


BMJ Open 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 (SpO₂). However, the optimal SpO₂ 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 SpO₂ target (target 90% and goal range: 88%–92%), an intermediate SpO₂ target (target 94% and goal range: 92%–96%) and a higher SpO₂ target (target 98% and goal range: 96%–100%). The study units are assigned to a single SpO₂ target (cluster-level allocation) for each 2-month study block, and the assigned SpO₂ 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).

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

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.

inspired oxygen (FiO₂) to maintain arterial oxygen saturation (SpO₂) within a goal range. Despite decades of ICU practice, however, the optimal SpO₂ target remains unknown. Higher SpO₂ targets (96%–100%) provide a margin of safety against hypoxaemia, but may increase exposure to excess FiO₂, hyperoxaemia, and tissue hyperoxia, causing oxidative damage,^{6–8} inflammation^{9 10} and increased alveolar-capillary permeability.¹¹ Lower SpO₂ targets (88%–92%) minimise exposure to excess FiO₂, hyperoxaemia and tissue hyperoxia,^{4 12 13} but may increase the risk of hypoxaemia and tissue hypoxia.^{14 15} An intermediate SpO₂ 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 SpO₂ or PaO₂ 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 targets²⁵ 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 SpO₂ values as low as 88%^{28–30} to pursuing SpO₂ 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 SpO₂ 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 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), SpO₂ 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

TIMEPOINT	STUDY PERIOD			
	Allocation and Enrollment	On-Study		Study Termination
	<i>First receipt of invasive mechanical ventilation in a study location</i>	<i>Receiving invasive mechanical ventilation in study location</i>	<i>Hospitalized but not receiving invasive mechanical ventilation in a study location</i>	<i>Discharge or 28 days after enrolment</i>
ENROLMENT:				
Eligibility screen	X			
Allocation	X			
INTERVENTIONS:				
Higher SpO₂ Target <i>Titration FIO₂ to SpO₂ 96–100%</i>	X	X		
Intermediate SpO₂ Target <i>Titration FIO₂ to SpO₂ 92–96%</i>	X	X		
Lower SpO₂ Target <i>Titration FIO₂ to SpO₂ 88–92%</i>	X	X		
Screening for indications for SpO ₂ 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. FiO₂, fraction of inspired oxygen; SpO₂, arterial oxygen saturation.

lower SpO₂ target (target 90% and goal range: 88%–92%), an intermediate SpO₂ target (target 94% and goal range: 92%–96%) and a higher SpO₂ 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 SpO₂ target (cluster-level allocation). Every 2 months, the ICU will switch between use of a lower SpO₂ target (target 90% and goal range: 88%–92%), use of an intermediate SpO₂ target (target 94% and goal range: 92%–96%) and use of a higher SpO₂ 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 SpO₂ 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 SpO₂, 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 SpO₂ target to a period assigned to another SpO₂ 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 SpO₂ target to a period assigned to another SpO₂ target will be analysed in the SpO₂ 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	Sep-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 SpO₂ target. In this figure, the letters 'A', 'B' and 'C' each correspond to one of the three possible SpO₂ 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 SpO₂ target. SpO₂, arterial oxygen saturation.

Table 1 SpO₂ and PaO₂ 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 SpO₂ target and goal range are displayed. PaO₂ is used to guide titration of FiO₂ for participants without reliable pulse oximetry monitoring.

FiO₂, fraction of inspired oxygen; PaO₂, arterial oxygen tension; SpO₂, arterial oxygen saturation.

Study interventions

Choice of SpO₂ targets

In clinical practice, 98% of SpO₂ 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 SpO₂ values to be as low as 88%^{28–29} to avoid excess FiO₂, hyperoxaemia and hyperoxia; (2) titrating within an intermediate range of SpO₂ values, such as 92%–96%³⁸; or (3) targeting higher SpO₂ to avoid the risks of hypoxaemia and hypoxia.³¹ The PILOT trial has three study groups, each emulating a different approach to SpO₂ targets represented in guidelines and clinical practice (table 1).

Oxygen titration

In the study ED and ICU, titration of FiO₂ to maintain SpO₂ 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 FiO₂ to achieve each of the three study SpO₂ targets.

For patients enrolled in the study, respiratory therapists are instructed to begin titrating FiO₂ to the target SpO₂ value within 15 min of the initiation of mechanical ventilation. During the maintenance of invasive mechanical ventilation, SpO₂ is assessed by continuous pulse oximetry. The protocol directs the respiratory therapist managing the patient's ventilator to target an SpO₂ value of 90% in the lower SpO₂ target group, an SpO₂ value of 94% in the intermediate SpO₂ target group and an SpO₂ value of 98% in the higher SpO₂ target group (table 1). Respiratory therapists and other treating clinicians titrate FiO₂ when the SpO₂ is out of the goal range, when the SpO₂ is within the goal range but closer alignment with the assigned SpO₂ target is desired, to facilitate weaning from mechanical ventilation, or for other clinical indications. SpO₂ is reassessed 5 min after each change in FiO₂ or sooner if clinically indicated.

The protocol determines the SpO₂ 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 SpO₂ target modification sheet by treating clinicians or (4) end of the 2-month study period. The protocol does not determine the SpO₂ target during time periods in which the patient is not physically located in a study location (eg, during transport) or when FiO₂ is being administered for purposes other than achieving a target SpO₂ (eg, when an FiO₂ 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 SpO₂ target other than that assigned by the study would be best for the optimal treatment of the patient for any reason, the SpO₂ target for that patient is modified. To modify the target, the respiratory therapist and supervising physician complete a one-page SpO₂ target modification sheet documenting the new SpO₂ target and the rationale for modifying the target. Examples of conditions for which the assigned SpO₂ 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 SpO₂ 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 FiO₂ to the assigned SpO₂ 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 SpO₂ 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 review⁴¹ 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 criteria⁴⁸
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 infarction⁵⁰

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 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 intraclass 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 SpO₂ 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 SpO₂ target groups among all patients enrolled in the trial except¹ those admitted during one of the 7-day washout periods and² 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 SpO₂ 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 SpO₂ 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 SpO₂ target as a general policy.⁵² Since an SpO₂ 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 SpO₂ 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 SpO₂ 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 SpO₂ 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 analysis⁵⁵ 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, including¹ patients initiated on invasive mechanical ventilation in a study location during one of the prespecified 7-day washout periods and² 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 SpO₂ target) and time. In addition to assessing for an overall group effect within the model, we will estimate the differences between each pair of SpO₂ 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 SpO₂ 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 performed 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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