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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 intraperiod 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

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REFERENCES

1 Wunsch H, Linde-Zwirble WT, Angus DC, *et al*. The epidemiology of mechanical ventilation use in the United States. *Crit Care Med* 2010;38:1947–53.
2 Wunsch H, Angus DC, Harrison DA, *et al*. Comparison of medical admissions to intensive care units in the United States and United Kingdom. *Am J Respir Crit Care Med* 2011;183:1666–73.
3 Adhikari NKJ, Fowler RA, Bhagwanjee S, *et al*. Critical care and the global burden of critical illness in adults. *Lancet* 2010;376:1339–46.
4 , Brower RG, Matthay MA, *et al*, Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–8.
5 Esteban A, Frutos-Vivar F, Muriel A, *et al*. Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med* 2013;188:220–30.
6 Fridovich I. Oxygen toxicity: a radical explanation. *J Exp Biol* 1998;201:1203–9.
7 Heffner JE, Repine JE. Pulmonary strategies of antioxidant defense. *Am Rev Respir Dis* 1989;140:531–54.
8 Freeman BA, Crapo JD. Hyperoxia increases oxygen radical production in rat lungs and lung mitochondria. *J Biol Chem* 1981;256:10986–92.
9 Waxman AB, Einarsson O, Seres T, *et al*. Targeted lung expression of interleukin-11 enhances murine tolerance of 100% oxygen and diminishes hyperoxia-induced DNA fragmentation. *J Clin Invest* 1998;101:1970–82.
10 Griffith DE, Garcia JG, James HL, *et al*. Hyperoxic exposure in humans. Effects of 50 percent oxygen on alveolar macrophage leukotriene B4 synthesis. *Chest* 1992;101:392–7.
11 Davis WB, Rennard SI, Bitterman PB, *et al*. Pulmonary oxygen toxicity. early reversible changes in human alveolar structures induced by hyperoxia. *N Engl J Med* 1983;309:878–83.
12 Aggarwal NR, Brower RG. Targeting normoxemia in acute respiratory distress syndrome may cause worse short-term outcomes because of oxygen toxicity. *Ann Am Thorac Soc* 2014;11:1449–53.
13 Meade MO, Cook DJ, Guyatt GH, *et al*. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:637–45.
14 Eastwood G, Bellomo R, Bailey M, *et al*. Arterial oxygen tension and mortality in mechanically ventilated patients. *Intensive Care Med* 2012;38:91–8.
15 de Jonge E, Peelen L, Keijzers PJ, *et al*. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008;12:R156.
16 Allen BS, Ilbawi MN. Hypoxia, reoxygenation and the role of systemic leukodepletion in pediatric heart surgery. *Perfusion* 2001;16 Suppl:19–29.
17 Allen BS. The reoxygenation injury: is it clinically important? *J Thorac Cardiovasc Surg* 2002;124:16–19.
18 Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. *Pediatrics* 2000;105:295–310.
19 SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, *et al*. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959–69.
20 Schmidt B, Whyte RK, Asztalos EV, *et al*. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. *JAMA* 2013;309:2111–20.
21 BOOST II United Kingdom Collaborative Group, BOOST II Australia Collaborative Group, BOOST II New Zealand Collaborative Group, *et al*. Oxygen saturation and outcomes in preterm infants. *N Engl J Med* 2013;368:2094–104.
22 Panwar R, Hardie M, Bellomo R, *et al*. Conservative versus liberal oxygenation targets for mechanically ventilated patients. a pilot multicenter randomized controlled trial. *Am J Respir Crit Care Med* 2016;193:43–51.
23 Asfar P, Schortgen F, Boisramé-Helms J, *et al*. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respir Med* 2017;5:180–90.
24 Girardis M, Busani S, Damiani E, *et al*. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. *JAMA* 2016;316:1583–9.
25 Barrot L, Asfar P, Mauny F, *et al*. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med* 2020;382:999–1008.
26 ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Mackle D, Bellomo R, *et al*. Conservative oxygen therapy during mechanical ventilation in the ICU. *N Engl J Med* 2020;382:989-998.
27 Schjørring OL, Klitgaard TL, Perner A, *et al*. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. *N Engl J Med Overseas Ed* 2021;384:1301–11.
28 Siemieniuk RAC, Chu DK, Kim LH-Y, *et al*. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ* 2018;363:k4169.
29 National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Rice TW, Wheeler AP, *et al*. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012;307:795–803.
30 Rice TW, Wheeler AP, Thompson BT, *et al*. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA* 2011;306:1574–81.
31 O'Driscoll BR, Howard LS, Earis J, *et al*. Bts guideline for oxygen use in adults in healthcare and emergency settings. *Thorax* 2017;72:ii1–90.
32 Panwar R, Capellier G, Schmutz N, *et al*. Current oxygenation practice in ventilated patients-an observational cohort study. *Anaesth Intensive Care* 2013;41:505–14.
33 Suzuki S, Eastwood GM, Peck L, *et al*. Current oxygen management in mechanically ventilated patients: a prospective observational cohort study. *J Crit Care* 2013;28:647–54.

34 Helmerhorst HJ, Schultz MJ, van der Voort PH, *et al*. Self-reported attitudes versus actual practice of oxygen therapy by ICU physicians and nurses. *Ann Intensive Care* 2014;4:23.
35 Self WH, Semler MW, Rice TW. Oxygen targets for patients who are critically ill: emerging data and state of equipoise. *Chest* 2020;157:487–8.
36 SPIRIT. Explanation and elaboration: guidance for protocols of clinical trials. - PubMed - NCBI, 2013. Available: https://www.ncbi.nlm.nih.gov/pubmed/23303884 [Accessed 08 Jan 2018].
37 Ware JH, Hamel MB. Pragmatic trials--guides to better patient care? *N Engl J Med* 2011;364:1685–7.
38 Beasley R, Chien J, Douglas J, *et al*. Thoracic society of Australia and New Zealand oxygen guidelines for acute oxygen use in adults: 'swimming between the flags'. *Respirology* 2015;20:1182–91.
39 Brower RG, Lanken PN, MacIntyre N, *et al*. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327–36.
40 Briel M, Meade M, Mercat A, *et al*. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010;303:865–73.
41 Semler MW, Rice TW, Shaw AD, *et al*. Identification of major adverse kidney events within the electronic health record. *J Med Syst* 2016;40:167.
42 Semler MW, Noto MJ, Stollings J. Effect of saline versus balanced crystalloids on major adverse kidney events in the medical intensive care unit: the salt randomized trial. *Am J Respir Crit Care Med* 2016;193:A4290.
43 Semler MW, Self WH, Wang L, *et al*. Balanced crystalloids versus saline in the intensive care unit: study protocol for a cluster-randomized, multiple-crossover trial. *Trials* 2017;18.
44 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
45 Schoenfeld DA, Bernard GR, ARDS Network. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med* 2002;30:1772–7.
46 Harhay MO, Wagner J, Ratcliffe SJ, *et al*. Outcomes and statistical power in adult critical care randomized trials. *Am J Respir Crit Care Med* 2014;189:1469–78.
47 Vincent JL, Moreno R, Takala J, *et al*. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. on behalf of the Working group on sepsis-related problems of the European Society of intensive care medicine. *Intensive Care Med* 1996;22:707–10.
48 , Ranieri VM, Rubenfeld GD, *et al*, ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307:2526–33.
49 Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney inter* 2012;2:8 https://kdigo.org/guidelines/acute-kidney-injury/
50 Thygesen K, Alpert JS, Jaffe AS, *et al*. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018;72:2231–64.
51 Semler MW, Self WH, Wanderer JP, *et al*. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med* 2018;378:829–39.
52 Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics* 1988;44:1049–60.
53 Turner RM, White IR, Croudace T, *et al*. Analysis of cluster randomized cross-over trial data: a comparison of methods. *Stat Med* 2007;26:274–89.
54 Parienti J-J, Kuss O. Cluster-crossover design: a method for limiting clusters level effect in community-intervention studies. *Contemp Clin Trials* 2007;28:316–23.
55 Beitler JR, Sarge T, Banner-Goodspeed VM, *et al*. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA* 2019;321:846.
56 Munshi L, Ferguson ND. Evolving issues in oxygen therapy in acute care medicine. *JAMA* 2020;323:607.