-100%.[32,33] Within this range, current guidelines for oxygen therapy in mechanically ventilated adults outline three contrasting approaches: [1] tolerating SpO_2 values as low as 88% (NIH/NHLBI ARDS Network),[22] [2] titrating within the range 92-96% (Thoracic Society of Australia and New Zealand),[34] or

[3] pursuing SpO_2 values as high as 98% (British Thoracic Society).[24] The PILOT trial will have three study groups, each emulating an approach to SpO_2 targets represented in guidelines and clinical practice (Table).

Study Group	SpO_2 target	SpO_2 range	PaO_2 target	PaO_2 range
Lower SpO_2 target	90%	88-92%	60 mm Hg	55-65 mm Hg
Intermediate SpO_2 target	94%	92-96%	70 mm Hg	65-80 mm Hg
Higher SpO_2target	98%	96-100%	110 mm Hg	> 80 mm Hg

The SpO_2 target and range of SpO_2 values considered to be compliant are displayed for each study group. PaO_2 will be used to guide oxygen titration for participants without functioning pulse oximetry monitoring.

SpO_2 versus PaO_2: SpO_2 is measured continuously via non-invasive pulse oximetry for nearly all mechanically ventilated ICU patients. In contrast, PaO_2 is assessed via arterial puncture intermittently and selectively, particularly among more severely ill patients earlier in their clinical course. Similar to prior studies of oxygen therapy during mechanical ventilation[29], the PILOT trial will target ranges of SpO_2 for all patients with functioning non-invasive pulse oximetry monitoring. For patients in the PILOT trial for whom non-invasive pulse oximetry monitoring is unavailable (e.g., inadequate plethysmography signal due to hypoperfusion), PaO_2 values corresponding to the assigned SpO_2 target will be used to guide oxygen therapy (see above Table).[35]

Oxygen Titration: In the study ED and ICU, and in the United States generally, titration of FiO_2 to maintain SpO_2 for mechanically ventilated adults is most commonly performed by respiratory therapists, with input from nurses and physicians. Other aspects of mechanical ventilation (selection of tidal volume, titration of positive end-expiratory pressure, screening for spontaneous breathing trials) are governed by respiratory therapy protocols jointly developed by respiratory therapy and physician leaders. In preparation for the PILOT trial, we collaborated with respiratory therapy leaders in the study ED and ICU to adapt existing ventilator management protocols to provide guidance for respiratory therapists in titrating FiO_2 to achieve each of the three study SpO_2 targets.

Initiation of Mechanical Ventilation: The study protocol guides respiratory therapists and treating clinicians to begin titrating FiO_2 to the target SpO_2 value within 15 minutes of the initiation of mechanical ventilation in the participating ED or ICU. This initial 15-minute window is intended to give the treating clinicians adequate time after emergent tracheal intubation to stabilize the patient's hemodynamics and initiate basic ventilator settings, but also to intervene early enough to control the FiO_2 and SpO_2 during the

critical early period of mechanical ventilation when exposure to excess FiO_2 and hyperoxemia is most common.

Oxygen Titration during Mechanical Ventilation: SpO_2 will be assessed by continuous pulse oximetry. The respiratory therapist managing the patient's ventilator will target an SpO_2 value of 98% in the higher SpO_2 group, 94% in the intermediate SpO_2 group, and 90% in the lower SpO_2 group. The respiratory therapist will titrate FiO_2 as directed by the oxygen titration protocol when SpO_2 values are outside of the range 96-100% in the higher SpO_2 group, 92-96% in the intermediate SpO_2 group, and 88-92% in the lower SpO_2 group. Respiratory therapists and other treating clinicians may also titrate FiO_2 when SpO_2 values are not outside the range considered to be at goal in order to achieve SpO_2 values closer to the assigned SpO_2 target, to facilitate weaning from mechanical ventilation, or for other clinical reasons. SpO_2 will be reassessed 5 minutes after each change in FiO_2 or sooner if clinically indicated. Study protocol determines the SpO_2 target from enrollment until the first of: (1) extubation from invasive mechanical ventilation, (2) transfer out of a participating study location, (3) completion of an SpO_2 target modification sheet by treating clinicians, or (4) end of the two-month study period. Study protocol does not determine the SpO_2 target during time-periods in which the patient is not physically located in a study location (e.g., during transport) or when FiO_2 is not being titrated to achieve an SpO_2 target (e.g., when an FiO_2 of 1.0 is being administered for a procedure).

Liberation from Mechanical Ventilation: Each day of mechanical ventilation, all patients in the study ICU are assessed for safety of a spontaneous awakening trial (SAT) and spontaneous breathing trial (SBT)[36] using the SAT and SBT safety criteria from the Awakening and Breathing Controlled trial.[37] To prevent patients in the higher SpO_2 target group from experiencing delays in qualifying for an SBT based on receipt of higher FiO_2 to achieve the higher SpO_2 target, during the PILOT trial we will allow patients in all groups to qualify for an SAT and SBT regardless of their current FiO_2 or PEEP settings, as long as the other SAT and SBT Safety Screen criteria are met and treating clinicians feel performance of an SAT and SBT is safe. Definitions of SAT and SBT failure and the ventilator settings and duration of the SBT will not be changed from those used in the ABC trial and during usual care in the study ICU. For patients who have passed an SAT and SBT, the decision to discontinue invasive mechanical ventilation will be made by the treating clinicians.

Modification of SpO_2 Targets: At any time during the course of the study, if a treating clinician or a patient, family member, or surrogate feels an SpO_2 target other than that assigned by the study is required for the safe treatment of a specific patient, the SpO_2 target for that patient may be modified. To modify the target, the supervising physician will complete a one-page SpO_2 target modification sheet documenting the rationale for modifying the target. Details of each SpO_2 target modification will be collected and

monitored. In our prior cluster-crossover trial using the same approach to modification of therapy assignment, treating clinicians exercised the ability to modify the assigned therapy for < 5% of patients.[38]

Anticipated examples of conditions for which treating clinicians may elect to override the assigned SpO_2 target include:

- pneumothorax
- pneumomediastinum
- carbon monoxide poisoning
- decompression sickness
- bleomycin toxicity
- paraquat toxicity

SpO_2 Monitoring: For all mechanically ventilated patients in the study ICU, SpO_2 is continuously monitored using Nellcor™ SpO_2 Adhesive Sensors (Medtronic, Minneapolis, MN), which measure changes in red and infrared light absorption in an arteriolar bed throughout the pulse cycle to report a non-normalized real-time plethysmographic waveform and arterial hemoglobin saturation values averaged over the prior 6 seconds with a mean difference between SpO_2 and SaO_2 < 2% for SpO_2 values 80-100%.[39] Plethysmography and SpO_2 values are displayed [1] on IntelliVue MP90 bedside patient monitors (PHILIPS, Amsterdam, Netherlands) in each ICU room, [2] on telemetry monitors located at ICU nursing stations and adjacent to the respiratory therapy office, and [3] in real-time in the institutional EHR, available from any physical location. SpO_2 values are archived every 60 seconds into an intuitional data warehouse.[40,41] Collecting SpO_2 values every 60 seconds will allow the PILOT trial report with far greater accuracy the incidence, severity, and duration of desaturation than prior trials in which SpO_2 values were collected every 4-24 hours.[29,30]

Feedback on SpO_2 Target Adherence: [1] During the study, the IntelliVue MP90 bedside patient monitors in each room will be set to generate an alarm for SpO2 values outside the range considered to be at goal for the assigned SpO2 target group. For example, for patients in the intermediate SpO2 target group, SpO2 values 92-96% generate no alarm, whereas SpO2 values ≤ 91% or ≥ 97% generate an alarm alerting nursing staff and respiratory therapy to the out-of-range value. [2] Study personnel will remotely monitor SpO_2 values every four hours from 4 AM through 10 PM Monday through Friday and during a 10% sample of night and weekend hours to identify instances of lag between out of range SpO_2 values and FiO_2 titration, provide feedback and reinforcement to bedside nurses and respiratory therapists, and identify any barriers to SpO_2 target compliance. [3] Study personnel will attend respiratory therapy group meetings, nursing unit board meetings, and ICU physician leadership meetings to educate staff about the study, solicit safety concerns and adverse events, and identify and address barriers to SpO_2 target compliance. This approach to daily monitoring and

intermittent feedback to clinical personnel successfully achieved 95% compliance with the assigned intervention in a prior cluster-crossover trial in the same ICU.[38]

Co-interventions: Institutional protocols in the study setting will ensure that mechanically ventilated patients in PILOT receive: [1] ventilation targeting 6 mL/kg of predicted body weight and plateau pressure ≤ 30 cm H_2O,[6] [2] PEEP titration according to the ARDSNet Lower PEEP/higher FiO_2 table (except for patients with severe ARDS, for whom the Higher PEEP/lower FiO_2 table is applied),[42,43] [3] management of pain, agitation, and delirium[44] targeting Critical Care Pain Observation Tool (CPOT),[45] Richmond Agitation-Sedation Scale (RASS),[46,47] and Confusion Assessment Method for the ICU (CAM-ICU) scores,[48,49] and [4] daily spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT).[36,37]

7.2 Blinding: Similar to prior SpO_2 target studies among critically ill adults[29,30], patients and clinicians will not be blinded to study group assignment. Observer bias will be minimized by use of objective endpoints collected *in duplicate* by [1] study personnel blinded to group assignment and [2] automated data extraction from the EHR (see *Data Collection* below).

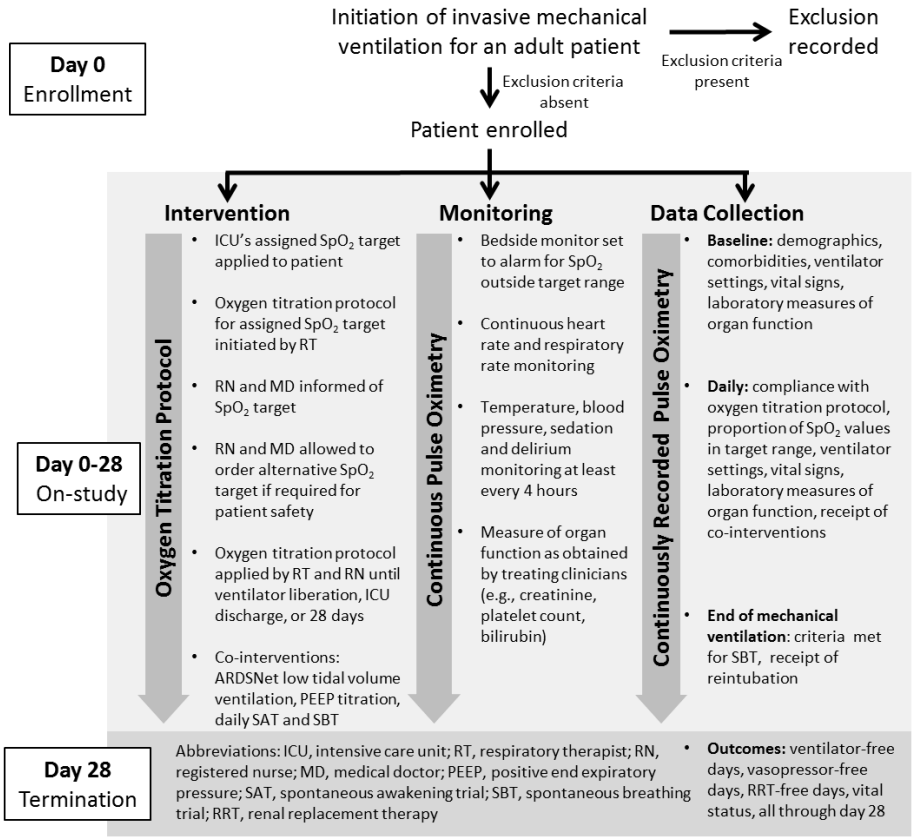
7.3 Data Collection: The PILOT trial will primarily use structured data collected in routine clinical care, exported daily from the institution's EHR into an Enterprise Data Warehouse, along with data from the patient registration, billing, and laboratory clinical information systems. We have previously validated the quality of this method of data collection against the reference standard of two-physician manual chart review,[50] and the planned approach to electronic dataset generation for the PILOT trial has already been successfully employed for the conduct of three prior pragmatic trials.[38,38,51]

Electronically extracted data elements will include:
Enrollment (Day 0): age; sex; race; ethnicity; height, weight; APACHE II score;[52] non-respiratory SOFA score;[53] Glasgow Coma Scale score;[54] Elixhauser Comorbidity Index;[55] history of present illness; vital signs (temperature, heart rate, systolic blood pressure, diastolic blood pressure, SpO_2); mechanical ventilator settings (mode, set and exhaled tidal volume, set and actual respiratory rate, positive end-expiratory pressure, peak pressure, FiO_2); serum laboratory values (white blood cell count, hemoglobin, platelet count, sodium, potassium, bicarbonate, creatinine, bilirubin, alanine aminotransferase, aspartate aminotransferase, lactate, arterial pH, PaO_2, SaO_2).

Daily On-Study (Days 0-28): Vital signs, ventilator settings, screening for and performance of spontaneous awakening trials and spontaneous breathing trials, and serum laboratory values (as above); receipt of red cell transfusion; number of arterial blood gases; non-respiratory SOFA score; ARDS by Berlin criteria;[56] Stage II or greater

AKI by KDIGO criteria;[57] atrial arrhythmia, ventricular arrhythmia, cardiac arrest, pneumothorax or pneumomediastinum, ischemic stroke, myocardial infarction.

Termination (Days 0-28): Vital status at 28 days; time of liberation from invasive mechanical ventilation; receipt and duration of vasopressors; receipt and duration of renal replacement therapy; duration of ICU and hospital admission.



Data elements collected manually by study personnel will include: [1] all data elements for a randomly selected 10% of participants to ensure the quality of electronically extracted data, [2] all primary and secondary outcomes collected at study termination for 100% of participants to ensure duplicate data collection of key study outcomes, and [3] any data elements for which electronic data extraction has not been developed and validated, including etiology of respiratory failure, indication for mechanical ventilation, protocol violations, and adverse events. Data will be stored, curated, and secured in the online database, REDCap.[58]

7.4 Outcome Measures

Primary Outcome:

The primary outcome is ventilator-free days (VFDs) to study day 28. VFDs will be defined as the number of calendar days alive and free of invasive mechanical ventilation from the final receipt of invasive mechanical ventilation through 28 days after enrollment. For the assessment of VFDs, the day of enrollment (defined as the day on which the patient first receives invasive mechanical ventilation in a participating study location), will be considered to be day 0. Outcome ascertainment will cease at the time of hospital discharge or 28 days after enrollment, whichever occurs first. Receipt of invasive mechanical ventilation will be considered to end when patients undergo the final tracheal extubation or disconnection of the ventilator from the endotracheal tube or tracheostomy tube between enrollment and 28 days after enrollment. Patients who continue to receive invasive mechanical ventilation at day 28 will receive zero VFDs. Patient who die prior to day 28 will receive zero VFDs. Patients who are discharged from the hospital prior to day 28 and are receiving invasive mechanical ventilation at the time of discharge will receive zero VFDs. Patients who are removed from invasive mechanical ventilation and are discharged from the hospital without invasive mechanical ventilation prior to 28 days will be assumed to remain free of invasive mechanical ventilation between hospital discharge and day 28. For patients who are removed from invasive mechanical ventilation, return to invasive mechanical ventilation, and are subsequently removed again from invasive mechanical ventilation prior to day 28, VFDs will be counted from the final receipt of invasive mechanical ventilation prior to day 28. We chose VFDs as the primary outcome for the PILOT trial as choice of SpO_2 target may simultaneously affect both mortality and duration of invasive mechanical ventilation.

Secondary Outcome:

The sole pre-specified secondary outcome is 28-day in-hospital mortality, defined as death from any cause between enrollment and the first of hospital discharge or 28 days after enrollment.

Exploratory Clinical Outcomes:

1. ICU mortality
2. Vasopressor-free days
3. Renal replacement therapy-free days
4. ICU-free days
5. Hospital-free days

Exploratory Organ Function Outcomes: (All exploratory organ function outcomes will employ only laboratory values and imaging obtained as a part of routine clinical care)

1. Daily non-respiratory SOFA score

2. Daily creatinine
3. Daily lactate
4. Presence of acute respiratory distress syndrome
5. Stage II or greater AKI by KDIGO criteria

Exploratory Safety Outcomes:

1. Atrial arrhythmia
2. Ventricular arrhythmia
3. Cardiac arrest
4. Pneumothorax or pneumomediastinum
5. Ischemic stroke
6. Myocardial infarction

Measures of Separation between Groups:

1. SpO_2
2. SaO_2
3. FiO_2
4. PaO_2
5. Episodes of hypoxemia, including:
    a. $SpO_2 < 85\%$ for ≥ 5 minutes
    b. $SpO_2 < 80\%$ for ≥ 5 minutes
    c. $SpO_2 < 70\%$ for ≥ 2 minutes
6. Episodes of hyperoxemia, including:
    a. $SpO_2 > 98\%$ for ≥ 5 minutes
    b. $SpO_2 > 98\%$ for ≥ 30 minutes
7. Proportion of patients with a value for PaO2 < 55 mm Hg
8. Proportion of patients with a value for PaO2 > 120 mm Hg

Exploratory Processes of Care Outcomes:

1. Tidal volume
2. Positive end expiratory pressure
3. Peak airway pressure
4. Receipt of mandatory ventilator mode
5. Number of arterial blood gasses
6. Hemoglobin
7. Red cell transfusion

8.0 Risks and Benefits:

Among adult patients for whom the treating clinicians have decided invasive mechanical ventilation is required, there are currently no established risks or benefits to targeting a higher, intermediate, or lower SpO_2. At this time, there is no reason to

believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by critically ill patients receiving invasive mechanical ventilation as a part of routine care. The greater benefit of the study would be to society in the form of improved understanding of safe and effective provision of oxygen therapy during mechanical ventilation for critically ill patients.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. After publication, a de-identified database will be generated to protect participant privacy.

9.0 Safety Monitoring and Adverse Events:

9.1 Safety Monitoring

The PILOT trial will take place in a high-acuity clinical care environment during delivery of a high-acuity procedure required for routine clinical care. During the time of the study intervention, the patient will have a critical care or emergency medicine nurse with a low patient-to-nurse staffing ratio, immediate access to a respiratory therapist, and a team of critical care physicians physically located on the study unit twenty-four hours a day. As a part of routine care all patients will be receiving continuous invasive or non-invasive monitoring of heart rate, blood pressure, respiratory rate, and oxygen saturation.

Study personnel will monitor compliance with the study inclusion and exclusion criteria, study protocol, and study safety measures daily. Study personnel will be readily available to answer questions at any time from patients, legally authorized representatives, or treating clinicians. If, at any point in a patient's clinical course, the treating clinicians believe an SpO_2 target different from the assigned target is required for the safe treatment of the patient, the SpO_2 target will be modified to the target the treating clinicians judge to be safest.

A structured plan for prospective collection of study outcomes has been specified, in addition to a process by which Adverse Events and Serious Adverse Events will be managed and reported as required to regulatory bodies.

A Data and Safety Monitoring Board (DSMB) will be appointed to oversee the study. The DSMB will be available throughout the trial to monitor enrollment, protocol compliance, safety, and adverse events. Additionally the DSMB will perform an interim analysis for safety and efficacy.

9.2 Adverse Event Reporting

A system has been established to report and track clinical outcomes and adverse events (AEs). Study personnel will monitor the safety of subjects and follow AEs until the event resolves or is explained.

Clinical Outcomes (not considered Adverse Events). In this study of critically ill patients who are at high risk for death or other adverse outcomes due to their underlying critical illness, clinical outcomes, including death and organ dysfunction, will be systematically tracked (collected in the case report form) and will be included as part of the analyses for this study. For the purposes of reporting, death and organ dysfunction will not be recorded as AEs unless the investigator believes the event may have been caused by the study or is more severe or prolonged than expected given the underlying critical illness. This approach—considering death and organ dysfunction as outcomes rather than AEs and systemically tracking expected outcomes for analysis rather than solely recording individual AEs—is common in ICU trials because these outcomes/events occur commonly in the ICU and this system mandates that data regarding death, organ dysfunction, and expected outcomes be tracked systematically for all patients and analyzed appropriately. Clinical outcomes will be systemically tracked throughout the study period. Listed below are events that will be tracked as primary, secondary, or exploratory clinical outcomes and will not therefore be reported as AEs during this study (unless believed to be study related and more severe or prolonged than expected given the underlying critical illness):

1. Death (all deaths occurring prior to hospital discharge will be reported on the CRF in the vital status at hospital discharge section);
2. Recurrence of respiratory failure, including need for re-intubation or non-invasive mechanical ventilation, presence of acute respiratory distress syndrome, or presence of pneumothorax or pneumomediastinum;
3. Circulatory failure, including cardiac arrest or shock with or without receipt of vasopressors;
4. Incidence of sustained atrial and ventricular arrhythmias;
5. Acute kidney injury, including leading to increased creatinine or receipt of renal replacement therapy;
6. Hepatic injury or failure leading to increased bilirubin, AST, or ALT;
7. Coagulation derangements leading to elevated PT/INR or PTT, DIC, thrombocytopenia, or thrombocytosis;
8. Lactic acidosis;
9. Delirium, disability, and physical or cognitive impairment believed to be newly acquired;
10. All values for SpO_2, SaO_2, FiO_2, PaO_2, or PaO_2/FiO_2 ratio;
11. All values for vital signs (e.g., temperature, respiratory rate, SpO_2);
12. Receipt of co-interventions (e.g., number of arterial blood gasses, red cell transfusion)

13. Duration of ICU admission, ICU readmission;
14. Duration of hospitalization, hospital readmission;
15. Alterations in routine labs, including chemistries, complete blood counts, liver function tests, and hemostasis profiles.

Adverse Event Classifications. An Adverse Event (AE) will be any untoward medical occurrence for a patient enrolled in the trial that is not tracked as a clinical outcome, regardless of whether the event is considered study related or not. All AEs occurring during the observational study period will be recorded on the CRF. All AEs will then be assessed as to whether they are (1) related to study procedures, (2) serious, and/or (3) unexpected according to the following definitions:

I. Related to study procedures. AEs that the investigator suspects are related to the study will be classified as study related. Certainty of relatedness is not required as long as a reasonable possibility exists that the AE is related to a study procedure.

II. Serious. AEs that meet any of the criteria below will be considered Serious Adverse Events (SAEs):
   a. Results in death
   b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
   c. Prolongs an existing hospitalization
   d. Results in persistent or significant disability or incapacity
   e. Results in a congenital anomaly or birth defect
   f. Important medical event that requires an intervention to prevent any of a-e above.

III. Unexpected. AEs that are more severe or prolonged than expected based on the investigator's discretion will be considered Unexpected.

The PILOT trial will monitor, track, and report all Clinical Outcomes and AEs as required by regulatory bodies.

Communication and Reporting of Adverse Events. In order to ensure proper and timely reporting of all adverse events, there will be a clear communication plan for all study personnel to follow. AEs will be recorded in the AE CRF in the electronic database and reported to the PI within 5 days of occurrence. The PI will provide a report of all AEs annually to the IRB and DSMB as part of the annual review process as required. All SAEs will be reported to the PI within 72 hours of occurrence. The PI will, in turn, report all SAEs to the IRB, DSMB, and funding body within 7 calendar days of occurrence.

9.3 Frequency of Monitoring and Interim Analysis.

Study personnel will continuously monitor enrollment, protocol compliance, and AEs and SAEs throughout the course of the trial. Semi-annually, the DSMB will formally review enrollment, protocol compliance, and AEs and SAEs as part of a formal DSMB meeting. Additionally, the DSMB will be available to convene a meeting at any point in the course of the trial to review urgent issues related to AEs, protocol compliance, or unexpected adverse events. Study personnel and DSMB members will adhere to the expectations for reporting and managing AEs and unexpected adverse events outlined in the DSMB charter.

Interim Analysis. In addition to ongoing monitoring of safety throughout the trial, the DSMB will conduct a single interim analysis for efficacy and safety at the anticipated halfway point of the PILOT trial. The interim analysis will include patients enrolled during the first 18 months of the trial. The stopping boundary for efficacy will be met if the P value for the difference between groups is <0.001. Use of the conservative Haybittle-Peto boundary ($P < 0.001$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$). Given the minimal risk nature of the study and current use of all SpO_2 target as a part of usual care, there will be no stopping boundary for futility. The DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

9.4 Data and Safety Monitoring Board (DSMB). A formal independent DSMB will oversee the conduct of the trial and the planned interim analysis. The DSMB will be composed of at least one physician outside the study institution experienced in the conduct of critical care clinical trials and one biostatistical expert who will assist with study monitoring and performance of the interim analysis.

9.5 Data Monitoring Plan. To ensure data are accurately and completely collected during the PILOT trial, the study team will follow a specific Data Monitoring Plan. All clinical outcomes will be collected in duplicate by both electronic data collection and by the study nurse. All study data from random sample of 10% of study records will be collected in duplicate by electronic data collection and by the study nurse. Each of these records will also be reviewed annually by the primary investigator to ensure data collection is accurate, complete, and current. The study biostatistician will run periodic data cleans throughout the study looking for outliers or overtly erroneous data. This Monitoring Plan will serve as a method for identifying and resolving systematic problems and therefore increase data quality. We will submit progress reports to the local IRB annually, or more frequently if requested.

10.0 Study Withdrawal/Discontinuation

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI.

The reason and date of every withdrawal will be recorded in the patient study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or other safety parameter that could have led to discontinuation. Follow-up will be conducted until the condition has resolved, until diagnosis of the adverse event or safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well.

11.0 Statistical Considerations

Power calculation.

In a prior cluster-randomized cluster-crossover trial in the same ICU,[51] 880 mechanically ventilated adults were enrolled per year (73.3 per month), with a median of 22 VFDs [IQR 0-25 VFDs] and an intra-cluster intra-period correlation of 0.01. During the planned 36-month PILOT trial, we estimate 2,640 mechanically ventilated adults will be admitted to the study ICU, of whom 390 will be enrolled during washout periods and excluded from the primary analysis and 2,250 will be included in the primary analysis. With a total enrollment of 2,250 patients, a standard deviation in the primary outcome of VFDs of 11.4 days, and a two-sided alpha of 0.05, ***the PILOT trial will have 92 percent statistical power to detect an absolute difference between groups in VFDs of 2.0 days*** (similar to the numerical difference in VFDs between SpO_2 target groups reported in prior studies[29,30]).

Primary analysis of the Primary Outcome.

The primary analysis will be an intention-to-treat comparison of the primary outcome of VFDs between the higher, intermediate, and lower SpO2 target groups among all patients enrolled in the trial except [1] those admitted during one of the 7-day washout periods and [2] those with a laboratory-confirmed diagnosis of Coronavirus disease 2019 (COVID-19). We will use a proportional odds model with independent covariates of group assignment (higher, intermediate, or lower SpO2 target) and time. Time (in days) will be treated as a continuous variable with values ranging from 1 (first day of enrollment) to 1,097 (final day of enrollment) and will be analyzed using restricted cubic splines with multiple knots to allow for non-linearity resulting from seasonality or secular trends. For the purposes of declaring a statistically significant

difference between groups in the primary endpoint, we will consider the conditional effect from the proportional odds model and a two-sided P value of 0.05. In addition to the overall comparison of the three study groups, we will perform pair-wise comparisons between the lower and intermediate groups, lower and higher groups, and intermediate and higher groups using the same statistical approach.

Sensitivity Analyses of the Primary Outcome

- We will repeat the primary analysis using alternative statistical approaches to comparing the VFDs outcome between groups. These statistical approaches will include:
    - zero-inflated Poisson regression;
    - zero-inflated negative binomial regression;
    - global rank scale analysis (see Supplementary Appendix); and
    - Fine and Gray competing risk regression in which extubation from invasive mechanical ventilation is the event of interest and mortality is a competing event.
- We will repeat the primary analysis with adjustment for pre-specified baseline covariates.
- We will repeat the primary analysis replacing the continuous covariate of time with a categorical covariate of season defined as: winter (January, February, March); spring (April, May, June); summer (July, August, September); and fall (October, November, December).
- We will repeat the primary analysis among all patients enrolled in the trial, including [1] patients initiated on invasive mechanical ventilation in a study location during one of the pre-specified 7-day washout periods and [2] patients with a diagnosis of COVID-19 (estimated sample size of 3,000 patients).

Analysis of Effect Modification for the Primary Outcome.

We will examine whether pre-specified baseline variables modify the effect of study group on the primary outcome using formal tests of statistical interaction in a proportional odds model. Independent variables will include study group assignment, the potential effect modifier of interest, and the interaction between the two (e.g., study group * presence of sepsis or septic shock) and time. Significance will be determined by the P value for the interaction term, with values less than 0.10 considered to suggest a potential interaction and values less than 0.05 considered to confirm an interaction.

We will examine whether the following baseline variables modify the effect of study group on the primary outcome:

- Age (continuous variable);
- Race and ethnicity (Hispanic, Non-Hispanic Black, Non-Hispanic White, Other);
- Source of admission to the ICU (ED, hospital ward, another ICU in the study hospital, operating room, outside hospital);

- Duration of invasive mechanical ventilation prior to enrollment (0 minutes; 1 to 360 minutes; >360 minutes);
- Chronic comorbidities (categories are not mutually exclusive)
    - Receipt of supplemental oxygen at place of residence prior to hospital admission (yes, no);
    - Coronary artery disease or heart failure with reduced ejection fraction (yes, no);
- Acute diagnoses at enrollment (categories are not mutually exclusive)
    - cardiac arrest (yes, no);
    - acute myocardial infarction (yes, no);
    - sepsis or septic shock (yes, no);
    - acute respiratory distress syndrome (yes, no);
- Receipt of vasopressors at enrollment (yes, no);
- Non-respiratory SOFA score at enrollment (continuous variable);
- Time period (before the COVID-19 pandemic [July 2018 - December 2019], during the COVID-19 pandemic [January 2020 – August 2021]).

Analysis of the Secondary Outcome

The sole pre-specified secondary outcome of 28-day in-hospital mortality will be compared between the three study groups in an intention-to-treat fashion in the primary analysis population using a logistic regression model with independent covariates of group assignment (higher, intermediate, or lower SpO2 target) and time. We also will perform pair-wise comparisons between the lower and intermediate groups, lower and higher groups, and intermediate and higher groups using the same statistical approach.

Analysis of the Exploratory Outcomes

Each of the exploratory outcomes will be compared between groups in an intention-to-treat fashion in the primary analysis population. Continuous outcomes will be compared between groups using a proportional odds model with independent covariates of group assignment (higher, intermediate, or lower SpO2 target) and time. Categorical outcomes will be compared between groups using a logistic regression model with independent covariates of group assignment (higher, intermediate, or lower SpO2 target) and time.

Corrections for multiple testing

We have pre-specified a single primary outcome and a single secondary outcome. Consistent with recommendations of the Food and Drug Administration and the European Medicines Association, each will be tested using a two-sided p-value with a significance level of 0.05. For all other analyses, emphasis will be placed on the estimate of effect size with 95% confidence intervals, as recommended by the

International Committee of Medical Journal Editors, and no corrections for multiple comparisons will be performed.

Handling of missing data

The primary outcome of VFDs is not anticipated to be missing for any patients. Missing data will not be imputed for the primary outcome or any secondary or exploratory outcomes. In adjusted analyses, missing data for covariates will be imputed using multiple imputations.

Interim Analysis

We will plan for the DSMB to conduct a single interim analysis for efficacy and safety at the anticipated halfway point of the trial. The interim analysis will include patients enrolled during the first 18 months of the trial. The stopping boundary for efficacy will be met if the P value for the difference between groups is <0.001 using a proportional odds model with independent covariates of group assignment (higher, intermediate, or lower SpO2 target) and time with regard to the primary outcome of VFDs. Use of the conservative Haybittle-Peto boundary ($P < 0.001$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$). Given the minimal risk nature of the study and current use of all SpO_2 target as a part of usual care, there will be no stopping boundary for futility. The DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

If the 18-month interim analysis reveals an enrollment indicative of <80% statistical power at completion, we will ask the DSMB to approve extending enrollment of the study to ensure the trial is not underpowered to detect the planned difference between groups in the primary outcome.

12.0 Privacy/Confidentiality Issues

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the treating clinician modification of SpO_2 target sheet will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

13.0 Follow-up and Record Retention

Patients will be followed after enrollment for 28 days or until hospital discharge, whichever occurs first. Data collected from the medical record will be entered into the

secure online database REDCap. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

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Tracking of Protocol Versions:

Version 1.0 – Initial Protocol (5/1/2018)

Version 1.1 – Revisions after initial meeting with DSMB (6/8/18)

- Updated protocol to specify that the primary analysis will use a proportional odd mixed effects model with a fixed effect of study group and a random effect of study period.
- Added sensitivity analyses using a zero-inflated Poisson model and a state-transitions model
- Specified the plan for sample size re-estimation at the interim analysis as follows: "*If the 18-month interim analysis reveals an enrollment indicative of <80% statistical power at completion, we will ask the DSMB to approve extending enrollment of the study to ensure the trial is not underpowered to detect the planned difference between groups in the primary outcome*."
- Specified that "*Patients will be provided with an information sheet providing an IRB-approved lay language summary of the study activities. The information sheet will contain the contact information for the primary investigator who will remain available throughout the study period to provide additional information to patients and families upon request. All contact between patients, families, and surrogates and study personnel will be tracked in a case report form and available to investigators and the DSMB."*

Version 1.2 – Protocol revisions during implementation (11/14/18)

- Updated protocol to remove FiO2 and PEEP criteria from the SBT Safety Screen to allow patients who pass other elements of the SBT Safety Screen to attempt a daily SBT regardless of their current FiO2 or PEEP.
- Revised the Patient Information Sheet based on feedback from the Community-Engaged Research Core and patients on the Community Advisory Council to create a structured format with headers, make the narrative more conversational, and decrease the reading level.

Version 1.3 – Protocol revisions prior to Continuing Review (6/19/19)

- Updated protocol to provide additional detail regarding (a) the process used to provide information about the study the patients, families, and surrogates in the study setting and (b) the documentation of this process.
- Updated the figures to match the changes to the SAT and SBT safety screen made during the 11/14/18 amendment.

Version 1.4 – Protocol revisions to incorporate final Statistical Analysis Plan (10/20/20)

- Revised trial name from "Preliminary Investigation of optimaL Oxygen Targets" to "Pragmatic Investigation of optimaL Oxygen Targets" to reflect the design
- Added details on the calculation of the primary outcome of VFDs to match SAP.
- Separated out the sole pre-specified secondary outcome of 28-day in-hospital

mortality from the exploratory outcomes to match SAP.

- Added details on "Primary Analysis of the Primary Outcome", "Sensitivity Analyses of the Primary Outcome", "Analysis of Effect Modification for the Primary Outcome", "Analysis of the Secondary Outcome", "Analysis of the Exploratory Outcomes", "Corrections for multiple testing", and "Handling of missing data" to match the SAP.
- Updated figure with study group assignments to reflect paused enrollment in April and May of 2020 due to COVID-19.

Version 1.5 – Protocol revisions to incorporate updates to Statistical Analysis Plan during peer review (4/7/2021)

- Revise statistical analysis plan to clarify how patients with a diagnosis of COVID-19 will be analyzed in the primary analysis, sensitivity analyses, and analyses of effect modification.
- Revise statistical analysis plan to define how race and ethnicity will be defined in the analysis of effect modification.

Summary of Changes to the PILOT Trial Protocol

Version 1.0 – Initial Protocol (5/1/2018)

Version 1.1 – Revisions after initial meeting with DSMB (6/8/18)

- Updated protocol to specify that the primary analysis will use a proportional odd mixed effects model with a fixed effect of study group and a random effect of study period.
- Added sensitivity analyses using a zero-inflated Poisson model and a state-transitions model
- Specified the plan for sample size re-estimation at the interim analysis as follows: "*If the 18-month interim analysis reveals an enrollment indicative of <80% statistical power at completion, we will ask the DSMB to approve extending enrollment of the study to ensure the trial is not underpowered to detect the planned difference between groups in the primary outcome*."
- Specified that "*Patients will be provided with an information sheet providing an IRB-approved lay language summary of the study activities. The information sheet will contain the contact information for the primary investigator who will remain available throughout the study period to provide additional information to patients and families upon request. All contact between patients, families, and surrogates and study personnel will be tracked in a case report form and available to investigators and the DSMB."*

Version 1.2 – Protocol revisions during implementation (11/14/18)

- Updated protocol to remove FiO2 and PEEP criteria from the SBT Safety Screen to allow patients who pass other elements of the SBT Safety Screen to attempt a daily SBT regardless of their current FiO2 or PEEP.
- Revised the Patient Information Sheet based on feedback from the Community-Engaged Research Core and patients on the Community Advisory Council to create a structured format with headers, make the narrative more conversational, and decrease the reading level.

Version 1.3 – Protocol revisions prior to Continuing Review (6/19/19)

- Updated protocol to provide additional detail regarding (a) the process used to provide information about the study the patients, families, and surrogates in the study setting and (b) the documentation of this process.
- Updated the figures to match the changes to the SAT and SBT safety screen made during the 11/14/18 amendment.

Version 1.4 – Protocol revisions to incorporate final Statistical Analysis Plan (10/20/20)

- Revised trial name from "Preliminary Investigation of optimaL Oxygen Targets" to "Pragmatic Investigation of optimaL Oxygen Targets" to reflect the design
- Added details on the calculation of the primary outcome of VFDs to match SAP.
- Separated out the sole pre-specified secondary outcome of 28-day in-hospital mortality from the exploratory outcomes to match SAP.
- Added details on "Primary Analysis of the Primary Outcome", "Sensitivity Analyses of the Primary Outcome", "Analysis of Effect Modification for the Primary Outcome", "Analysis of the Secondary Outcome", "Analysis of the Exploratory Outcomes", "Corrections for multiple testing", and "Handling of missing data" to match the SAP.
- Updated figure with study group assignments to reflect paused enrollment in April and May of 2020 due to COVID-19.

Version 1.5 – Protocol revisions to incorporate updates to Statistical Analysis Plan during peer review (4/7/2021)

- Revise statistical analysis plan to clarify how patients with a diagnosis of COVID-19 will be analyzed in the primary analysis, sensitivity analyses, and analyses of effect modification.
- Revise statistical analysis plan to define how race and ethnicity will be defined in the analysis of effect modification.

Protocol and Statistical Analysis Plan for the Pragmatic Investigation of Optimal Oxygen Targets (PILOT) Clinical Trial

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* A full list of the PILOT Investigators may be found in supplemental file 1, section 1.

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ABSTRACT:

Introduction: Mechanical ventilation of intensive care unit (ICU) patients universally involves titration of the fraction of inspired oxygen (FiO_2) to maintain arterial oxygen saturation (SpO_2). However, the optimal SpO_2 target remains unknown.

Methods and Analysis: The Pragmatic Investigation of optimaL Oxygen Targets (PILOT) trial is a prospective, unblinded, pragmatic, cluster-crossover trial being conducted in the emergency department and medical ICU at Vanderbilt University Medical Center in Nashville, TN, USA. PILOT compares use of a lower SpO_2 target (target 90% and goal range 88-92%), an intermediate SpO_2 target (target 94% and goal range 92-96%), and a higher SpO_2 target (target 98% and goal range 96-100%). The study units are assigned to a single SpO_2 target (cluster-level allocation) for each two-month study block, and the assigned SpO_2 target switches every two months in a randomly generated sequence (cluster-level crossover). The primary outcome is ventilator-free days to study day 28, defined as the number of days alive and free of invasive mechanical ventilation from the final receipt of invasive mechanical ventilation through 28 days after enrollment.

Ethics and dissemination: The trial was approved by the Vanderbilt Institutional Review Board. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences.

Trial Registration: The trial protocol was registered with ClinicalTrials.gov on May 25, 2018 prior to initiation of patient enrollment (ClinicalTrials.gov identifier: NCT03537937).

ARTICLE SUMMARY

Strengths and limitations of this study

- This ongoing pragmatic trial will provide information on the optimal oxygen saturation target during invasive mechanical ventilation of critically ill adults – informing a common therapy in current clinical practice for which there is limited available evidence on which to base care
- Broad inclusion criteria will increase generalizability and the sample size will allow examination of important patient subgroups
- The trial is being conducted at a single center
- The nature of the study intervention does not allow blinding
- Decisions regarding oxygen administration before and after invasive mechanical ventilation are deferred to treating clinicians

INTRODUCTION

Each year 2-3 million intensive care unit (ICU) patients receive invasive mechanical ventilation [1–3]. Despite recent advances in lung-protective ventilation [4], in-hospital mortality among mechanically ventilated ICU patients remains 25-35% [5].

Mechanical ventilation for ICU patients universally involves titrating the fraction of inspired oxygen (FiO_2) to maintain arterial oxygen saturation (SpO_2) within a goal range. Despite decades of ICU practice, however, the optimal SpO_2 target remains unknown. Higher SpO_2 targets (96-100%) provide a margin of safety against hypoxemia, but may increase exposure to excess FiO_2, hyperoxemia, and tissue hyperoxia, causing oxidative damage [6–8], inflammation [9,10], and increased alveolar-capillary permeability [11]. Lower SpO_2 targets (88-92%) minimize exposure to excess FiO_2, hyperoxemia, and tissue hyperoxia [4,12,13], but may increase the risk of hypoxemia and tissue hypoxia [14,15]. An intermediate SpO_2 target (92-96%) may avoid the risks of both hyperoxia and hypoxia or, conversely, may expose patients intermittently to both sets of risks [16,17].

The relative risks and benefits of different SpO_2 or PaO_2 targets have been extensively examined in the setting of the neonatal ICU [18–21] and have been examined among adult ICU patients in a series of recently-published clinical trials [22–27]. Together, these trials have suggested that both higher and lower oxygenation targets are safe – although some trials have potentially suggested better outcomes with higher targets[25] and other trials have suggested potentially better outcomes with lower targets[24].

Given the still incomplete evidence from randomized trials, current guidelines offer divergent recommendations – ranging from tolerating SpO_2 values as low as 88% [28–30] to pursuing SpO_2 values as high as 98% [31]. In clinical practice, hyperoxemia remains common [32,33], even among patients cared for by clinicians who self-identify as avoiding high oxygen levels [34].

The wide variation in current practice, conflicting guidelines, and conflicting data from some available trials indicate the need for further clinical trials to determine the effect of SpO_2 target on patient outcomes [12,35]. We designed the Pragmatic Investigation of optimaL Oxygen Targets (PILOT) trial to examine the effects of higher, intermediate, and lower SpO2 targets on the number of days alive and free of invasive mechanical ventilation among mechanically ventilated ICU patients.

METHODS AND ANALYSIS

This manuscript was prepared in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Figure 1; SPIRIT checklist in online supplemental file 1, section 2). [36] This manuscript describes key elements of the trial protocol and statistical analysis plan. The Supplemental Methods in supplemental file 1 provide additional background on prior trials (section 3), rationale for design decisions (sections 4-5), SpO_2 monitoring and management (sections 6-8), institutional protocols for mechanical ventilation (sections 9-17), a complete list of data elements (section 18), definitions of exploratory outcomes and measures of separation between groups (sections 19-21), and details of the interim analysis (section 22) and secondary analyses (sections 23-25).

Study Design

The PILOT trial is a prospective, unblinded, pragmatic, cluster-crossover trial being conducted in the emergency department and medical ICU at Vanderbilt University Medical Center in Nashville, TN, USA. PILOT compares use of a lower SpO_2 target (target 90% and goal range 88-92%), an intermediate SpO_2 target (target 94% and goal range 92-96%), and a higher SpO_2 target (target 98% and goal range 96-100%) with regard to the number of days alive and free of invasive mechanical ventilation among mechanically ventilated ICU patients. Consistent with the concept of a pragmatic clinical trial [37], the eligibility criteria are broad, the delivery of the intervention is embedded in routine clinical care and executed by clinical personnel, and data collection prioritizes clinical outcomes over mechanistic evaluation. The trial was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB) (IRB 171272). The trial is investigator-initiated with funding provided by the National Heart, Lung, and Blood Institute (K23HL143053). The trial protocol was registered with ClinicalTrials.gov on May 25, 2018 prior to initiation of patient enrollment on July 1, 2018 (ClinicalTrials.gov identifier: NCT03537937).

Patient and Public Involvement

Materials used to communicate about the study with patients and families were developed with input from the Vanderbilt Community Engaged Research Core and the Vanderbilt Community Advisory Council.

Study Site and Population

The trial is being conducted in the adult emergency department (ED) and medical ICU at Vanderbilt University Medical Center.

The inclusion criteria are:

1. Age ≥ 18 years
2. Receiving mechanical ventilation through an endotracheal tube or tracheostomy
3. Admitted to the study ICU or admission to the study ICU from the ED is planned

The exclusion criteria are:

1. Known pregnancy or beta hCG level greater than the laboratory upper limit of normal in a patient capable of becoming pregnant (if measured clinically)
2. Known to be a prisoner

Adults located in the study ICU or for whom admission to the study ICU from the ED is planned who meet inclusion criteria and do not meet exclusion criteria are enrolled immediately upon receipt of invasive mechanical ventilation in a study location. The time of enrollment for the trial ("time zero") is the time of first receipt of invasive mechanical ventilation in a participating study location.

Randomization and Treatment Allocation

For each of the 18 two-month blocks during the 36 months of enrollment in the PILOT trial, the medical ICU is assigned to a single SpO_2 target (cluster-level

allocation). Every two months, the ICU will switch between use of a lower SpO_2 target (target 90% and goal range 88-92%), use of an intermediate SpO_2 target (target 94% and goal range 92-96%), and use of a higher SpO_2 target (target 98% and goal range 96-100%) in a randomly generated sequence (cluster-level crossover) (Figure 2). The order of study group assignments for each two-month block was generated by computerized randomization using permuted blocks of 3 to minimize the impact of seasonal variation and temporal changes. For the 36 months of enrollment in the PILOT trial, patients receiving invasive mechanical ventilation in the ED for whom admission to the medical ICU is planned will receive the same SpO_2 target assigned to the medical ICU. The study did not enroll in April and May of 2020 due to disruptions in research and clinical care from the Coronavirus Infectious Disease 2019 (COVID-19) pandemic (Figure 2).

Washout Periods

The last 7 days of each two-month block are considered an analytic washout period during which the ICU continues to target the assigned SpO_2 but data from new patients are not included in the primary analysis. Assuming a median duration of mechanical ventilation of 3 [IQR 3-5] days, a 7-day washout period will ensure that 98% patients in the primary analysis do not experience a "crossover" from a period assigned to one assigned SpO_2 target to a period assigned to another SpO_2 target. Data from patients admitted during washout periods will be included in a pre-specified sensitivity analysis (see *Statistical Analysis* section). Any patient who does remain mechanically ventilated in the study ICU through a crossover from a period assigned to one SpO_2

target to a period assigned to another SpO_2 target will be analyzed in the SpO_2 target group to which the ICU was assigned at the time of the patient's enrollment in the trial (intention-to-treat analysis).

Study Interventions

Choice of SpO_2 targets

In clinical practice, 98% of SpO_2 values experienced by mechanically ventilated adults fall between 88-100% [32,33]. Within this range, current guidelines for oxygen therapy in mechanically ventilated adults outline three contrasting approaches: (1) allowing the lower end of the range of acceptable SpO_2 values to be as low as 88% [28,29] to avoid excess FiO_2, hyperoxemia, and hyperoxia; (2) titrating within an intermediate range of SpO_2 values, such as 92-96% [38]; or (3) targeting higher SpO_2 to avoid the risks of hypoxemia and hypoxia [31]. The PILOT trial has three study groups, each emulating a different approach to SpO_2 targets represented in guidelines and clinical practice (Table 1).

Oxygen Titration

In the study ED and ICU, titration of FiO_2 to maintain SpO_2 for mechanically ventilated adults is typically performed by respiratory therapists with input from nurses and physicians. In preparation for the PILOT trial, we collaborated with respiratory therapy leaders in the study ED and ICU to adapt existing ventilator management protocols to provide guidance for respiratory therapists in titrating FiO_2 to achieve each of the three study SpO_2 targets.

For patients enrolled in the study, respiratory therapists are instructed to begin titrating FiO_2 to the target SpO_2 value within 15 minutes of the initiation of mechanical ventilation. During the maintenance of invasive mechanical ventilation, SpO_2 is assessed by continuous pulse oximetry. The protocol directs the respiratory therapist managing the patient's ventilator to target an SpO_2 value of 90% in the lower SpO_2 target group, an SpO_2 value of 94% in the intermediate SpO_2 target group, and an SpO_2 value of 98% in the higher SpO_2 target group (Table 1). Respiratory therapists and other treating clinicians titrate FiO_2 when the SpO_2 out of the goal range, when the SpO_2 is within the goal range but closer alignment with the assigned SpO_2 target is desired, to facilitate weaning from mechanical ventilation, or for other clinical indications. SpO_2 is reassessed 5 minutes after each change in FiO_2 or sooner if clinically indicated.

The protocol determines the SpO_2 target from enrollment until the first of: (1) discontinuation of invasive mechanical ventilation, (2) transfer out of a participating study location, (3) completion of an SpO_2 target modification sheet by treating clinicians, or (4) end of the two-month study period. The protocol does not determine the SpO_2 target during time-periods in which the patient is not physically located in a study location (e.g., during transport) or when FiO_2 is being administered for purposes other than achieving a target SpO_2 (e.g., when an FiO_2 of 1.0 is being administered for a procedure).

At any time, if a treating clinician or a patient, family member, or surrogate feels that an SpO_2 target other than that assigned by the study would be best for the optimal treatment of the patient for any reason, the SpO_2 target for that patient is modified. To modify the target, the respiratory therapist and supervising physician complete a one-

page SpO_2 target modification sheet documenting the new SpO_2 target and the rationale for modifying the target. Examples of conditions for which the assigned SpO_2 target may be modified that were specified in the initial trial protocol included: pneumothorax; pneumomediastinum; carbon monoxide poisoning; decompression sickness; bleomycin toxicity; paraquat toxicity. Examples of conditions for which the assigned SpO_2 target may be modified that were not explicitly specified in the initial trial protocol include: severe chronic obstructive pulmonary disease; severe acute respiratory distress syndrome; severe anemia; status post lung transplantation; and receipt of extracorporeal membrane oxygenation support. Trial protocol directs only the titration of FiO_2 to the assigned SpO_2 target. Other aspects of invasive mechanical ventilation, such as tidal volume [4], positive end-expiratory pressure [39,40], and use of rescue therapies for hypoxemia, are determined by institutional protocols and treating clinicians (see sections 9-17 of supplemental file 1).

Blinding

Similar to prior studies of SpO_2 targets among critically ill adults [22,24,26], patients and clinicians will not be blinded to study group assignment.

Data Collection

The PILOT trial uses data collected by two methods to minimize observer bias: (1) manual data collection by study personnel and (2) automated collection of structured data recorded in routine clinical care, exported daily from the institution's electronic health record and patient registration, billing, and laboratory clinical information systems

into an Enterprise Data Warehouse. We have previously validated the quality of the automated method of data collection against the reference standard of two-physician manual chart review [41] and have employed this approach for the conduct of prior pragmatic trials [42,43]. Data are stored, curated, and secured in REDCap [44].

Outcomes

Primary Outcome

The primary outcome is ventilator-free days (VFDs) to study day 28. VFDs will be defined as the number of whole calendar days alive and free of invasive mechanical ventilation beginning at midnight on the day of the final receipt of invasive mechanical ventilation through day 28 after enrollment [45,46]. Outcome ascertainment will cease at the time of hospital discharge or 28 days after enrollment, whichever occurs first. Receipt of invasive mechanical ventilation will be considered to end when patients undergo the final tracheal extubation or disconnection of the ventilator from the endotracheal tube or tracheostomy tube between enrollment and 28 days after enrollment. Patients whose final receipt of invasive mechanical ventilation occurs on the day of enrollment will receive 27 VFDs. Patients who continue to receive invasive mechanical ventilation 28 days after enrollment will receive 0 VFDs. Patient who die prior to day 28 will receive 0 VFDs. Patients who are discharged from the hospital prior to day 28 and are receiving invasive mechanical ventilation at the time of discharge will receive 0 VFDs. Patients who are removed from invasive mechanical ventilation and are discharged from the hospital without invasive mechanical ventilation prior to 28 days will be assumed to remain free of invasive mechanical ventilation between hospital

discharge and day 28. For patients who are removed from invasive mechanical ventilation, return to invasive mechanical ventilation, and are subsequently removed again from invasive mechanical ventilation prior to day 28, VFDs will be counted from the final receipt of invasive mechanical ventilation prior to day 28.

Secondary Outcome

The sole pre-specified secondary outcome is 28-day in-hospital mortality, defined as death from any cause between enrollment and the first of hospital discharge or 28 days after enrollment.

Exploratory Clinical Outcomes

1. ICU mortality – death in the ICU between enrollment and the first of 28 days after enrollment or hospital discharge
2. Free-day outcomes – defined as whole calendar days from last receipt of therapy until 28 days (supplemental file 1, section 19)
    a. Vasopressor-free days
    b. Renal replacement therapy-free days
    c. ICU-free days
    d. Hospital-free days

Exploratory Organ Function Outcomes

1. Daily non-respiratory SOFA score (Table S1) [47]
2. Plasma creatinine concentration (mg/dL)

3. Plasma lactate concentration (mmol/L)
4. Presence of acute respiratory distress syndrome by Berlin criteria [48]
5. Stage II or greater AKI by Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria [49]

Exploratory Safety Outcomes

1. Atrial arrhythmia
2. Ventricular arrhythmia
3. Cardiac arrest with return of spontaneous circulation
4. Pneumothorax or pneumomediastinum
5. Ischemic stroke
6. Myocardial infarction [50]

Additional Long-term Patient-Important Outcomes

The independently-funded Cognitive Outcomes in the Pragmatic Investigation of Optimal Oxygen Targets (CO-PILOT) study (R21AG063126) will assess cognitive, physical, and psychological outcomes at 12 months after enrollment in the PILOT trial. The protocol and statistical analysis plan for the CO-PILOT study will be published separately.

Statistical Analysis and Reporting

Sample Size Estimation and Power Calculation

In a prior cluster-randomized cluster-crossover trial in the same ICU [51], 880 mechanically ventilated adults were enrolled per year (73.3 per month), with a median of 22 VFDs [IQR 0-25 VFDs] and an intra-cluster intra-period correlation of 0.01. We estimate 2,640 mechanically ventilated adults will be admitted to the study ICU during the 36-month PILOT trial, of whom 390 will be excluded from the primary analysis for initial receipt of invasive mechanical ventilation in a study location during a washout period and 2,250 will be enrolled and included in the primary analysis. With a total enrollment of 2,250 patients, a standard deviation in the primary outcome of VFDs of 11.4 days, and a two-sided alpha of 0.05, we calculated using a t-test that the PILOT trial will have 92 percent statistical power to detect an absolute reduction in VFDs of 2.0 days (similar to the numerical difference in VFDs between SpO_2 target groups reported in prior studies [22,24]).

Data and Safety Monitoring Board and Interim Analysis

An independent Data and Safety Monitoring Board (DSMB) oversees the trial. On March 23, 2020 the DSMB conducted a single, planned interim analysis at the anticipated halfway point of the trial and recommended the trial continue without modification (see DSMB charter in online supplemental file 2 and details of interim analysis in supplemental file 1, section 22). The DSMB is composed of two physicians outside the study institution with expertise in adult pulmonary and critical care medicine clinical practice and clinical research, one bioethicist, and one biostatistician.

Statistical Analysis Principles

R (R Foundation for Statistical Computing, Vienna, Austria) will be used for analyses. Analyses will be conducted at the level of an individual patient during an individual hospitalization in an intent-to-treat fashion, unless otherwise specified. Continuous variables will be reported as mean ± SD or median and IQR; categorical variables will be reported as frequencies and proportions.

Main Analysis of the Primary Outcome

The main analysis will be an intention-to-treat comparison of the primary outcome of VFDs between the higher, intermediate, and lower SpO_2 target groups among all patients enrolled in the trial except [1] those admitted during one of the 7-day washout periods and [2] those with a laboratory-confirmed diagnosis of COVID-19. Patients with a diagnosis of COVID-19 will be excluded from the main analysis for two reasons. First, the majority of the PILOT trial occurred prior the COVID-19 pandemic, with too few two-month study blocks occurring during the pandemic to ensure balance in the number of patients with COVID-19 between trial groups. Second, at the study hospital, ICU patients diagnosed with COVID-19 are transferred to a separate, dedicated COVID-19 ICU that was not participating in the PILOT trial. Thus, patients with COVID-19 are unlikely to have received significant exposure to the SpO_2 target intervention in the PILOT trial. Patients enrolled during washout periods and patients diagnosed with COVID-19 will be included in sensitivity analyses (see *Sensitivity Analyses* below).

It is possible to estimate a conditional effect, which is interpreted as the effect of a given SpO_2 target on an individual patient given the values of the covariates for that

patient, or a marginal effect, which is interpreted as the population effect of implementing a given SpO_2 target as a general policy [52]. Since an SpO_2 target intervention may be applied both at the patient level as an individual intervention and at the unit level as a general policy, both may be of interest.

To estimate the conditional effect, we will use a proportional odds model with independent covariates of group assignment (higher, intermediate, or lower SpO_2 target) and time [53,54]. Time (in days) will be treated as a continuous variable with values ranging from 1 (first day of enrollment) to 1,097 (final day of enrollment) and will be analyzed using restricted cubic splines with multiple knots to allow for non-linearity resulting from seasonality or secular trends. For the purposes of declaring a statistically significant difference between groups in the primary endpoint, we will consider the conditional effect from the proportional odds model and a two-sided P value of 0.05.

To estimate the marginal effect, we will use generalized estimating equations (GEE) with study period as the cluster and an independent variable for group assignment (higher, intermediate, or lower SpO_2 target).

For both approaches, in addition to assessing for an overall group effect within the model, we will estimate the differences between each pair of SpO_2 targets by extracting 95% confidence intervals from the model.

Sensitivity Analyses of the Primary Outcome

- We will repeat the primary analysis using alternative statistical approaches to comparing the VFDs outcome between groups such as zero-inflated Poisson

regression or zero-inflated negative binomial regression, global rank scale analysis [55], and Fine and Gray competing risk regression.

- We will repeat the primary analysis with adjustment for pre-specified baseline covariates of age, sex, race and ethnicity, source of ICU admission, vasopressor receipt, and acute diagnoses at enrollment, and severity of illness as assessed by the non-respiratory SOFA score.
- We will repeat the primary analysis replacing the continuous covariate of time with a categorical covariate of season defined as: winter (January, February, March); spring (April, May, June); summer (July, August, September); and fall (October, November, December).
- We will repeat the primary analysis among all patients enrolled in the trial, including [1] patients initiated on invasive mechanical ventilation in a study location during one of the pre-specified 7-day washout periods and [2] patients with a diagnosis of COVID-19.

Analysis of Effect Modification for the Primary Outcome

We will examine whether pre-specified baseline variables modify the effect of study group on the primary outcome using formal tests of statistical interaction in a proportional odds model. Independent variables will include study group assignment, the potential effect modifier of interest, and the interaction between the two (e.g., study group * presence of sepsis or septic shock) and time. Significance will be determined by the P value for the interaction term, with values less than 0.10 considered to suggest a potential interaction and values less than 0.05 considered to confirm an interaction.

We will examine whether the following baseline variables modify the effect of study group on the primary outcome:

1. Age;
2. Race and ethnicity (Hispanic, Non-Hispanic Black, Non-Hispanic White, Other);
3. Source of admission to the ICU (ED, hospital ward, another ICU in the study hospital, operating room, outside hospital);
4. Duration of invasive mechanical ventilation prior to enrollment;
5. Chronic comorbidities (categories are not mutually exclusive)
    a. Receipt of supplemental oxygen at place of residence prior to hospital admission (yes, no);
    b. Coronary artery disease or heart failure with reduced ejection fraction (yes, no);
6. Acute diagnoses at enrollment (categories are not mutually exclusive) [56]
    a. cardiac arrest (yes, no);
    b. acute myocardial infarction (yes, no);
    c. sepsis or septic shock (yes, no);
    d. acute respiratory distress syndrome (yes, no);
7. Receipt of vasopressors at enrollment (yes, no);
8. Non-respiratory SOFA score at enrollment;
9. Time period (before the COVID-19 pandemic [July 2018 - December 2019], during the COVID-19 pandemic [January 2020 – August 2021]).

Analysis of the Secondary Outcome

The sole pre-specified secondary outcome of 28-day in-hospital mortality will be compared between the three study groups in an intention-to-treat fashion in the main analysis population using a logistic regression model with independent covariates of group assignment (higher, intermediate, or lower SpO_2 target) and time. In addition to assessing for an overall group effect within the model, we will estimate the differences between each pair of SpO_2 targets by extracting 95% confidence intervals from the model.

Analysis of the Exploratory Outcomes

Each of the exploratory outcomes will be compared between groups in an intention-to-treat fashion in the main analysis population. Exploratory outcomes will be compared between study groups in a similar manner as for primary and secondary outcomes. A logistic model will be used for binary outcomes, a multinomial model for categorical outcomes, and a proportional odds model will be used for ordinal and continuous outcomes.

Trial Status

PILOT is an ongoing pragmatic trial comparing higher, intermediate, and lower SpO_2 targets for mechanically ventilated critically ill adults. Patient enrollment began on July 1, 2018 and is anticipated to conclude on August 31, 2021.

Ethics and dissemination

IRB Approval

The trial was approved by the Institutional Review Board (IRB) of Vanderbilt University Medical Center with a waiver of informed consent (IRB# 171272), details of which are provided in supplemental file 1, section 26. Participants who regain capacity to provide informed consent, or legally authorized surrogate decision-makers for those patients who do not regain the capacity to provide informed consent, are approached to provide informed consent for assessment of long-term outcomes as a part of the independently-funded Cognitive Outcomes in the Pragmatic Investigation of Optimal Oxygen Targets (CO-PILOT) study (R21AG063126).

Information for Patients and Families

An information sheet providing an IRB-approved lay language summary of the study and containing the contact information for investigators (who remain available throughout the study period to provide additional information to patients and families upon request) is made available throughout the study period in glass display cases near the public entrance to the ICU and near the center of the ICU, in the 'welcome packet' of information about the ICU, which is distributed at the time of ICU admission to patients, families, and surrogates by the medical receptionist or charge nurse as a part of routine admission processes, in a brochure holder in the family waiting room for the study ICU, and by treating physicians and respiratory therapist to any patients, families, or surrogates with questions or concerns about the study.

Protocol Changes

Any changes to the trial protocol will be recorded on ClinicalTrials.Gov as per SPIRIT guidelines (see section 27 of supplemental file 1).

Data Handling and Sharing

For details of privacy, data handling, and data sharing, see sections 28-29 of supplemental file 1.

Dissemination Plan

Trial results will be submitted to a peer-reviewed journal for consideration of publication and will be presented at scientific conferences. The results of the study will be disseminated to patients and the public at the completion of the trial.

Contributorship statement: Study concept and design: M.W.S., J.D.C., C.J.L., G.R.B., W.H.S., T.W.R.; Drafting of the manuscript: M.W.S., L.W., C.J.L.; Critical revision of the manuscript for important intellectual content: M.W.S., J.D.C., B.D.L., P.G.H., M.A.H., M.R., J.L.S., J.H.B., K.G.B., L.W., C.J.L., R.E.F., J.P.W., G.R.B., W.H.S., T.W.R; Statistical analysis: L.W., C.J.L.; Study supervision: G.R.B., W.H.S., T.W.R.

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FIGURES

Figure 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, Interventions, and Assessments.

Figure 2. Group assignment during the trial. For each of the 18 two-month study periods, the study ICU is randomly assigned to a higher, intermediate, or lower SpO_2 target. In this figure, the letters “A”, “B”, and “C” each correspond to one of the three possible SpO_2 targets, the allocation sequence of which remains concealed until the start of each two-month study period. The study did not enroll in April and May of 2020 due to disruptions in research and clinical care from the Coronavirus Infectious Disease 2019 (COVID-19) pandemic. As a result, March and June of 2020 represent a single-two-month block assigned to one SpO_2 target.

TABLES

Table 1. SpO_2 and PaO_2 targets and goal ranges by study group.

Study Group	SpO_2 target	SpO_2 goal range	PaO_2 target	PaO_2 goal range
Lower SpO_2 target	90%	88-92%	60 mm Hg	55-65 mm Hg
Intermediate SpO_2 target	94%	92-96%	70 mm Hg	65-80 mm Hg
Higher SpO_2target	98%	96-100%	110 mm Hg	> 80 mm Hg

For each study group, the SpO_2 target and goal range are displayed. PaO_2 is used to guide titration of FiO_2 for participants without functioning pulse oximetry monitoring.

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Protocol and statistical analysis plan for the Pragmatic Investigation of optimaL Oxygen Targets (PILOT) clinical trial

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ABSTRACT

Introduction Mechanical ventilation of intensive care unit (ICU) patients universally involves titration of the fraction of inspired oxygen to maintain arterial oxygen saturation (SpO_2). However, the optimal SpO_2 target remains unknown.

Methods and analysis The Pragmatic Investigation of optimaL Oxygen Targets (PILOT) trial is a prospective, unblinded, pragmatic, cluster-crossover trial being conducted in the emergency department (ED) and medical ICU at Vanderbilt University Medical Center in Nashville, Tennessee, USA. PILOT compares use of a lower SpO_2 target (target 90% and goal range: 88%–92%), an intermediate SpO_2 target (target 94% and goal range: 92%–96%) and a higher SpO_2 target (target 98% and goal range: 96%–100%). The study units are assigned to a single SpO_2 target (cluster-level allocation) for each 2-month study block, and the assigned SpO_2 target switches every 2 months in a randomly generated sequence (cluster-level crossover). The primary outcome is ventilator-free days (VFDs) to study day 28, defined as the number of days alive and free of invasive mechanical ventilation from the final receipt of invasive mechanical ventilation through 28 days after enrolment.

Ethics and dissemination The trial was approved by the Vanderbilt Institutional Review Board. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences.

Trial registration number The trial protocol was registered with ClinicalTrials.gov on 25 May 2018 prior to initiation of patient enrolment (ClinicalTrials.gov identifier: NCT03537937).

Strengths and limitations of this study

- This ongoing pragmatic trial will provide information on the optimal oxygen saturation target during invasive mechanical ventilation of critically ill adults—informing a common therapy in current clinical practice for which there is limited available evidence on which to base care.
- Broad inclusion criteria will increase generalisability and the sample size will allow examination of important patient subgroups.
- The trial is being conducted at a single centre.
- The nature of the study intervention does not allow blinding.
- Decisions regarding oxygen administration before and after invasive mechanical ventilation are deferred to treating clinicians.

INTRODUCTION

Each year 2–3 million intensive care unit (ICU) patients receive invasive mechanical ventilation.[1–3] Despite recent advances in lung-protective ventilation,[4] in-hospital mortality among mechanically ventilated ICU patients remains 25%–35%.[5]

Mechanical ventilation for ICU patients universally involves titrating the fraction of inspired oxygen (FiO_2) to maintain arterial oxygen saturation (SpO_2) within a goal range. Despite decades of ICU practice, however, the optimal SpO_2 target remains unknown. Higher SpO_2 targets (96%–100%) provide a margin of safety against hypoxaemia, but may increase exposure to excess FiO_2, hyperoxaemia, and tissue hyperoxia, causing oxidative damage,[6–8] inflammation[9 10] and increased alveolar-capillary permeability.[11] Lower SpO_2 targets (88%–92%) minimise exposure to excess FiO_2, hyperoxaemia and tissue hyperoxia,[4 12 13] but may increase the risk of hypoxaemia and tissue hypoxia.[14 15] An intermediate SpO_2 target (92%–96%) may avoid the risks of both hyperoxia and hypoxia or, conversely, may expose patients intermittently to both sets of risks.[16 17]

The relative risks and benefits of different SpO_2 or PaO_2 targets have been extensively examined in the setting of the neonatal ICU[18–21] and have been examined among

adult ICU patients in a series of recently published clinical trials.[22–27] Together, these trials have suggested that both higher and lower oxygenation targets are safe—although some trials have potentially suggested better outcomes with higher targets[25] and other trials have suggested potentially better outcomes with lower targets.[24]

Given the still incomplete evidence from randomised trials, current guidelines offer divergent recommendations—ranging from tolerating SpO_2 values as low as 88%[28–30] to pursuing SpO_2 values as high as 98%.[31] In clinical practice, hyperoxaemia remains common,[32 33] even among patients cared for by clinicians who self-identify as avoiding high oxygen levels.[34]

The wide variation in current practice, conflicting guidelines and conflicting data from some available trials indicate the need for further clinical trials to determine the effect of SpO_2 target on patient outcomes.[12 35] We designed the Pragmatic Investigation of optimaL Oxygen Targets (PILOT) trial to examine the effects of higher, intermediate and lower SpO_2 targets on the number of days alive and free of invasive mechanical ventilation among mechanically ventilated ICU patients.

METHODS AND ANALYSIS

This manuscript was prepared by the PILOT investigators (online supplemental file 1, section 1) in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (figure 1; SPIRIT checklist in online supplemental file 1, section 2).[36] This manuscript describes key elements of the trial protocol and statistical analysis plan. The supplemental methods in online supplemental file 1 provide additional background on prior trials (section 3), rationale for design decisions (sections 4–5), SpO_2 monitoring and management (sections 6–8), institutional protocols for mechanical ventilation (sections 9–17), a complete list of data elements (section 18), definitions of exploratory outcomes and measures of separation between groups (sections 19–21), and details of the interim analysis (section 22) and secondary analyses (sections 23–25).

Study design

The PILOT trial is a prospective, unblinded, pragmatic, cluster-crossover trial being conducted in the ED and medical ICU at Vanderbilt University Medical Center in Nashville, Tennessee, USA. PILOT compares use of a

	STUDY PERIOD			
	Allocation and Enrollment	On-Study		Study Termination
TIMEPOINT	***First receipt of invasive mechanical ventilation in a study location***	***Receiving invasive mechanical ventilation in study location***	***Hospitalized but not receiving invasive mechanical ventilation in a study location***	***Discharge or 28 days after enrolment***
ENROLMENT:	X			
Eligibility screen	X			
Allocation	X			
INTERVENTIONS:				
Higher SpO2 Target *Titrating FiO2 to SpO2 96-100%*	X	X		
Intermediate SpO2 Target *Titrating FiO2 to SpO2 92-96%*	X	X		
Lower SpO2 Target *Titrating FiO2 to SpO2 88-92%*	X	X		
Screening for indications for SpO2 target modification	X	X		
ASSESSMENTS:				
Baseline Variables	X			
On-study Variables	X	X	X	
Clinical Outcomes				X

Figure 1 Standard Protocol Items: Recommendations for Interventional Trials checklist. Enrolment, interventions and assessments. FiO_2, fraction of inspired oxygen; SpO_2, arterial oxygen saturation.

lower SpO_2 target (target 90% and goal range: 88%–92%), an intermediate SpO_2 target (target 94% and goal range: 92%–96%) and a higher SpO_2 target (target 98% and goal range: 96%–100%) with regard to the number of days alive and free of invasive mechanical ventilation among mechanically ventilated ICU patients. Consistent with the concept of a pragmatic clinical trial,[37] the eligibility criteria are broad, the delivery of the intervention is embedded in routine clinical care and executed by clinical personnel, and data collection prioritises clinical outcomes over mechanistic evaluation. The trial was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB 171272). The trial is investigator initiated with funding provided by the National Heart, Lung, and Blood Institute (K23HL143053). The trial protocol was registered with ClinicalTrials.gov on 25 May 2018 prior to initiation of patient enrolment on 1 July 2018 (ClinicalTrials.gov identifier: NCT03537937).

Patient and public involvement

Materials used to communicate about the study with patients and families were developed with input from the Vanderbilt Community Engaged Research Core and the Vanderbilt Community Advisory Council.

Study site and population

The trial is being conducted in the adult ED and medical ICU at Vanderbilt University Medical Center.

The inclusion criteria are

1. Age ≥18 years.
2. Receiving mechanical ventilation through an endotracheal tube or tracheostomy.
3. Admitted to the study ICU or admission to the study ICU from the ED is planned.

The exclusion criteria are

1. Known pregnancy or beta-human chorionic gonadotropin level greater than the laboratory upper limit of normal in a patient capable of becoming pregnant (if measured clinically).
2. Known to be a prisoner.

Adults located in the study ICU or for whom admission to the study ICU from the ED is planned who meet inclusion criteria and do not meet exclusion criteria are enrolled immediately on receipt of invasive mechanical ventilation in a study location. The time of enrolment for the trial ('time zero') is the time of first receipt of invasive mechanical ventilation in a participating study location.

Randomisation and treatment allocation

For each of the 18 2-month blocks during the 36 months of enrolment in the PILOT trial, the medical ICU is assigned to a single SpO_2 target (cluster-level allocation). Every 2 months, the ICU will switch between use of a lower SpO_2 target (target 90% and goal range: 88%–92%), use of an intermediate SpO_2 target (target 94% and goal range: 92%–96%) and use of a higher SpO_2 target (target 98% and goal range: 96%–100%) in a randomly generated sequence (cluster-level crossover) (figure 2). The order of study group assignments for each 2-month block was generated by computerised randomisation using permuted blocks of three to minimise the impact of seasonal variation and temporal changes. For the 36 months of enrolment in the PILOT trial, patients receiving invasive mechanical ventilation in the ED for whom admission to the medical ICU is planned will receive the same SpO_2 target assigned to the medical ICU. The study did not enrol in April and May of 2020 due to disruptions in research and clinical care from the COVID-19 pandemic (figure 2).

Washout periods

The last 7 days of each 2-month block are considered an analytic washout period during which the ICU continues to target the assigned SpO_2, but data from new patients are not included in the primary analysis. Assuming a median duration of mechanical ventilation of 3 (IQR: 3–5) days, a 7-day washout period will ensure that 98% patients in the primary analysis do not experience a 'crossover' from a period assigned to one assigned SpO_2 target to a period assigned to another SpO_2 target. Data from patients admitted during washout periods will be included in a prespecified sensitivity analysis (see Statistical analysis section). Any patient who does remain mechanically ventilated in the study ICU through a crossover from a period assigned to one SpO_2 target to a period assigned to another SpO_2 target will be analysed in the SpO_2 target group to which the ICU was assigned at the time of the patient's enrolment in the trial (intention-to-treat analysis).

Study Year 1						Study Year 2						Study Year 3					
Jul-Aug	Sep-Oct	Nov-Dec	Jan-Feb	Mar-Apr	May-Jun	Jul-Aug	Sep-Oct	Nov-Dec	Jan-Feb	*Mar & Jun*	Jul-Aug	Sept-Oct	Nov-Dec	Jan-Feb	Mar-Apr	May-Jun	Jul-Aug
2018			2019						2020			2021					
A	B	C	B	C	A	C	B	A	A	B	C	B	A	C	B	A	C

Figure 2 Group assignment during the trial. For each of the 18 2-month study periods, the study intensive care unit is randomly assigned to a higher, intermediate or lower SpO_2 target. in this figure, The letters 'A', 'B' and 'C' each correspond to one of the three possible SpO_2 targets, the allocation sequence of which remains concealed until the start of each 2-month study period. The study did not enrol in April and May of 2020 due to disruptions in research and clinical care from the COVID-19 pandemic. As a result, March and June of 2020 represent a single 2-month block assigned to one SpO_2 target. SpO_2, arterial oxygen saturation.

Table 1 SpO_2 and PaO_2 targets and goal ranges by study group

Study group	SpO_2 target	SpO_2 goal range	PaO_2 target (mm Hg)	PaO_2 goal range (mm Hg)
Lower SpO_2 target	90%	88%–92%	60	55–65
Intermediate SpO_2 target	94%	92%–96%	70	65–8
Higher SpO_2 target	98%	96%–100%	110	>80

For each study group, the SpO_2 target and goal range are displayed. PaO_2 is used to guide titration of FiO_2 for participants without reliable pulse oximetry monitoring.
FiO_2, fraction of inspired oxygen; PaO_2, arterial oxygen tension; SpO_2, arterial oxygen saturation.

Study interventions

Choice of SpO_2 targets

In clinical practice, 98% of SpO_2 values experienced by mechanically ventilated adults fall between 88% and 100%.[32 33] Within this range, current guidelines for oxygen therapy in mechanically ventilated adults outline three contrasting approaches: (1) allowing the lower end of the range of acceptable SpO_2 values to be as low as 88%[28 29] to avoid excess FiO_2, hyperoxaemia and hyperoxia; (2) titrating within an intermediate range of SpO_2 values, such as 92%–96%[38]; or (3) targeting higher SpO_2 to avoid the risks of hypoxaemia and hypoxia.[31] The PILOT trial has three study groups, each emulating a different approach to SpO_2 targets represented in guidelines and clinical practice (table 1).

Oxygen titration

In the study ED and ICU, titration of FiO_2 to maintain SpO_2 for mechanically ventilated adults is typically performed by respiratory therapists with input from nurses and physicians. In preparation for the PILOT trial, we collaborated with respiratory therapy leaders in the study ED and ICU to adapt existing ventilator management protocols to provide guidance for respiratory therapists in titrating FiO_2 to achieve each of the three study SpO_2 targets.

For patients enrolled in the study, respiratory therapists are instructed to begin titrating FiO_2 to the target SpO_2 value within 15 min of the initiation of mechanical ventilation. During the maintenance of invasive mechanical ventilation, SpO_2 is assessed by continuous pulse oximetry. The protocol directs the respiratory therapist managing the patient's ventilator to target an SpO_2 value of 90% in the lower SpO_2 target group, an SpO_2 value of 94% in the intermediate SpO_2 target group and an SpO_2 value of 98% in the higher SpO_2 target group (table 1). Respiratory therapists and other treating clinicians titrate FiO_2 when the SpO_2 is out of the goal range, when the SpO_2 is within the goal range but closer alignment with the assigned SpO_2 target is desired, to facilitate weaning from mechanical ventilation, or for other clinical indications. SpO_2 is reassessed 5 min after each change in FiO_2 or sooner if clinically indicated.

The protocol determines the SpO_2 target from enrolment until the first of: (1) discontinuation of invasive mechanical ventilation, (2) transfer out of a participating study location, (3) completion of an SpO_2 target modification sheet by treating clinicians or (4) end of the 2-month study period. The protocol does not determine the SpO_2 target during time periods in which the patient is not physically located in a study location (eg, during transport) or when FiO_2 is being administered for purposes other than achieving a target SpO_2 (eg, when an FiO_2 of 1.0 is being administered for a procedure).

At any time, if a treating clinician or a patient, family member or surrogate feels that an SpO_2 target other than that assigned by the study would be best for the optimal treatment of the patient for any reason, the SpO_2 target for that patient is modified. To modify the target, the respiratory therapist and supervising physician complete a one-page SpO_2 target modification sheet documenting the new SpO_2 target and the rationale for modifying the target. Examples of conditions for which the assigned SpO_2 target may be modified that were specified in the initial trial protocol included pneumothorax, pneumomediastinum, carbon monoxide poisoning, decompression sickness, bleomycin toxicity and paraquat toxicity. Examples of conditions for which the assigned SpO_2 target may be modified that were not explicitly specified in the initial trial protocol include severe chronic obstructive pulmonary disease, severe acute respiratory distress syndrome, severe anaemia, status post lung transplantation and receipt of extracorporeal membrane oxygenation support. Trial protocol directs only the titration of FiO_2 to the assigned SpO_2 target. Other aspects of invasive mechanical ventilation, such as tidal volume,[4] positive end-expiratory pressure[39 40] and use of rescue therapies for hypoxaemia, are determined by institutional protocols and treating clinicians (see sections 9–17 of online supplemental file 1).

Blinding

Similar to prior studies of SpO_2 targets among critically ill adults,[22 24 26] patients and clinicians will not be blinded to study group assignment.

Data collection

The PILOT trial uses data collected by two methods to minimise observer bias: (1) manual data collection by study personnel and (2) automated collection of structured data recorded in routine clinical care, exported daily from the institution's electronic health record and

patient registration, billing and laboratory clinical information systems into an Enterprise Data Warehouse. We have previously validated the quality of the automated method of data collection against the reference standard of two-physician manual chart review[41] and have employed this approach for the conduct of prior pragmatic trials.[42 43] Data are stored, curated and secured in REDCap.[44]

Outcomes

Primary outcome

The primary outcome is VFDs to study day 28. VFDs will be defined as the number of whole calendar days alive and free of invasive mechanical ventilation beginning at midnight on the day of the final receipt of invasive mechanical ventilation through day 28 after enrolment.[45 46] Outcome ascertainment will cease at the time of hospital discharge or 28 days after enrolment, whichever occurs first. Receipt of invasive mechanical ventilation will be considered to end when patients undergo the final tracheal extubation or disconnection of the ventilator from the endotracheal tube or tracheostomy tube between enrolment and 28 days after enrolment. Patients whose final receipt of invasive mechanical ventilation occurs on the day of enrolment will receive 27 VFDs. Patients who continue to receive invasive mechanical ventilation 28 days after enrolment will receive 0 VFDs. Patients who die prior to day 28 will receive 0 VFDs. Patients who are discharged from the hospital prior to day 28 and are receiving invasive mechanical ventilation at the time of discharge will receive 0 VFDs. Patients who are removed from invasive mechanical ventilation and are discharged from the hospital without invasive mechanical ventilation prior to 28 days will be assumed to remain free of invasive mechanical ventilation between hospital discharge and day 28. For patients who are removed from invasive mechanical ventilation, return to invasive mechanical ventilation, and are subsequently removed again from invasive mechanical ventilation prior to day 28, VFDs will be counted from the final receipt of invasive mechanical ventilation prior to day 28.

Secondary outcome

The sole prespecified secondary outcome is 28-day in-hospital mortality, defined as death from any cause between enrolment and the first of hospital discharge or 28 days after enrollment.

Exploratory clinical outcomes

1. ICU mortality—death in the ICU between enrolment and the first of 28 days after enrolment or hospital discharge
2. Free-day outcomes—defined as whole calendar days from last receipt of therapy until 28 days (online supplemental file 1, section 19)
   i. Vasopressor-free days
   ii. Renal replacement therapy-free days
   iii. ICU-free days
   iv. Hospital-free days

Exploratory organ function outcomes

1. Daily non-respiratory Sequential Organ Failure Assessment (SOFA) score (online supplemental table S1)[47]
2. Plasma creatinine concentration (mg/dL)
3. Plasma lactate concentration (mmol/L)
4. Presence of acute respiratory distress syndrome by Berlin criteria[48]
5. Stage II or greater acute kidney injury (AKI) by Kidney Disease: Improving Global Outcomes creatinine criteria.[49]

Exploratory safety outcomes

1. Atrial arrhythmia
2. Ventricular arrhythmia
3. Cardiac arrest with return of spontaneous circulation
4. Pneumothorax or pneumomediastinum
5. Ischaemic stroke
6. Myocardial infarction[50]

Additional long-term patientimportant outcomes

The independently funded Cognitive Outcomes in the Pragmatic Investigation of Optimal Oxygen Targets (CO-PILOT) study (R21AG063126) will assess cognitive, physical and psychological outcomes at 12 months after enrolment in the PILOT trial. The protocol and statistical analysis plan for the CO-PILOT study will be published separately.

Statistical analysis and reporting

Sample size estimation and power calculation

In a prior cluster-randomised cluster-crossover trial in the same ICU,[51] 880 mechanically ventilated adults were enrolled per year (73.3 per month), with a median of 22 VFDs (IQR: 0–25 VFDs) and an intracluster intra-period correlation of 0.01. We estimate 2640 mechanically ventilated adults will be admitted to the study ICU during the 36-month PILOT trial, of whom 390 will be excluded from the primary analysis for initial receipt of invasive mechanical ventilation in a study location during a washout period and 2250 will be enrolled and included in the primary analysis. With a total enrolment of 2250 patients, a SD in the primary outcome of VFDs of 11.4 days, and a two-sided alpha of 0.05, we calculated using a t-test that the PILOT trial will have 92% statistical power to detect an absolute reduction in VFDs of 2.0 days (similar to the numerical difference in VFDs between SpO_2 target groups reported in prior studies[22 24]).

DSMB and interim analysis

An independent Data and Safety Monitoring Board (DSMB) oversees the trial. On 23 March 2020 the DSMB conducted a single, planned interim analysis at the anticipated halfway point of the trial and recommended the trial to continue without modification (see DSMB charter in online supplemental file 2) and details of interim analysis in online supplemental file 1, section 22). The

DSMB is composed of two physicians outside the study institution with expertise in adult pulmonary and critical care medicine clinical practice and clinical research, one bioethicist and one biostatistician.

Statistical analysis principles

R (R Foundation for Statistical Computing, Vienna, Austria) will be used for analyses. Analyses will be conducted at the level of an individual patient during an individual hospitalisation in an intent-to-treat fashion, unless otherwise specified. Continuous variables will be reported as mean±SD or median and IQR; categorical variables will be reported as frequencies and proportions.

Main analysis of the primary outcome

The main analysis will be an intention-to-treat comparison of the primary outcome of VFDs between the higher, intermediate and lower SpO_2 target groups among all patients enrolled in the trial except[1] those admitted during one of the 7-day washout periods and[2] those with a laboratory-confirmed diagnosis of COVID-19. Patients with a diagnosis of COVID-19 will be excluded from the main analysis for two reasons. First, the majority of the PILOT trial occurred prior the COVID-19 pandemic, with too few 2-month study blocks occurring during the pandemic to ensure balance in the number of patients with COVID-19 between trial groups. Second, at the study hospital, ICU patients diagnosed with COVID-19 are transferred to a separate, dedicated COVID-19 ICU that was not participating in the PILOT trial. Thus, patients with COVID-19 are unlikely to have received significant exposure to the SpO_2 target intervention in the PILOT trial. Patients enrolled during washout periods and patients diagnosed with COVID-19 will be included in sensitivity analyses (see Sensitivity analyses below).

It is possible to estimate a conditional effect, which is interpreted as the effect of a given SpO_2 target on an individual patient given the values of the covariates for that patient, or a marginal effect, which is interpreted as the population effect of implementing a given SpO_2 target as a general policy.[52] Since an SpO_2 target intervention may be applied both at the patient level as an individual intervention and at the unit level as a general policy, both may be of interest.

To estimate the conditional effect, we will use a proportional odds model with independent covariates of group assignment (higher, intermediate or lower SpO_2 target) and time.[53 54] Time (in days) will be treated as a continuous variable with values ranging from 1 (first day of enrolment) to 1097 (final day of enrolment) and will be analysed using restricted cubic splines with multiple knots to allow for non-linearity resulting from seasonality or secular trends. For the purposes of declaring a statistically significant difference between groups in the primary endpoint, we will consider the conditional effect from the proportional odds model and a two-sided p value of 0.05.

To estimate the marginal effect, we will use generalised estimating equations with study period as the cluster and an independent variable for group assignment (higher, intermediate or lower SpO_2 target).

For both approaches, in addition to assessing for an overall group effect within the model, we will estimate the differences between each pair of SpO_2 targets by extracting 95% CIs from the model.

Sensitivity analyses of the primary outcome

- We will repeat the primary analysis using alternative statistical approaches to comparing the VFDs outcome between groups such as zero-inflated Poisson regression or zero-inflated negative binomial regression, global rank scale analysis[55] and Fine and Gray competing risk regression.
- We will repeat the primary analysis with adjustment for prespecified baseline covariates of age, sex, race and ethnicity, source of ICU admission, vasopressor receipt, acute diagnoses at enrolment, and severity of illness as assessed by the non-respiratory SOFA score.
- We will repeat the primary analysis replacing the continuous covariate of time with a categorical covariate of season defined as: winter (January, February, March); spring (April, May, June); summer (July, August, September); and fall (October, November, December).
- We will repeat the primary analysis among all patients enrolled in the trial, including[1] patients initiated on invasive mechanical ventilation in a study location during one of the prespecified 7-day washout periods and[2] patients with a diagnosis of COVID-19.

Analysis of effect modification for the primary outcome

We will examine whether prespecified baseline variables modify the effect of study group on the primary outcome using formal tests of statistical interaction in a proportional odds model. Independent variables will include study group assignment, the potential effect modifier of interest and the interaction between the two (eg, study group × presence of sepsis or septic shock) and time. Significance will be determined by the p value for the interaction term, with values <0.10 considered to suggest a potential interaction and values <0.05 considered to confirm an interaction.

We will examine whether the following baseline variables modify the effect of study group on the primary outcome:

1. Age;
2. Race and ethnicity (Hispanic, non-Hispanic Black, non-Hispanic white, Other);
3. Source of admission to the ICU (ED, hospital ward, another ICU in the study hospital, operating room, outside hospital);
4. Duration of invasive mechanical ventilation prior to enrollment;
5. Chronic comorbidities (categories are not mutually exclusive)
   i. Receipt of supplemental oxygen at place of residence prior to hospital admission (yes, no);

ii. Coronary artery disease or heart failure with reduced ejection fraction (yes, no);

6. Acute diagnoses at enrollment (categories are not mutually exclusive)[56]
   i. cardiac arrest (yes, no);
   ii. acute myocardial infarction (yes, no);
   iii. sepsis or septic shock (yes, no);
   iv. acute respiratory distress syndrome (yes, no);
7. Receipt of vasopressors at enrollment (yes, no);
8. Non-respiratory SOFA score at enrollment;
9. Time period before the COVID-19 pandemic (July 2018 to December 2019), and during the COVID-19 pandemic (January 2020 to August 2021).

Analysis of the secondary outcome

The sole prespecified secondary outcome of 28-day in-hospital mortality will be compared between the three study groups in an intention-to-treat fashion in the main analysis population using a logistic regression model with independent covariates of group assignment (higher, intermediate or lower SpO_2 target) and time. In addition to assessing for an overall group effect within the model, we will estimate the differences between each pair of SpO_2 targets by extracting 95% CIs from the model.

Analysis of the exploratory outcomes

Each of the exploratory outcomes will be compared between groups in an intention-to-treat fashion in the main analysis population. Exploratory outcomes will be compared between study groups in a similar manner as for primary and secondary outcomes. A logistic model will be used for binary outcomes, a multinomial model for categorical outcomes, and a proportional odds model will be used for ordinal and continuous outcomes.

Trial status

PILOT is an ongoing pragmatic trial comparing higher, intermediate and lower SpO_2 targets for mechanically ventilated critically ill adults. Patient enrolment began on 1 July 2018 and is anticipated to conclude on 31 August 2021.

Ethics and dissemination

IRB approval

The trial was approved by the IRB of Vanderbilt University Medical Center with a waiver of informed consent (IRB# 171272), details of which are provided in (online supplemental file 1, section 26). Participants who regain capacity to provide informed consent, or legally authorised surrogate decision-makers for those patients who do not regain the capacity to provide informed consent, are approached to provide informed consent for assessment of long-term outcomes as a part of the independently funded CO-PILOT study (R21AG063126).

Information for patients and families

An information sheet providing an IRB approved lay language summary of the study and containing the contact information for investigators (who remain available throughout the study period to provide additional information to patients and families on request) is made available throughout the study period in glass display cases near the public entrance to the ICU and near the centre of the ICU, in the 'welcome packet' of information about the ICU, which is distributed at the time of ICU admission to patients, families and surrogates by the medical receptionist or charge nurse as a part of routine admission processes, in a brochure holder in the family waiting room for the study ICU, and by treating physicians and respiratory therapist to any patients, families, or surrogates with questions or concerns about the study.

Protocol changes

Any changes to the trial protocol will be recorded on ClinicalTrials.Gov as per SPIRIT guidelines (see section 27 of online supplemental file 1).

Data handling and sharing

For details of privacy, data handling and data sharing, see sections 28–29 of online supplemental file 1.

Dissemination plan

Trial results will be submitted to a peer-reviewed journal for consideration of publication and will be presented at scientific conferences. The results of the study will be disseminated to patients and the public at the completion of the trial.

The full list of the PILOT investigators may be found in (online supplemental file 1, section 1).

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Contributors Study concept and design was done by MWS, JDC, CJL, GB, WHS and TWR. Drafting of the manuscript was done by MWS, LW and CJL. Critical revision of the manuscript for important intellectual content was performd by MWS, JDC, BDL, PH, MH, MR, JS, JB, KGB, LW, CJL, RF, JPW, GB, WHS and TWR. LW and

CJL were responsible for statistical analysis. Study supervision was done by GB, WHS and TWR.

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Competing interests All authors completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. RF reported receiving grant funding and consulting fees from Medtronic and stock from 3M outside the current work. TWR reported receiving consulting fees from Cumberland Pharmaceuticals outside the current work. The authors declared no potential conflicts of interest with the current work.

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ONLINE SUPPLEMENT TO:

Protocol and Statistical Analysis Plan for the Pragmatic Investigation of Optimal Oxygen Targets (PILOT) Clinical Trial

Contents

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SUPPLEMENTAL METHODS

1. List of PILOT Investigators

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2. SPIRIT 2013 Checklist

SPIRIT 2013 Checklist:
Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	7
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, sup 2
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1-2

	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___1___
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____5-6___
	6b	Explanation for choice of comparators	__5,6, 9____
Objectives	7	Specific objectives or hypotheses	____6____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____6-7____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___7_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___7-8_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__9-11____

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__11-12___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__Sup 17__
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__12-13__
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__14-17__
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	___Fig 1__
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__15-16___
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	___15____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	_8-9__
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_8-9, Fig 2__
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	_8-10___
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_12___
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_NA___
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_13-14_
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__13__

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__13___
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__16-21__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__16-21__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__16,21__
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__16__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Sup 34_
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_Sup 17,34__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Sup 17___

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___22__
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__Sup 40__
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	___22__
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___22___
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Sup 40__
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___2___
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_Sup 40-42_
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__NA___
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__23___
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Sup 2__

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_ Sup 42_
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	_NA_
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__NA_

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

3. Prior Clinical Trials of Oxygen Targets for Adult ICU Patients

To date, five small-to-moderate sized clinical trials have examined SpO2 targets among adult ICU patients [1–6]. The first trial compared a lower SpO_2 target (88-92%) with a higher SpO_2 target (96-100%) among 103 mechanically ventilated patients [1]. Targeting these SpO_2 ranges produced adequate separation between groups in SpO_2, PaO_2, and FiO_2 without any concern for safety, but the trial was not powered to detect differences in clinical outcomes. The second trial enrolled mechanically ventilated adults with septic shock and reported a numerically higher mortality for those randomized to an FiO_2 of 1.0 compared with those randomized to an SpO_2 target of 88-95% [2]. The third trial reported an 8% absolute reduction in mortality with use of an SpO_2 target of 94-98% compared to 97-100% among 434 patients in a single ICU [3]. These findings were limited by early study termination and the authors concluded that a larger trial was needed [3]. The fourth trial compared use of an SpO_2 target of 88-92% versus 96-100% among 205 mechanically ventilated adults with acute respiratory distress syndrome [4]. No statistically significant difference was observed between groups. Although outcomes appeared to numerically favor the higher SpO_2 target group, interpretation was limited by early study termination. The fifth trial enrolled 1000 ICU patients within 2 hours of the initiation of mechanical ventilation [5]. Patients in the intervention group received the lowest FiO_2 that maintained $SpO_2 > 90\%$. Patients in the control group received oxygen therapy at the discretion of treating clinicians targeting SpO2 values between 91-100%. No difference between groups in clinical outcomes was observed, although modest separation between groups and sample size may have limited power to detect differences in patient-centered outcomes. The sixth trial randomized 2,928 adult ICU

patients with acute hypoxemic respiratory failure on at least 10 liters of oxygen per minute or a fraction of inspired oxygen of at least 0.5 to a PaO_2 target of either 60 mm Hg or 90 mm Hg. The trial reported no significant differences between groups in 90-day mortality, ventilator-free days, or new episodes of shock, myocardial ischemia, ischemic stroke, or intestinal ischemia.

4. Rationale for Cluster-level Allocation

Group assignment in the PILOT trial occurs at the level of the ICU (cluster) for several reasons. In routine clinical care in the study ICU, titration of FiO_2 to maintain SpO_2 for all mechanically ventilated adults is performed by 2 to 4 respiratory therapists, with input from nurses and physicians. The management of mechanical ventilation (selection of tidal volume, titration of positive end-expiratory pressure, screening for and performance of spontaneous breathing trials) is governed by unit-wide protocols implemented by the 2 to 4 respiratory therapists for all patients in the unit. Assigning the entire unit to a single SpO_2 target emulates the way mechanical ventilation is managed during clinical care and limits contamination that might result from a respiratory therapist managing multiple patients assigned to different SpO_2 targets.

Additionally, exposure to excess FiO_2, hyperoxemia, and hyperoxia is most common in the minutes-to-hours immediately following initiation of invasive mechanical ventilation [7,8]. In a recent randomized trial examining tracheal intubation of critically ill adults, the median values for lowest SpO_2 and highest FiO_2 were 97% and 1.0, respectively, in the first hour of invasive mechanical ventilation, compared with 96% and 0.6 between 1 hour and 6 hours and 94% and 0.5 between 6 hours and 24 hours [9]. Even brief periods of early hyperoxia or hypoxia may affect organ function [10–12] and clinical outcomes [13–16]. Enrollment immediately after initiation of invasive mechanical ventilation minimizes pre-study exposure to excess FiO_2, hyperoxemia, and hyperoxia and facilitates on-study separation between groups. Multiple prior trials examining SpO_2 targets have aimed to enroll patients shortly after the initiation of invasive mechanical ventilation [5,17]. In these patient-level parallel-group trials,

however, the logistical challenges of performing screening, enrollment, randomization, and study group assignment immediately following initiation of invasive mechanical ventilation resulted in the exclusion of 60-90% of eligible patients – raising concern for systematic exclusion of important patient groups (e.g., patients with higher acuity of illness). In PILOT, group assignment at the cluster level allows enrollment immediately on initiation of invasive mechanical ventilation in the ED or ICU. This approach emulates the manner in which oxygen therapy is managed in practice, precludes systematic exclusion of important patient groups, decreases pre-study exposure to hyperoxia and hypoxia, and facilitates early separation in oxygen therapy between groups.

5. Rationale for Targeting SpO_2 versus PaO_2

SpO_2 is measured continuously via non-invasive pulse oximetry for nearly all mechanically ventilated ICU patients. In contrast, PaO_2 is assessed via arterial puncture intermittently and selectively, with most measurements occurring early in the admission of severely ill patients. Similar to prior clinical trials of oxygen therapy during mechanical ventilation [1,5], the PILOT trial targets SpO_2 rather than PaO_2 for patients with functioning non-invasive pulse oximetry monitoring. For patients in the PILOT trial for whom non-invasive pulse oximetry monitoring is unavailable or inaccurate (e.g., inadequate plethysmography signal due to hypoperfusion), PaO_2 values corresponding to the assigned SpO_2 target are used to guide oxygen therapy [18].

6. Approach to Monitoring SpO_2

For all mechanically ventilated patients in the study ED and ICU, SpO_2 is continuously monitored using Nellcor™ SpO_2 Adhesive Sensors (Medtronic, Minneapolis, MN), which measure changes in red and infrared light absorption in an arteriolar bed throughout the pulse cycle to report a non-normalized real-time plethysmographic waveform and arterial hemoglobin saturation values averaged over the prior 6 seconds with a mean difference between SpO_2 and SaO_2 < 2% for SpO_2 values 80-100% [19]. Plethysmography and SpO_2 values are displayed [1] on IntelliVue MP90 bedside patient monitors (PHILIPS, Amsterdam, Netherlands) in each ED and ICU room, [2] on telemetry monitors located at ED and ICU nursing stations and adjacent to the respiratory therapy office, and [3] in real-time in the institutional electronic health record, available from any physical location. SpO_2 values are archived every 60 seconds into an Enterprise Data Warehouse [20–22].

7. Feedback on SpO_2 Target Adherence

During the study, the IntelliVue MP90 bedside patient monitors in each room are set to generate an alarm for SpO_2 values outside the range considered to be at goal for the assigned SpO_2 target group. For example, for patients in the intermediate SpO_2 target group, SpO_2 values 92-96% generate no alarm, whereas SpO_2 values ≤ 91% or ≥ 97% generate an alarm alerting nursing staff and respiratory therapy to the out-of-range value.

Study personnel remotely monitor SpO_2 values every four hours from 4 AM through 10 PM Monday through Friday and during a 10% sample of night and weekend hours to identify instances of lag between out-of-range SpO_2 values and FiO_2 titration, provide feedback and support to respiratory therapists and bedside nurses, and identify barriers to achieving the assigned SpO_2 target.

Prior to the trial, all respiratory therapists, nurses, and supervising physicians who practice in the study ICU received formal training in the study protocol. Throughout the duration of the study, study personnel attend respiratory therapy group meetings, nursing unit board meetings, and ICU physician leadership meetings to provide continuing education about the study, reinforce elements of the study protocol including the process for SpO_2 target modification by treating clinicians, screen for safety concerns or potential adverse events, and identify and address barriers to achieving the SpO_2 targets.

8. SpO_2 Targets in Patients who return to Invasive Mechanical Ventilation

Patients who discontinue invasive mechanical ventilation and return to invasive mechanical ventilation in a study location during the same two-month study period continue to be managed using the same assigned SpO_2 target. Similarly, patients who are transferred out from a study location and return to receiving invasive mechanical ventilation in a study location during the same two-month study period continue to be managed using the same assigned SpO_2 target. Patients who remain on invasive mechanical ventilation in a study location through the end of a two-month study period receive the SpO_2 target assigned by the study until midnight on the night that the two-month study period ends, after which time treating clinicians determine the SpO_2 target with which the patient is managed. Similarly, for patients who are enrolled during one two-month study period, discontinue invasive mechanical ventilation or transferred out of the study location, and return to receiving invasive mechanical ventilation during a subsequent two-month study period, treating clinicians determine the SpO_2 target with which the patient is managed during the subsequent episode of invasive mechanical ventilation.

9. Liberation from Mechanical Ventilation

Each day of mechanical ventilation, all patients in the study ICU are assessed for safety of a spontaneous awakening trial (SAT) and spontaneous breathing trial (SBT) [23] using the SAT and SBT safety criteria from the Awakening and Breathing Controlled trial [24]. To prevent patients in the higher SpO_2 target group from experiencing delays in qualifying for an SBT based on receipt of higher FiO_2 to achieve the higher SpO_2 target, patients in all groups are allowed to qualify for an SAT and SBT regardless of their current FiO_2 or PEEP settings, as long as the other SAT and SBT Safety Screen criteria are met and treating clinicians feel performance of an SAT and SBT is safe. Definitions of SAT and SBT failure and the ventilator settings and duration of the SBT are the same as those used in the ABC trial and during clinical care in the study ICU. For patients who have passed an SBT, the decision to discontinue invasive mechanical ventilation is made by the treating clinicians.

Semler MW, *et al. BMJ Open* 2021; 11:e052013. doi: 10.1136/bmjopen-2021-052013

10. Protocol for Ventilator Management in the Study ICU

Predicted Body Weight (PBW) Calculation:

Males: PBW (kg) = (height in inches – 60)*2.3+50
Females: PBW (kg) = (height in inches – 60)*2.3+45.5

Mode: Assist Control

Tidal volume: 6 ml/kg PBW

Respiratory rate: Set to maintain 60-70% minute ventilation prior to tracheal intubation. Adjust rate to maintain pH 7.30-7.45, NOT TO EXCEED 35 bpm or PC02 < 25.

I:E Ratio: Avoid inverse ratio ventilation

PEEP titration:

FiO2	0.3-0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1
PEEP	5	8	8	10	10	10	12	14	14	14	16	18	18-25

Wean patient to the lowest level of FiO2 & PEEP while maintaining goal SpO2.

Acidosis Management:

1. If pH <7.30, increase RR to 35 as needed.
2. If pH remains <7.3 with RR = 35 call House Officer
3. If pH <7.15, consider bicarbonate administration, may increase TV by 1 ml/kg PBW increments until pH is >7.15 or TV = 8 ml/kg PBW (under these conditions Pplat targets [see below] may be exceeded).

Alkalosis Management: If pH >7.45, decrease RR.

Management of Tidal Volume:

1. Titrate TV by 1ml/kg increments (minimum of 4ml/kg PBW) to maintain a Pplat below 30cm H2O.
2. Measure & record Pplat (0.5 sec inspiratory pause), SpO2, Total RR, TV and pH (if available) at least every 4 hours AND after each change in PEEP or TV.

11. Protocol for Assessment of Pain (CPOT score) in the Study ICU

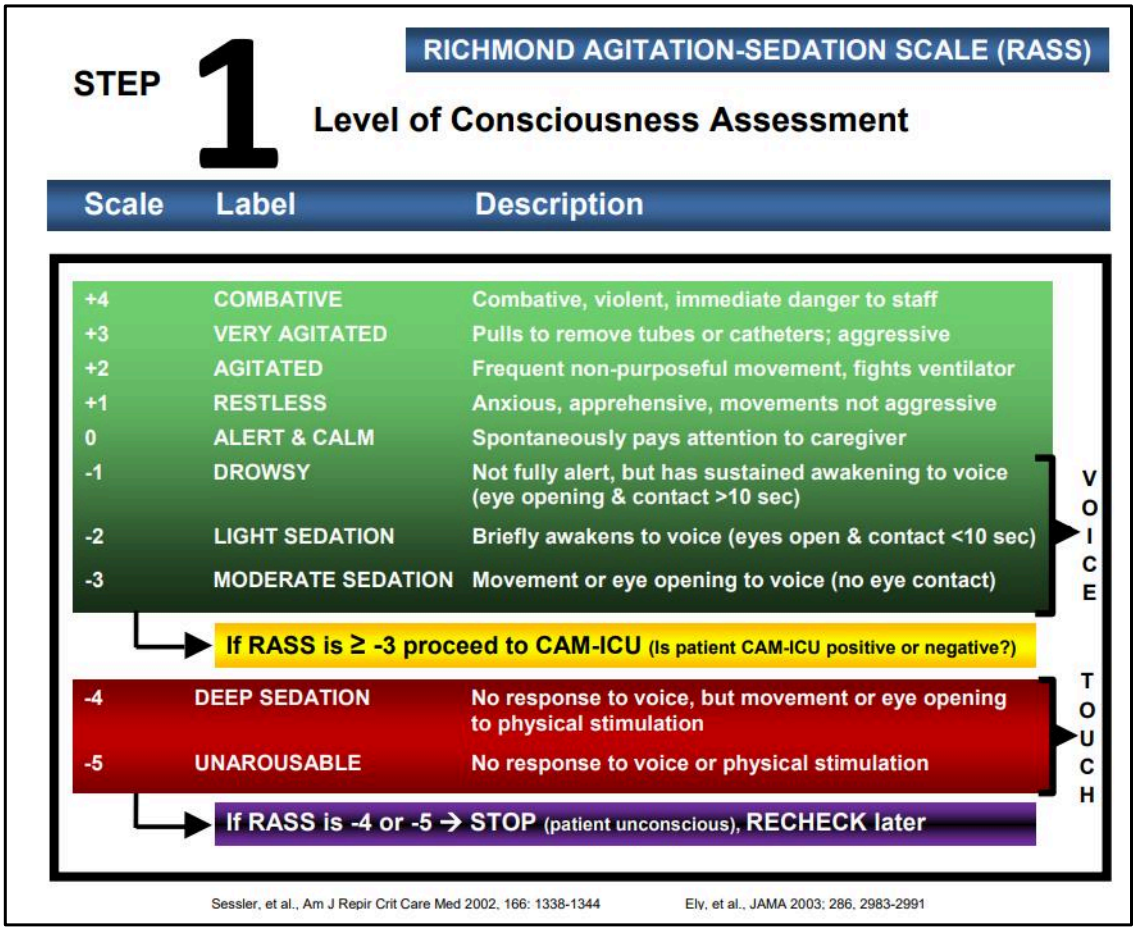
Indicator	Assessment	Score	Description
Facial expressions	Relaxed, neutral	0	No muscle tension observed
	Tense	1	Presence of frowning, brow lowering, orbit tightening and levator contraction or any other change (e.g. opening eyes or tearing during nociceptive procedures)
	Grimacing	2	All previous facial movements plus eyelid tightly closed (the patient may present with mouth open or biting the endotracheal tube)
Body movements	Absence of movements or normal position	0	Does not move at all (doesn't necessarily mean absence of pain) or normal position (movements not aimed toward the pain site or not made for the purpose of protection)
	Protection	1	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements
	Restlessness/Agitation	2	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed
Compliance with the ventilator (intubated patients)	Tolerating ventilator or movement	0	Alarms not activated, easy ventilation
	Coughing but tolerating	1	Coughing, alarms may be activated but stop spontaneously
	Fighting ventilator	2	Asynchrony: blocking ventilation, alarms frequently activated
OR			
Vocalizations (extubated patients)	Talking in normal tone or no sound	0	Talking in normal tone or no sound
	Sighing, moaning	1	Sighing, moaning
	Crying out, sobbing	2	Crying out, sobbing
Muscle tension	Relaxed	0	No resistance to passive movements
	Tense, rigid	1	Resistance to passive movements
Evaluate by passive flexion and extension of the upper limbs when patient is at rest or evaluation when patient is being turned	Very tense or rigid	2	Strong resistance to passive movements or incapacity to complete them
TOTAL		**___/8**	

Adapted from: https://www.icudelirium.org/medical-professionals/assess-prevent-and-manage-pain

Gélinas, C. (2010). Nurses' Evaluations of the Feasibility and the Clinical Utility of the Critical-Care Pain Observation Tool. Pain Management Nursing, 11(2), 115-125.

Arbour, C., & Gélinas, C. (2011). Ask the Experts. Setting Goals for Pain Management When Using a Behavioral Scale: Example With the Critical-Care Pain Observation Tool. Critical Care Nurse, 31, 66-68.

12. Protocol for Assessment of Agitation (RASS score) in the Study ICU



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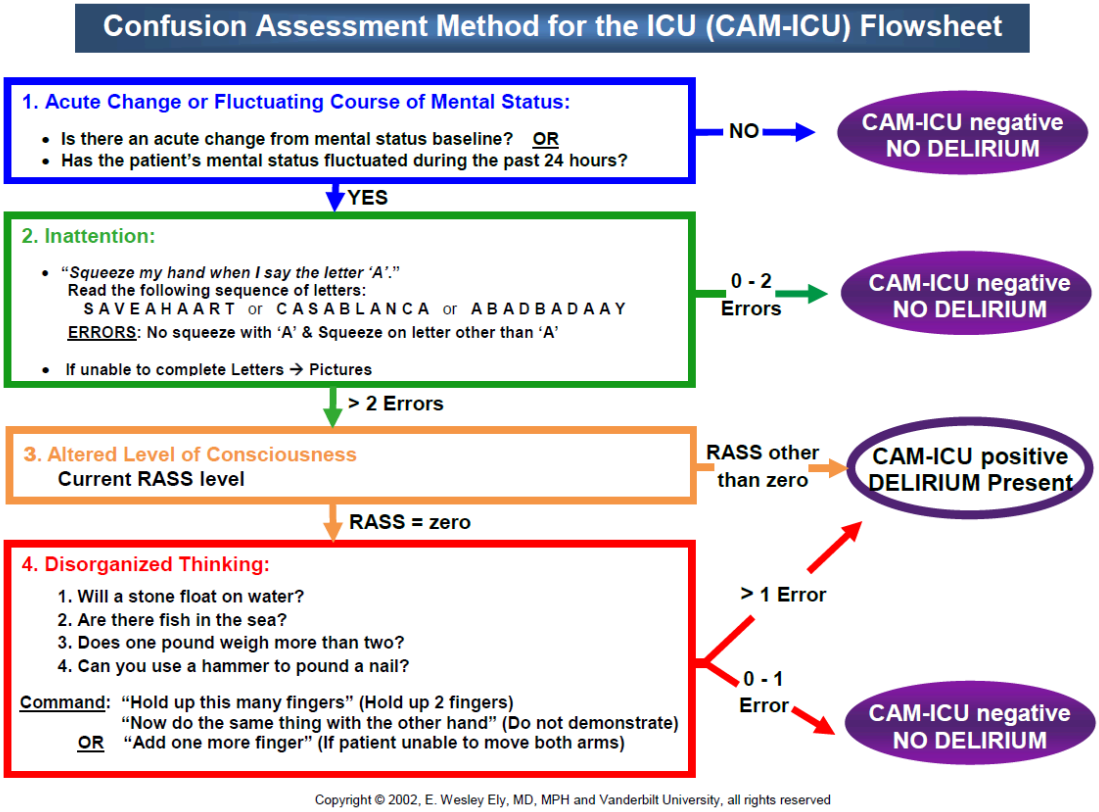
https://www.icudelirium.org/medical-professionals/delirium/monitoring-delirium-in-the-icu

13. Protocol for Delirium Assessment (CAM-ICU score) in the Study ICU



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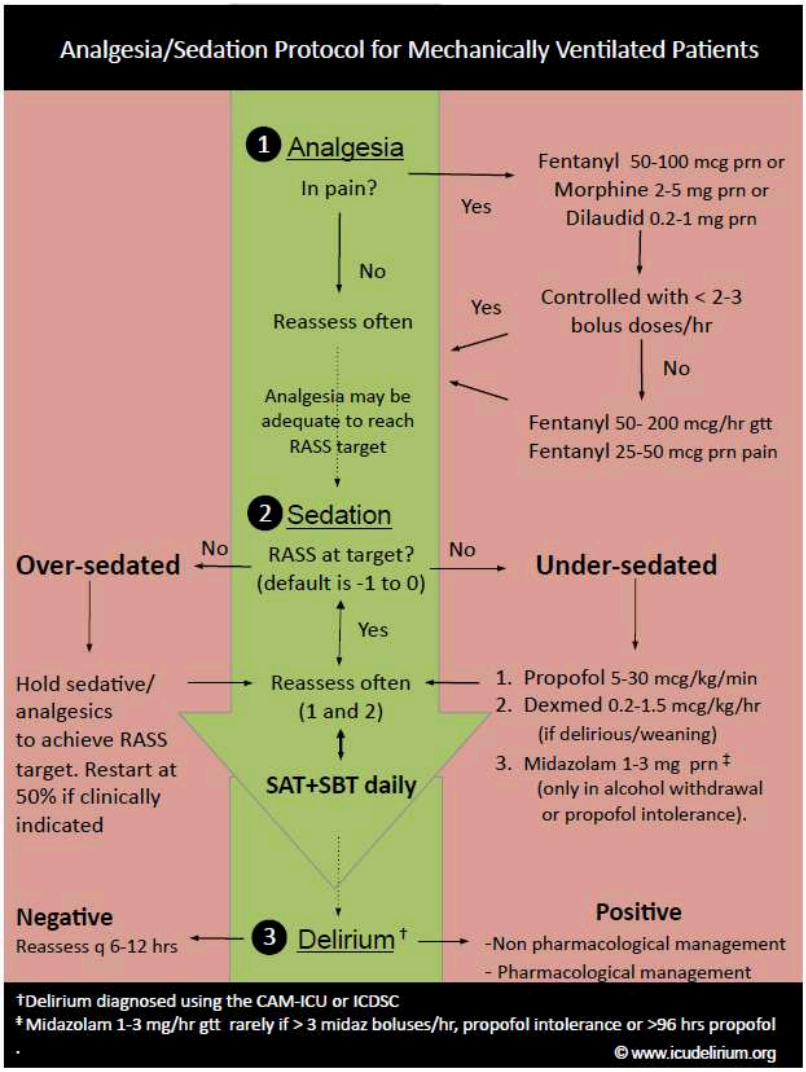
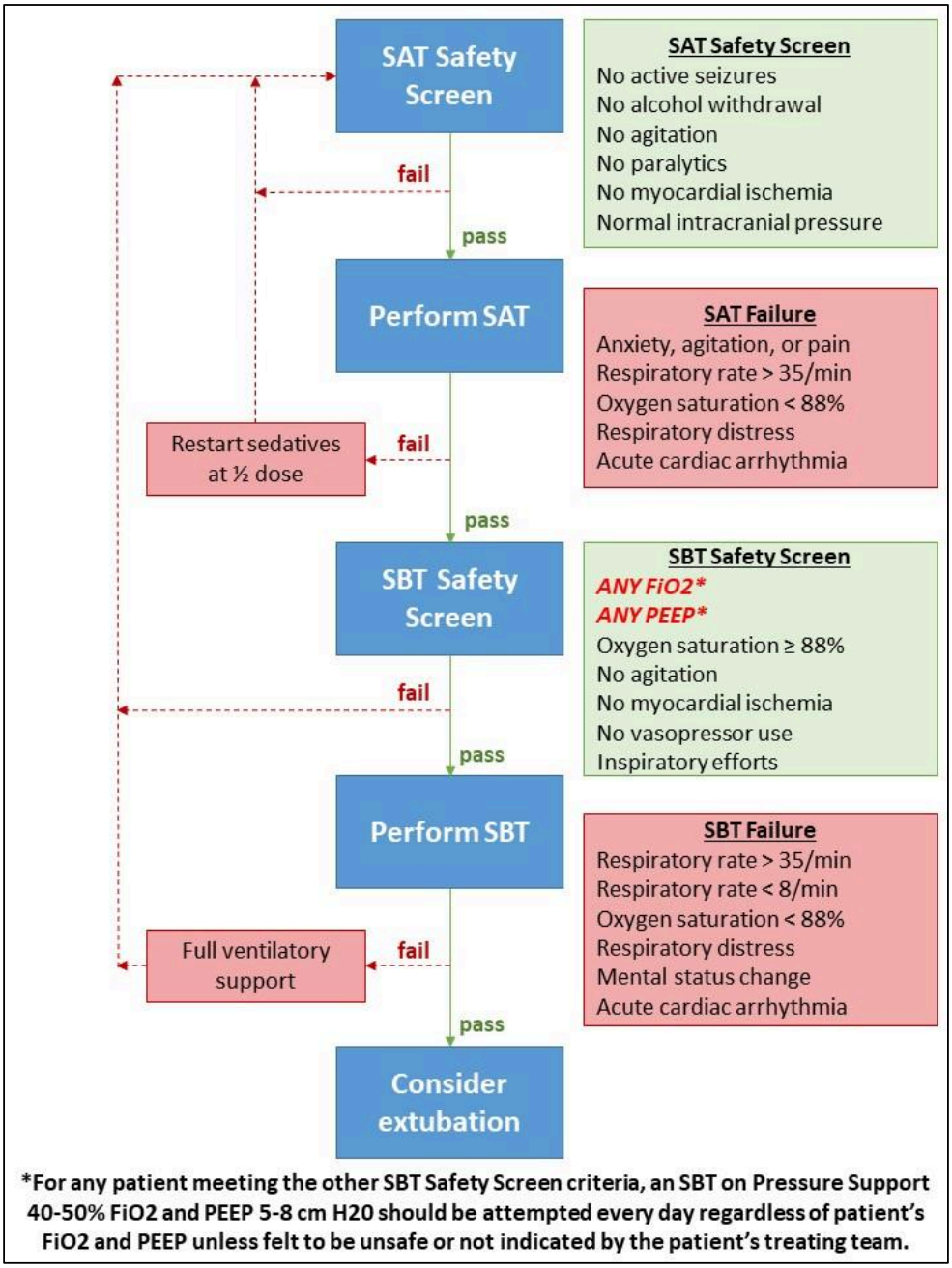
14. Protocol for Management of Pain, Agitation, and Delirium in the Study ICU



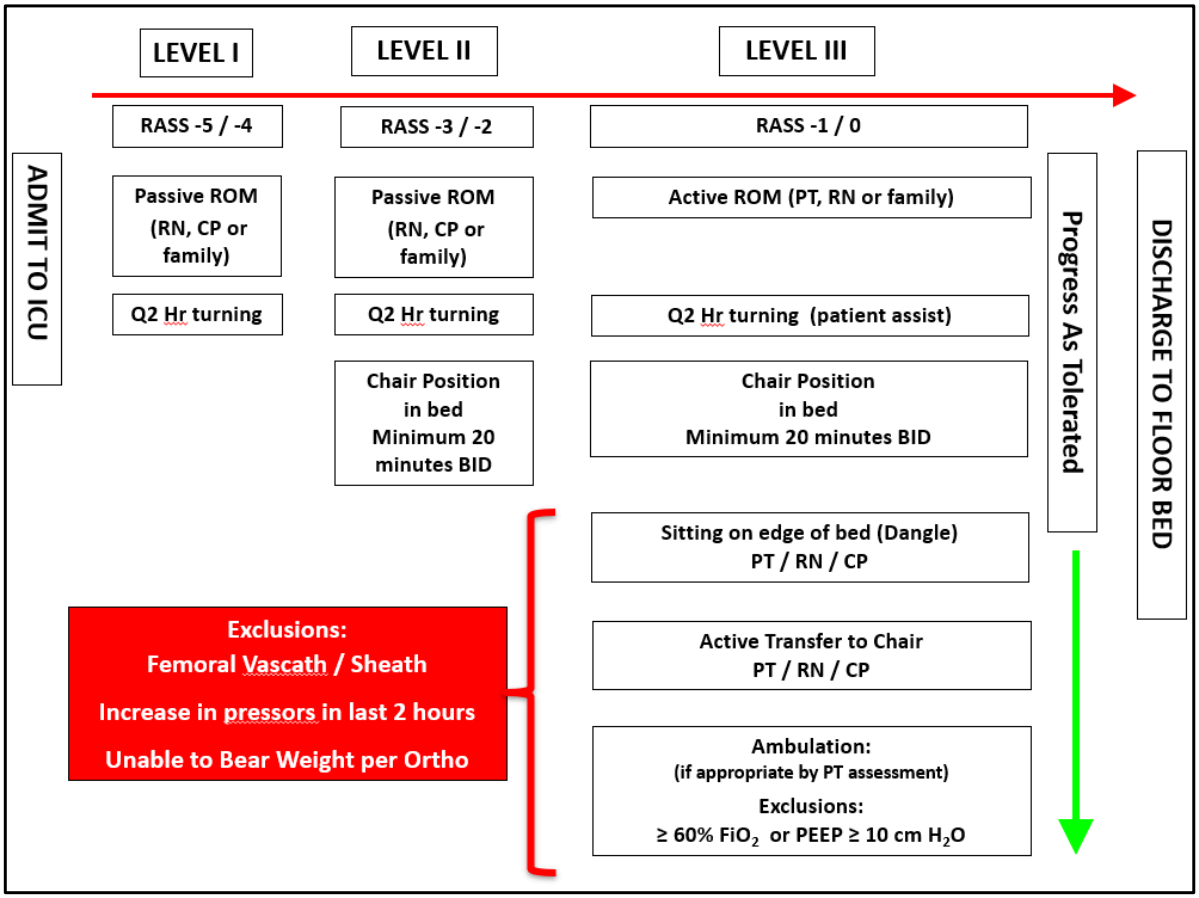
Reproduced with permission from:
https://www.icudelirium.org/medical-professionals/delirium/monitoring-delirium-in-the-icu

15. Protocol for Daily Spontaneous Awakening Trial (SAT) Safety Screen, SAT Performance, Spontaneous Breathing Trial (SBT) Safety Screen, and SBT Performance



Adapted for the PILOT trial from the "Wake Up and Breathe Flowchart", found at: https://www.icudelirium.org/medical-professionals/both-sat-and-sbt

16. Protocol for Early Mobility in the Study ICU



17. Treatment Decisions Determined by Treating Clinicians during the Study

All treatment decisions except choice of SpO_2 target during invasive mechanical ventilation of are made by treating clinicians, including: approach to oxygen therapy before invasive mechanical ventilation; use of non-invasive ventilation before invasive mechanical ventilation; choice of ventilator mode during invasive mechanical ventilation; approach to positive end-expiratory pressure during invasive mechanical ventilation; administration of neuromuscular blocking agents, inhaled epoprostenol, prone positioning, or extracorporeal membrane oxygenation; administration of vasopressors or ionotropes, antimicrobial medications, diuretics, intravenous fluid, or blood products; arterial or venous blood gas measurement, measurement of lactate concentration, measurement of central or mixed venous oxygen saturation.

18. Data Collected at Each Timepoint

Enrollment (Day 0)

1. Data collected by both manual and automated methods: age; sex; race; ethnicity; height, weight; time from presentation to the study hospital to enrollment; time from ICU admission to enrollment; time from first receipt of invasive mechanical ventilation to enrollment; study location at enrollment; source of admission to the ICU;
2. Data collected only by manual method: baseline comorbidities; acute illnesses at enrollment; indication for invasive mechanical ventilation
3. Data collected only by automated method: non-respiratory Sequential Organ Failure Assessment (SOFA) score [25] (see supplemental appendix); Elixhauser Comorbidity Index [26]; Glasgow Coma Scale score [27]; vital signs (temperature, heart rate, systolic blood pressure, diastolic blood pressure, SpO_2); mechanical ventilator settings (mode, set and exhaled tidal volume, set and actual respiratory rate, positive end-expiratory pressure, peak pressure, FiO_2); serum laboratory values (white blood cell count, hemoglobin, platelet count, sodium, potassium, bicarbonate, creatinine, bilirubin, alanine aminotransferase, aspartate aminotransferase, lactate, arterial pH, PaO_2, SaO_2).

On-Study (Days 0-28)

1. Data collected only by manual method:
    a. For the subset of all patient enrolled during the first 12 months of the trial, physician manual review blinded to study group assignment will determine

whether each patient experienced acute respiratory distress syndrome (ARDS) by Berlin criteria [28], atrial arrhythmia, ventricular arrhythmia, cardiac arrest, pneumothorax or pneumomediastinum, ischemic stroke, or myocardial infarction.

b. For the full duration of the trial, each time treating clinicians, patients, or families elect to modify the assigned SpO_2 target, study personnel will record the date and time of the modification, the SpO_2 range to which the target was modified, and the rationale for modifying the SpO_2 target.

c. Each weekday, study personnel will record for each patient the results of the SAT Safety Screen, SAT, SBT Safety Screen, and SBT.

2. Data collected only by automated method: vital signs, ventilator settings, and serum laboratory values (as above); receipt of extracorporeal membrane oxygenation; receipt of neuromuscular blockade; receipt of inhaled epoprostenol; receipt of red cell transfusion; number of arterial blood gases; non-respiratory SOFA score; Richmond Agitation and Sedation Score [29]; Confusion Assessment Method for the ICU (CAM-ICU) score [30].

Termination (Day 28)

Data collected by both manual and automated methods: death prior to hospital discharge; time from enrollment to death; duration of ICU admission; duration of hospital admission; duration of invasive mechanical ventilation; receipt of vasopressors; duration of vasopressor receipt; receipt of renal replacement therapy; duration of renal replacement therapy receipt.

19. Definition of Days Alive and Free of a Supportive Therapy

Each of the outcomes related to the number of days alive and free of a specific supportive therapy (e.g., vasopressor-free days, renal replacement therapy-free days, ICU-free days, and hospital-free days) will be defined using the same approach as the primary outcome of ventilator-free days.

Days alive and free of the supportive therapy will be defined as the number of calendar days alive and free of the supportive therapy from the final receipt of the supportive therapy through 28 days after enrollment [67,68]. The day of enrollment will be considered to be day 0. Outcome ascertainment will cease at the time of hospital discharge or 28 days after enrollment, whichever occurs first.

Receipt of the supportive therapy will be considered to end at the time of the patient's final receipt of the supportive therapy between enrollment and 28 days after enrollment. Patients who continue to receive the supportive therapy at day 28 will receive a value of zero. Patients who die prior to day 28 will receive a value of zero. Patients who are discharged from the hospital prior to day 28 and are receiving the supportive therapy at the time of discharge will receive a value of zero. Patients who are removed from the supportive therapy and are discharged from the hospital without the supportive therapy prior to 28 days will be assumed to remain free of the supportive therapy between hospital discharge and day 28. For patients who are removed from the supportive therapy, return to receiving the supportive therapy, and are subsequently removed again from the supportive therapy prior to day 28, days alive and free of the supportive therapy will be counted from the final receipt of the supportive therapy prior to day 28.

20. Measures of Separation between Groups and Processes of Care

Measures of Separation between Groups

1. SpO_2 during invasive mechanical ventilation
2. SaO_2 during invasive mechanical ventilation
3. FiO_2 during invasive mechanical ventilation
4. PaO_2 during invasive mechanical ventilation
5. Episodes of hypoxemia, including:
    a. $SpO_2 < 85\%$ for ≥ 5 minutes
    b. $SpO_2 < 80\%$ for ≥ 5 minutes
    c. $SpO_2 < 70\%$ for ≥ 2 minutes
6. Episodes of hyperoxemia, including:
    a. $SpO_2 > 98\%$ for ≥ 5 minutes
    b. $SpO_2 > 98\%$ for ≥ 30 minutes
7. Proportion of patients with a value for $PaO_2 < 55$ mm Hg
8. Proportion of patients with a value for $PaO_2 > 120$ mm Hg

Measures of Processes of Care

1. Tidal volume
2. Positive end-expiratory pressure
3. Peak airway pressure
4. Receipt of mandatory ventilator mode
5. Number of arterial blood gasses
6. Hemoglobin
7. Red cell transfusion

21. Assessment of Compliance with the Assigned SpO_2 Target

All SpO_2 values measured during invasive mechanical ventilation are assessed for compliance with the assigned SpO_2 target. An SpO_2 value is considered compliant with the trial protocol if any of the following conditions are met:

1. Measured SpO_2 is within the target range
2. Measured SpO_2 is above the target range and the FiO_2 is 21%
3. Measured SpO_2 is below the target range and the FiO_2 is 100%
4. Measured SpO_2 occurs after treating clinicians have completed an SpO_2 target modification sheet

22. Interim Analysis

On March 23, 2020, the DSMB conducted a single, planned interim analysis for efficacy and safety at the anticipated halfway point of the trial. The interim analysis included data from patients enrolled during the first 18 months of the trial. According to the criteria specified in the trial protocol, the stopping boundary for efficacy would have been met if the P value for the difference between groups was <0.001 using a proportional odds model with independent covariates of group assignment (higher, intermediate, or lower SpO_2 target) and time. A stopping boundary for futility was not pre-specified. After conducting the planned interim analysis, the DSMB recommended the study continue without modification.

The DSMB reserves the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

Use of the conservative Haybittle-Peto boundary ($P < 0.001$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$).

23. Pre-specified Baseline Co-variates

We will repeat the primary analysis with adjustment for the following pre-specified baseline covariates: age (continuous), sex (male, female), race and ethnicity (Hispanic, Non-Hispanic Black, Non-Hispanic White, Other), source of ICU admission (ED, hospital ward, another ICU in the study hospital, operating room, outside hospital), vasopressor receipt (yes, no), and acute diagnoses at enrollment (cardiac arrest, acute myocardial infarction, sepsis or septic shock, acute respiratory distress syndrome), and severity of illness as assessed by the non-respiratory SOFA score.

To account for non-linear relationships, continuous variables will be analyzed using restricted cubic splines with between 3 and 5 knots.

24. Corrections for Multiple Testing

We have pre-specified a single primary outcome and a single secondary outcome. Consistent with recommendations of the Food and Drug Administration [65] and the European Medicines Association [66], each will be tested using a two-sided p-value with a significance level of 0.05. For all other analyses, emphasis will be placed on the estimate of effect size with 95% confidence intervals, as recommended by the *International Committee of Medical Journal Editors* [67], and no corrections for multiple comparisons will be performed.

25. Handling of Missing Data

The primary outcome of VFDs is not anticipated to be missing for any patients. Missing data will not be imputed for the primary outcome or any secondary or exploratory outcomes. None of the covariates pre-specified for the adjusted analysis are anticipated to be missing for any patients. In additional adjusted analyses, any missing data for covariates will be imputed using multiple imputations.

26. Rationale for Waiver of Informed Consent

For all mechanically ventilated ICU patients, FiO_2 is titrated to maintain SpO_2 as a part of clinical care. In current clinical care, 98% of SpO_2 values experienced by mechanically ventilated adult ICU patients fall between 88-100% [31,32]. Within this range, current guidelines for oxygen therapy in mechanically ventilated adults advocate contrasting approaches: [1] tolerating SpO_2 values as low as 88% (NIH/NHLBI ARDS Network) [33], [2] titrating within the range 92-96% (Thoracic Society of Australia and New Zealand) [34], or [3] allowing SpO_2 values above 96% (British Thoracic Society) [35]. The lower SpO_2 target, intermediate SpO_2 target, and higher SpO_2 target examined in this study are all intermittently used in routine clinical care in the study ICU and are all within the range recommended by at least one international guideline. No high-quality data suggest that one SpO_2 target is better than the others for patient outcomes. During the PILOT trial, whenever treating clinicians feel that the optimal SpO_2 target for a specific patient is known, that SpO_2 target is used. Thus, the PILOT trial only determines the SpO_2 target for patients whose treating clinicians are uncertain which SpO_2 target would be optimal for the patient and feel all three targets represent comparable and reasonable approaches.

Because the SpO_2 targets being compared in the study [1] are common approaches to managing a universal supportive therapy to which patients would be exposed as a part of clinical care if not participating in the study, [2] have no high-quality data suggesting the superiority of one approach over the others, and [3] are all comparable approaches for the patient from the perspective of the treating clinician,

participation in the study presents minimal incremental risk compared to clinical care for mechanically ventilated ICU patients outside of the study.

Initiation of mechanical ventilation for critically ill patients is frequently a time-sensitive procedure. Despite the availability of a formal informed consent document for tracheal intubation and initiation of mechanical ventilation, time allows for discussion of risks and benefits of these clinical procedures in less than 10% of cases during clinical care in the study ICU. Titration of FiO_2 to target SpO_2 in PILOT begins within 15 minutes of the initiation of mechanical ventilation with a goal of intervening during the period with the highest prevalence of excess FiO_2, hyperoxemia, and hyperoxia. Moreover, in this cluster-randomized trial, the entire ICU is assigned to a single SpO_2 target delivered by the unit's respiratory therapists through a unit-wide oxygen titration protocol. Obtaining informed consent from every patient receiving invasive mechanical ventilation in the study ED and ICU prior to the initiation of invasive mechanical ventilation would be impracticable and would potentially delay delivery of a time-sensitive intervention.

Because the study presents minimal incremental risk, the study does not adversely affect the welfare or privacy rights of the participants, and obtaining informed consent prior to enrollment is impracticable, the study is being conducted with a waiver of informed consent.

27. Plan for Communication of Protocol Changes

Any changes to the trial protocol (e.g., changes to eligibility criteria, outcomes, analyses) will require a new version of the full trial protocol which will be tracked with the date of the update and the version number of the trial protocol. A list summarizing the changes that are made with each protocol revision will be included at the end of each protocol. The updated protocol will be sent to the Vanderbilt IRB for approval prior to implementation of the protocol change. At the time of publication, the original trial protocol and the final trial protocol, including the summary of changes made with each protocol change, will be included in the supplementary material for publication.

28. Patient Privacy and Data Storage

All patients are assigned a unique study ID number for tracking. Data collected from the medical record is entered into the secure online database REDCap. All data is maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified database will be generated.

29. Data Sharing Plan

Upon reasonable request, a completely de-identified data set may be provided by the authors. Request to share data from the PILOT trial should be sent to the principal investigator, Matthew W. Semler, at matthew.w.semler@vumc.org. The dataset will be provided to researchers whose proposed use of the data has been approved by the PILOT steering committee and an Institutional Review Board and is accompanied by an executed Data Use Agreement.

SUPPLEMENTAL TABLES

Table S1. Modified Non-respiratory SOFA Score.

	0	1	2	3	4
Coagulation **Platelets ($x10^3/mm^3$)**	> 150	101-150	51-100	21-50	≤ 20
Liver **Bilirubin (mg/dL)**	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥ 12
Cardiovascular **Blood pressure**	Mean arterial pressure ≥ 70 mmHg and no receipt of dopamine, dobutamine, epinephrine, or norepinephrine	Mean arterial pressure < 70 mmHg and no receipt of dopamine, dobutamine, epinephrine, or norepinephrine	On dopamine ≤ 5 mcg/kg/min or any dobutamine	On dopamine > 5 mcg/kg/min, epinephrine ≤ 0.1 mcg/kg/min, or norepinephrine ≤ 0.1 mcg/kg/min	On dopamine > 15 mcg/kg/min, epinephrine > 0.1 mcg/kg/min, or norepinephrine > 0.1 mcg/kg/min
Brain **Glascow coma score**	15	13-14	10-12	6-9	< 6
Kidney **Renal function**	Creatinine <1.2 mg/dL	Creatinine 1.2-1.9 mg/dL	Creatinine 2.0-3.4 mg/dL	Creatinine 3.5-4.9 mg/dL	Creatinine > 5 mg/dL

The Sequential Organ Failure Assessment (SOFA) score (Vincent et al Critical Care Medicine 1998) is composed of scores from six organ systems, graded from 0 to 4 according to the degree of dysfunction or failure. Scores range from 0 (no evidence of organ dysfunction or failure) to 24 (evidence of severe dysfunction failure in each of the six organ systems). The modified non-respiratory SOFA score is composed of scores from five of the six organ systems included in the complete SOFA score (excluding the respiratory system), graded on the same scale as the complete SOFA score. Scores range from 0 (no evidence of organ dysfunction or failure) to 20 (evidence of severe organ dysfunction or failure in each of the five organ systems assessed).

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DATA AND SAFETY MONITORING BOARD CHARTER

Charter, Data and Safety Monitoring Board for
"Preliminary Investigation of optimaL Oxygen Targets (PILOT) trial"

Matthew W. Semler MD, MSc
Li Wang, MS
Jonathan D. Casey, MD
Todd W. Rice, MD, MSc
Wesley H. Self, MD, MPH
Gordon R. Bernard, MD

Confidential Information
The information contained within this Charter is confidential and intended for the use of the DSMB members.

_____
DSMB Member Printed Name

_____ _____
DSMB Member Signature Date

Charter, Data and Safety Monitoring Board for the Preliminary Investigation of optimaL Oxygen Targets (PILOT) trial

Version 1.2
6/29/2018

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for the Preliminary Investigation of optimaL Oxygen Targets (PILOT) trial.

The Charter is intended to be a living document. The DSMB and investigators will review it at regular intervals to determine whether any changes in procedure are needed.

2. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The DSMB is an independent group advisory to the investigators and affiliated institution, and is required to provide recommendations about starting, continuing, and stopping the study. The DSMB makes recommendations about:

- Participant safety and risk/benefit ratio of study procedures and interventions, including whether new data from other sources affects the study
- Initial approval of the protocol and subsequent amendments (with specific attention to study population, intervention, and study procedures)
- Adherence to the protocol requirements
- Completeness, quality, and planned analysis of data
- Ancillary study burden on participants and main study

3. Communication Plan

Communication with DSMB members will be primarily through the DSMB Chair and the primary investigator (Dr. Semler) or study biostatistician (Ms. Wang). Study investigators will not communicate about the study with DSMB members outside of DSMB meetings. The primary investigator may contact the DSMB Chair when needed for urgent concerns or clarifications of recommendations.

4. DSMB Members and Research Staff

DSMB members and their expertise are listed in Appendix A. The DSMB Chair will perform the functions of the Executive Secretary (ES). He will draft meeting summaries, compose final recommendations, and assure the accurate and timely transmission of the final recommendations to the investigators. The primary investigator (Dr. Semler) will be responsible for timely notification of co-investigators of all DSMB recommendations. *Ad hoc* members may be added to supplement expertise for single or multiple meetings.

5. Scheduling, Timing, and Organization of Meetings

DSMB meetings will be held by teleconference. The purpose of the first meeting is to review and discuss this Charter, provide an overview of study activities, review the trial protocol, review the DSMB data reporting template, and finalize the Data and Safety Monitoring Plan. Each DSMB member will sign and return this Charter to the primary investigator (Dr. Semler) to

Semler MW, *et al. BMJ Open* 2021; 11:e052013. doi: 10.1136/bmjopen-2021-052013

indicate recommendation for approval. Enrollment in the trial will not begin until the DSMB has recommended approval and IRB approval has been obtained.

- Meetings by teleconference will be held twice a year, with additional meetings scheduled as needed. Conference calls will be scheduled by the primary investigator (Dr. Semler) in collaboration with the DSMB members.

- A single interim analysis will be performed in the 30 days after data on the primary outcome is available for patients enrolled in the first 18 months of the trial.

- The DSMB will conclude its operations when all study procedures, follow up, analysis, and publication of the primary results have been completed.

The agenda for DSMB meetings will be drafted by the primary investigator (Dr. Semler) and study biostatistician (Ms. Wang), and finalized in consultation with the DSMB Chair. The agenda and meeting materials will be distributed by the primary investigator (Dr. Semler) or his appointee, two (2) weeks before each meeting. The NHLBI Program Office will receive this material at the same time as DSMB members.

When the agenda is distributed, DSMB members will be asked to report any new conflicts of interest since the last DSMB meeting. New conflicts will be reviewed by the Chair and study staff to determine if the conflict limits the ability of the DSMB member to participate in the discussion according to conflict of interest policy at the study institution.

To ensure proper trial conduct, at each meeting the DSMB will review the following data:
- adverse events and other safety data,
- quality and completeness of study data, and
- enrollment data

At the single pre-planned interim analysis after 18 months of enrollment, the DSMB will review a formal interim analysis for efficacy by the primary endpoint (*as outlined below in the stopping guidelines*).

It is expected that all DSMB members will attend every meeting. For the purposes of voting on recommendations, a quorum is three (3) members of the Board. All standing Monitoring Board members are voting members. The Board may also decide in advance whether *ad hoc* members can vote.

6. Organization of Meetings

Meetings are organized into open, closed, and executive sessions.

- **Open session** - information is presented to the DSMB by the study investigators, with time for discussion.

- **Closed session** - the DSMB and blinded study staff (NHLBI program staff may be invited to attend at the Chair's discretion) discuss confidential data (any study data grouped by treatment arm), including information on efficacy and safety. The DSMB can decide to be unblinded to treatment assignments by the study statistician. The principal investigator and staff involved in subject enrollment and treatment may not be present or review grouped data.

- **Executive session** (optional) DSMB members (and NHLBI program staff at the Chair's discretion) may elect to convene to discuss study issues independently. If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

- **Recommendations** (optional) **–** Meeting attendees may be reconvened to receive the DSMB's recommendations.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators to ask questions to clarify the recommendations. The meeting is then adjourned.

7. Expedited Safety Reporting

A system has been established to track and report adverse events (AEs). Study personnel will monitor the safety of subjects and follow AEs until the event resolves or is explained.

Clinical Outcomes (not considered Adverse Events). In this study of critically ill patients who are at high risk for death or other adverse outcomes due to their underlying critical illness, clinical outcomes, including death and organ dysfunction, will be systematically tracked (collected in the case report form) and will be included as part of the analyses for this study. For the purposes of reporting, death and organ dysfunction will not be recorded as AEs unless the investigator believes the event may have been caused by the study or is more severe or prolonged than expected given the underlying critical illness. Listed below are events that will be tracked as primary or secondary clinical outcomes and will not therefore be reported as AEs (unless believed to be study related and more severe or prolonged than expected given the underlying critical illness):

1. Death (all deaths occurring prior to hospital discharge will be reported on the CRF in the vital status at hospital discharge section);
2. Recurrence of respiratory failure, including need for re-intubation or non-invasive mechanical ventilation, presence of acute respiratory distress syndrome, or presence of pneumothorax;
3. Circulatory failure, including cardiac arrest or shock with or without receipt of vasopressors;
4. Incidence of sustained atrial and ventricular arrhythmias;
5. Acute kidney injury, including leading to increased creatinine or receipt of renal replacement therapy;
6. Hepatic injury or failure leading to increased bilirubin, AST, or ALT;
7. Coagulation derangements leading to elevated PT/INR or PTT, DIC, thrombocytopenia, or thrombocytosis;
8. Lactic acidosis;
9. Delirium, disability, and physical or cognitive impairment believed to be newly acquired;
10. All values for SpO_2, SaO_2, FiO_2, PaO_2, or PaO2/FiO2 ratio;
11. All values for vital signs (e.g., temperature, respiratory rate, SpO2);
12. Receipt of co-interventions (e.g., net fluid balance, number of arterial blood gasses, red cell transfusion)
13. Duration of ICU admission, ICU readmission;

14. Duration of hospitalization, hospital readmission;
15. Alterations in routine labs, including chemistries, complete blood counts, liver function tests, and hemostasis profiles.

Adverse Event Classifications. An Adverse Event (AE) will be defined as any untoward medical occurrence for a patient enrolled in the trial that is not tracked as a clinical outcome, regardless of whether the event is considered study related or not. All AEs occurring during the observational study period will be recorded on the CRF. All AEs will then be assessed as to whether they are (1) related to study procedures, (2) serious, and/or (3) unexpected according to the following definitions:

I. Related to study procedures. AEs that the investigator suspects are related to the study will be classified as study related. Certainty of relatedness is not required as long as a reasonable possibility exists that the AE is related to a study procedure.

II. Serious. AEs that meet any of the criteria below will be considered Serious Adverse Events (SAEs):
   a. Results in death
   b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
   c. Prolongs an existing hospitalization
   d. Results in persistent or significant disability or incapacity
   e. Results in a congenital anomaly or birth defect
   f. Important medical event that requires an intervention to prevent any of a-e above.

III. Unexpected. AEs that are more severe or prolonged than expected based on the investigator's discretion will be considered Unexpected.

Communication and Reporting of Adverse Events. AEs will be recorded in the AE CRF in the electronic database and reported to the primary investigator (Dr. Semler) within 5 calendar days of occurrence. The primary investigator will provide a report of all AEs annually to the IRB, and semi-annually to the DSMB as part of the semi-annual DSMB meetings. All SAEs will be reported to the primary investigator within 72 hours of occurrence. The primary investigator will, in turn, report all SAEs to the IRB, DSMB, and funding body within 7 calendar days of occurrence. Consistent with NHLBI policy, unanticipated problems that do not qualify as an SAE will be reported by the investigator to the IRB, DSMB, and NHLBI within 14 calendar days of the investigator becoming aware of the problem.

Review by the DSMB. All AEs will be reviewed by the DSMB at the scheduled semi-annual DSMB meetings. All SAEs will be reviewed by the DSMB Chair within three (3) days of notification. The DSMB Chair will respond to the primary investigator (Dr. Semler) and NHLBI program office with recommendations within seven (7) days.

8. Reports to the DSMB

For each meeting, the study biostatistician (Ms. Wang) will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB will discuss at the first and subsequent meetings what data they wish to review and how it should be presented (Appendix B).

9. Reports of DSMB Deliberations

- **Full Summary and Recommendations**: The DSMB Chair/ES is responsible for sending the DSMB meeting summary to the Board within seven (7) calendar days of the meeting. The summary should be signed by the DSMB Chair and include key topics discussed, the response of the investigators to previous recommendations, and the recommendations of the DSMB. The study statistician may receive the full summary as decided by the DSMB chair on a meeting by meeting basis.

  Voting on recommendations will follow Roberts' Rules of Order (**Robert's Rules of Order Newly Revised (11th Edition) RONR.**

- **Board Recommendations** - signed by the DSMB Chair, will be sent to the investigators within fourteen (14) calendar days after the meeting. Recommendations should include a statement as to whether the study is approved to continue as planned, should continue with specified changes, or should be stopped. Requests for additional data from the investigators or DCC/statistician should include an expected due date. In addition to recommendations memos issued to investigators (for review and IRB distribution), recommendations related to blinded data or data analysis issues may be issued separately for DCCs or statisticians.

  The recommendations will be distributed by the principal investigator to co-investigators, to the local IRB, and to the NHLBI Program Office.

- **Action plan**: This lists the DSMB's recommendations and the primary investigator's action plan outlining the steps required to implement the DSMB recommendations. It is submitted to the NHLBI Program Office and DSMB within fourteen (14) calendar days after the DSMB meeting.

10. Statistical Monitoring Guidelines

In addition to ongoing monitoring of safety throughout the trial, the DSMB will conduct a single interim analysis for efficacy and safety at the anticipated halfway point of the trial. The interim analysis will include patients enrolled during the first 18 months of the trial. The stopping boundary for efficacy will be met if the P value for the difference between groups is <0.001 using a proportional odds mixed effects model accounting for fixed effects (group) and random effects (period) with regard to the primary outcome of VFDs. Use of the conservative Haybittle-Peto boundary ($P < 0.001$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$). There will be no stopping boundary for futility. The DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety. If the 18-month interim analysis reveals an enrollment indicative of <80% statistical power at completion, we will ask the DSMB to approve extending enrollment of the study to ensure the trial is not underpowered to detect the planned difference between groups in the primary outcome.

PILOT Trial Statistical Analysis Plan Revision Sequence

April 2, 2021	Original Statistical Analysis Plan completed
April 5, 2021	Original Statistical Analysis Plan submitted for publication
August 25, 2021	Statistical Analysis Plan submission completed peer review
August 31, 2021	Final patient enrolled
October 28, 2021	Final Statistical Analysis Plan* published:

Semler MW, Casey JD, Lloyd BD, Hastings PG, Hays M, Roth M, Stollings J, Brems J, Buell KG, Wang L, Lindsell CJ, Freundlich RE, Wanderer JP, Bernard GR, Self WH, Rice TW; PILOT Investigators and the Pragmatic Critical Care Research Group. Protocol and statistical analysis plan for the Pragmatic Investigation of optimaL Oxygen Targets (PILOT) clinical trial. *BMJ Open*. 2021 Oct 28;11(10):e052013. PMID: 34711597

**No changes to content of the statistical analysis plan occurred between submission of the Protocol and Statistical Analysis Plan and its publication.*