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Cognitive Outcomes in the Pragmatic Investigation of optimaL Oxygen Targets (CO-PILOT) trial: protocol and statistical analysis plan

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ABSTRACT

Introduction Long-term cognitive impairment is one of the most common complications of critical illness among survivors who receive mechanical ventilation. Recommended oxygen targets during mechanical ventilation vary among international guidelines. Different oxygen targets during mechanical ventilation have the potential to alter long-term cognitive function due to cerebral hypoxemia or hyperoxemia. Whether higher, intermediate or lower SpO_2 targets are associated with better cognitive function at 12-month follow-up is unknown.

Methods and analysis The Pragmatic Investigation of optimaL Oxygen Targets (PILOT) trial is an ongoing pragmatic, cluster-randomised, cluster-crossover trial comparing the effect of a higher SpO_2 target (target 98%, goal range 96%–100%), an intermediate SpO_2 target (target 94%, goal range 92%–96%) and a lower SpO_2 target (target 90%, goal range 88%–92%) on clinical outcomes in mechanically ventilated patients admitted to the medical intensive care unit at a single centre in the USA. For this ancillary study of long-term Cognitive Outcomes (CO-PILOT), survivors of critical illness who are in the PILOT trial and who do not meet exclusion criteria for CO-PILOT are approached for consent. The anticipated number of patients for whom assessment of long-term cognition will be performed in CO-PILOT is 612 patients over 36 months of enrolment. Cognitive, functional and quality of life assessments are assessed via telephone interview at approximately 12 months after enrolment in PILOT. The primary outcome of CO-PILOT is the telephone version of the Montreal Cognitive Assessment. A subset of patients will also complete a comprehensive neuropsychological telephone battery to better characterise the cognitive domains affected.

Ethics and dissemination The CO-PILOT ancillary study 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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The broad inclusion criteria will increase the generalisability of the findings, and the sample size will allow examination of both global cognition and individual cognitive domains commonly impacted by critical illness.
⇒ The anticipated sample size and study design will allow for the assessment of not only global cognition, but also individual cognitive domains that can be impacted by critical illness.
⇒ A robust and multidomain neuropsychological phone battery is used in this study, which will increase recruitment of patients who are cognitive and/or functionally impaired.
⇒ Enrolment in the primary study is limited to one US academic medical centre and enrolment in this ancillary study of long-term outcomes is limited to those patients able to complete follow-up.
⇒ The design of the study does not allow assessment of pre-illness cognition other than collecting data on pre-existing diagnoses of dementia and comorbidities from the electronic health record.

INTRODUCTION

Among critically ill patients, approximately one out of three survivors will develop long-term cognitive impairment (LTCI) of similar severity to that of mild Alzheimer's disease and related dementias.[1] LTCI disproportionately impacts patients requiring mechanical ventilation, affecting up to 75% of survivors.[2–6] LTCI is associated with reduced quality of life, employment and independence,[7 8] yet the causes of LTCI in critical illness remain multifactorial, complex and incompletely understood.

High or low oxygen levels in the brain are potentially important risk factors for LTCI identified in prior research.[9] The brain

consumes up to 20% of the body's total oxygen content, and it is uniquely vulnerable to hypoxemia.[10] Conversely, hyperoxemia and hyperoxia may produce free radicals, causing oxidative damage, neuronal injury and apoptosis.[11 12] Hyperoxemia and hyperoxia have been identified as risk factors for both mortality and LTCI after critical illnesses, such as cardiac arrest and traumatic brain injury.[13–15]

As part of routine care during mechanical ventilation of critically ill adults, the fraction of inspired oxygen is titrated to maintain a desired level of arterial oxygen saturation, as assessed by continuous peripheral pulse oximetry (SpO_2). Consensus regarding the optimal range of SpO_2, however, remains elusive. Current guidelines outline three contrasting approaches: (1) tolerating SpO_2 values as low as 88% (National Institutes of Health/National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network)[16]; (2) pursuing SpO_2 values as high as 98% (British Thoracic Society)[17]; or (3) titrating within the range of 92%–96% (Thoracic Society of Australia and New Zealand).[18]

Studies of clinical outcomes related to different SpO_2 targets have demonstrated mixed results. Lower SpO_2 targets resulted in significantly improved survival in one small trial[19] and demonstrated numerically greater survival in two other studies.[20 21] Three recent randomised trials have compared oxygen targets in critically ill patients, and none showed a difference in ventilator-free days or mortality.[22–24] The smallest trial was, however, stopped prematurely for mesenteric ischaemia in 5 of the 99 patients in the lower oxygen target group.[24] The effects of oxygen targets on long-term outcomes have been evaluated in two recent trials, one of which found potentially better functional outcomes with lower SpO_2 targets, particularly among patients who had experienced cardiac arrest prior to enrolment, and one which did not find differences in long-term mortality or health-related quality of life between higher and lower targets.[23 25]

The ongoing Pragmatic Investigation of optimaL Oxygen Targets (PILOT) trial is a pragmatic, cluster-randomised, cluster-crossover trial comparing the short-term outcomes of ventilator-free days and in-hospital mortality between higher, intermediate and lower SpO_2 targets for mechanically ventilated critically ill adults.[26] To evaluate the effect of higher, intermediate and lower SpO_2 targets on long-term outcomes, we designed the Cognitive Outcomes in the PILOT trial (CO-PILOT) ancillary study, which is assessing cognition and other functional outcomes 12 months after enrolment in the PILOT trial. The CO-PILOT ancillary study will test the hypothesis that lower SpO_2 targets during invasive mechanical ventilation are associated with poorer global cognition at 12 months.

METHODS AND ANALYSIS

This manuscript describes key elements of the study protocol and statistical analysis plan. This manuscript was prepared in accordance with Standard Protocol Items: Recommendations for Interventional Trials guidelines (figure 1).

	STUDY PERIOD			
	Allocation and Enrollment	On-Study		Study Termination
TIMEPOINT	*First receipt of invasive mechanical ventilation in a study location*	*Receiving invasive mechanical ventilation*	*Hospitalized but not receiving invasive mechanical ventilation*	*12-Month Follow-Up Cognitive Assessment*
ENROLLMENT:	P			C
Eligibility screen	P			C
Allocation	P			
INTERVENTIONS:				
Higher SpO2 Target *Titrating FiO2 to SpO2 96-100%*	P	P		
Intermediate SpO2 Target *Titrating FiO2 to SpO2 92-96%*	P	P		
Lower SpO2 Target *Titrating FiO2 to SpO2 88-92%*	P	P		
Screening for indications for SpO2 target modification	P	P		
ASSESSMENTS:				
Baseline Variables	P			C
On-Study Variables	P	P	P	
Clinical Outcomes		P	P	C

Figure 1 Standard Protocol Items: Recommendations for Interventional Trials checklist. Enrolment, interventions and assessments. C=CO-PILOT ancillary study procedures; P=PILOT trial study procedures. CO-PILOT, Cognitive Outcomes in the Pragmatic Investigation of optimaL Oxygen Targets; FiO_2, fraction of inspired oxygen.

Study design

The CO-PILOT trial is an ancillary study to the PILOT trial. The protocol for the PILOT trial has been previously published.[26] In brief, the PILOT trial is a prospective, unblinded, pragmatic, cluster-crossover trial being conducted in the emergency department and medical intensive care unit (ICU) at Vanderbilt University Medical Center in Nashville, Tennessee, USA. PILOT compares the number of days alive and free of invasive mechanical ventilation between mechanically ventilated ICU patients treated to a lower SpO_2 target (target 90% and goal range 88%–92%), 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%). The CO-PILOT ancillary study collects cognition and functional outcomes 12 months after enrolment in the parent PILOT trial over the phone. The Institutional Review Board at Vanderbilt University approved the PILOT trial (#171272) and the CO-PILOT ancillary study (#190315). The PILOT trial is funded by the National Heart, Lung, and Blood Institute (K23HL143053) and the CO-PILOT ancillary study is funded in part by the National Institute on Aging (R21AG063126) and in part by the National Center for Advancing Translational Sciences (UL1TR002243). The trial protocol for the parent PILOT trial was registered with ClinicalTrials.gov on 25 May 2018 prior to initiation of patient enrolment on 1 July 2018 (ClinicalTrials.gov Registry: NCT03537937).

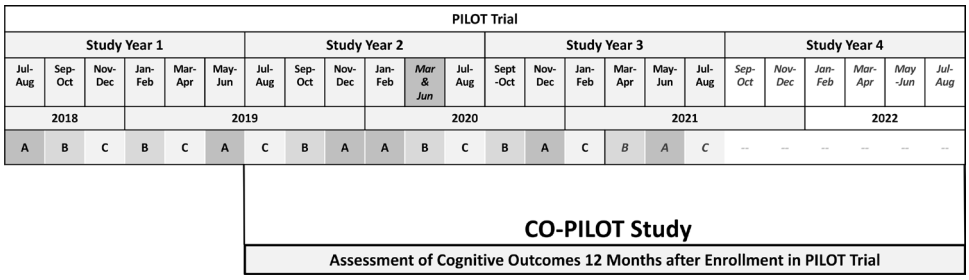

Figure 2 Timeline for the CO-PILOT Study. For each of the 2-month study periods in the parent PILOT trial, the study ICU is randomly assigned to a higher, intermediate or lower SpO_2 target. In this figure, the letters 'A', 'B' and 'C' each correspond to one of the three possible SpO_2 targets, the allocation sequence of which remains concealed until the start of each 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. Approximately 12 months (±2 months) after patients are enrolled in the PILOT trial, those who meet eligibility criteria for the CO-PILOT ancillary study are recruited for participation. The first assessments of cognitive outcomes at 12 months in CO-PILOT were performed in July of 2019 for patients enrolled in PILOT in July of 2018 and the final assessments in CO-PILOT will be performed by 31 August 2022. CO-PILOT, Cognitive Outcomes in the Pragmatic Investigation of optimaL Oxygen Targets; ICU, intensive care unit.

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 CO-PILOT ancillary study screens patients who were enrolled in the PILOT trial and meet the additional eligibility criteria for the CO-PILOT ancillary study. The PILOT trial enrols mechanically ventilated adults (age ≥18 years) admitted to the medical ICU at Vanderbilt University Medical Center who are not incarcerated or pregnant. The CO-PILOT Study enrols survivors and excludes those who are: deaf, aphasic, non-English speaking, incarcerated at follow-up, or without a working phone number or alternative contact. Patients who are deaf are excluded from CO-PILOT because neuropsychological testing includes auditory components. Patients who are aphasic are excluded because cognitive assessments may not be reliable in those who are unable to speak and cannot be conducted over the phone. Non-English-speaking patients are excluded because the study staff performing the neuropsychological assessment can only perform the testing in English (figure 2).

Treatment group assignment

The CO-PILOT ancillary study uses the treatment group assignments generated for the parent PILOT trial. 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 switches 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). The order of study group assignments for each 2-month block was generated by computerised randomisation using permuted blocks of 3 to minimise the impact of seasonal variation and temporal changes. The last 7 days of each 2-month block are a washout period during which the medical ICU continues to target the assigned SpO_2 but new patients are not enrolled in PILOT.

Blinding

Patients and clinicians are not blinded to study group assignment during the PILOT trial, an approach used in previous studies evaluating SpO_2 targets.[1] Study personnel performing 12-month outcome assessments for the CO-PILOT ancillary study are blinded to study group assignment.

Recruitment and enrolment

At approximately 9 months after enrolment in PILOT, CO-PILOT Study personnel review the patients' electronic medical record to determine eligibility for the CO-PILOT ancillary study. Patients who do not meet any of the exclusion criteria for the CO-PILOT ancillary study are then mailed a letter. This letter describes the CO-PILOT ancillary study and states that the patient will be contacted by phone the following month by the CO-PILOT Study team and provides an opportunity for the patient to decline to be contacted by the CO-PILOT Study team by mailing back the enclosed self-addressed and stamped postcard or by calling or emailing the study coordinator.

Four weeks after the letter is mailed and approximately 12 months after enrolment in the parent PILOT Study, patients who have not opted out of being contacted by the CO-PILOT Study team are contacted by phone. If the patient is alive at 12-month follow-up, CO-PILOT Study personnel read to the patient or legally authorised representative a phone script and then ask if the patient or legally authorised representative would like to receive more information about the study. If the patient or legally authorised representative agrees, then the CO-PILOT Study personnel proceed with the process for informed consent.

Consent

The Vanderbilt Institutional Review Board granted CO-PILOT an alteration of the process for informed consent that allowed consent to be obtained over the phone because: patients will receive follow-up by phone only with no face-to-face contact, all protected health information (PHI) and identifiers are removed once study participation is complete and therefore obtaining written informed consent would be the only link between CO-PILOT and the patient's PHI; in this minimal risk ancillary study, mailing back an informed consent document containing PHI would increase the risk of loss of confidentiality; and arranging for in-person written informed consent would place more of a burden on patients than the phone assessments comprising the study procedures. Study personnel obtained informed consent for outcome assessment from the patient or the legally authorised representative using a structured phone script.

Data collection

Data on cognition and functional outcomes at 12 months are collected by CO-PILOT Study personnel from patients or legally authorised representatives 12 months after enrolment in the PILOT trial. Trained neuropsychological research coordinators from the Critical Illness, Brain Dysfunction, and Survivorship Center at Vanderbilt University conduct all cognitive and functional assessments using structured and validated research batteries. Neuropsychological research coordinators who conduct all cognitive and functional outcomes assessments are blinded to the participants' study arm and are overseen by an expert neuropsychologist (JCJ) with extensive prior experience in the assessment of outcomes in survivors of critical illness for both research[27] and clinical purposes. All data are stored and managed within the REDCap secure web platform.[28 29]

Outcomes

The primary outcome for the CO-PILOT ancillary study is the telephone version of the Montreal Cognitive Assessment (T-MoCA), which is identical in form to the MoCA-Blind.[28–33] The T-MoCA consists of a wide array of questions that sample a variety of cognitive domains (attention, language, abstraction, delayed memory and orientation) without containing the questions requiring visual assessment or pen and paper that are present in the original MoCA. This allows for its use in remote assessments and among patients with visual impairment. The T-MoCA tool has been validated in multiple studies against the original MoCA assessment,[34–36] which is the assessment tool recommended for the screening of cognitive function in survivors of critical illness in consensus guidelines.[37] Use of the MoCA-Blind, which is identical to the T-MoCA, is also recommended for use in long-term outcome studies of acute respiratory failure in patients who are unable to complete in-person follow-up.[1]

On 1 January 2020, we received additional funding (R21AG063126) to expand the neuropsychological battery to provide a more detailed assessment of executive function, attention, immediate and short-term memory, language and abstraction (table 1), allowing for additional testing from that point forward in the study. Cognitive domains such as executive function and attention are commonly impaired in survivors of critical illness.[38] A battery of additional validated cognitive assessments measuring individual cognitive domains (table 1) was developed with expert input from a trained neuropsychologist and cognitive outcomes researcher with unique expertise in cognitive impairment after critical illness (JCJ).[1 38–41] In addition to reporting individual scores from these assessments, a Global Cognition Composite Score will also be calculated.[42] This approach generates standardised scores, or Z-scores, for each individual cognitive assessment that represents the number of SD units a patient's score is below or above a mean score. The Global Cognition Composite Score is then calculated by combining individual standardised scores.

Delirium and coma-free days during the index hospitalisation will be a secondary outcome. Delirium will be

Table 1 Cognitive assessments in expanded phone battery

Study assessment	Description	Cognitive domain
Hayling Sentence Completion Test[56]	Measure of aspects of executive function. It consists of two sets of 15 sentences; the examiner reads the questions aloud and subject completes the sentences.	Executive function
Wechsler Adult Intelligence Scale (WAIS) IV–Digit Span[57]	Recites a string of numbers forward and backward as a measure of attention and working memory, respectively	Attention/working memory
Controlled Oral Word Association[58]	Lists as many words that start with 'F', 'A' and 'S' in 60 s to measure verbal fluency	Verbal fluency
Craft Story–Immediate[59]	Patient immediately recalls a short story	Immediate memory
Craft Story–Delayed	Patient recalls a short story 20 min later	Delayed memory
WAIS IV–Similarities	Subject is given two words and then is asked how they are alike to assess reasoning	Verbal abstraction and concept formation

Table 2 Secondary outcome assessments

Study assessment	Description	Variable type
Delirium/coma-free days during index hospitalisation	Confusion Assessment Method for the Intensive Care Unit[43] and the Richmond Agitation Sedation Scale[44] are recorded twice daily by the bedside nurse	Continuous
Basic Activities of Daily Living[60]	Quantifies 6 basic ADLs	Continuous
Functional Activities Questionnaire[61]	Quantifies 10 instrumental ADLs	Continuous
Employment Survey	15-item survey that quantifies the patient's employment pre-acute and post-acute illness	Categorical
EQ-5D-5L[62–64]	EQ-5D-5L characterises health-related quality of life and contains 5 dimensions ('5D') related to everyday living: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, as well as a single self-rating question	Continuous
Nursing Home Placement	During patient contact, we will determine if the patient is placed in nursing home. The date of placement will be recorded.	Categorical

ADLs, activities of daily living.

determined by the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[43] and coma will be defined as a Richmond Agitation Sedation Scale (RASS)[44] of −4 or −5. The CAM-ICU and RASS are performed twice daily by the medical ICU bedside nurse and documented in the electronic medical record as part of their routine care. Additional secondary outcomes for CO-PILOT include 12-month assessments of basic and independent activities of daily living, health-related quality of life, employment status and nursing home placement (table 2). These measures represent important patient-centred outcomes impacted by critical illness. Assessment of cognition, health-related quality of life and physical function in critical illness survivors is recommended by consensus guidelines.[37 45] Disability in basic and instrumental activities of daily living following critical illness is common, and the presence of either hyperoxemia or hypoxemia may impact functional outcomes following critical illness.[14 15 46] Similarly, many ICU survivors are never able to return to work, which may be due to LTCI or other newly acquired disabilities.[45–47]

STATISTICAL ANALYSIS AND REPORTING

Statistical analysis principles

R (R Foundation for Statistical Computing, Vienna, Austria) will be used for the CO-PILOT analyses. Categorical variables will be presented as proportions and frequencies, while continuous variables will be presented as mean±SD or median and IQR. All analyses will be performed using an intent-to-treat approach, unless otherwise specified, for individual patients for each hospitalisation. We will conduct adjusted analyses for prespecified covariates to increase the precision of our estimates. We have prespecified a single primary analysis of a single primary outcome (T-MoCA score) for the CO-PILOT ancillary study. Additional analyses, including those of secondary cognitive outcomes, will be considered hypothesis generating to avoid the problem of multiple testing, and thus no adjustments for multiple comparisons will be performed. Multiple imputation will be performed only if there is partial missingness of the T-MoCA components.[1 47 48] We will use model-based single or multiple imputation for missing covariates.[49–51]

Main analysis of the primary outcome

In the primary analysis, we will use generalised estimating equations with T-MoCA as the dependent variable, study period as the cluster, and trial group assignment (higher, lower and intermediate SpO_2 target) as the independent variable and the following prespecified baseline covariates: age, sex, race/ethnicity, years of education, pre-illness dementia diagnosis, comorbidities (chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, end-stage renal disease), cardiac arrest and baseline non-respiratory Sequential Organ Failure Assessment (SOFA) score. The parent PILOT Study did not measure baseline cognition, and CO-PILOT participants are contacted for participation 1 year after critical illness, making it difficult to accurately characterise pre-illness cognition. When appropriate, continuous variables will be analysed using restricted cubic splines with multiple knots to allow for non-linearity. For the purpose of declaring a statistically significant difference between groups in the primary endpoint of T-MoCA, we will consider the effect from the proportional odds model and a two-sided p value of 0.05. 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.

Sample size estimation and power calculation

Over 36 months, the parent PILOT trial is anticipated to enrol approximately 2250 mechanically ventilated adults assigned to one of the three study groups. Assuming 60% survival, 66% meeting eligibility criteria for CO-PILOT,

and 78% follow-up rates at 12 months based on the original 'Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors' (BRAIN-ICU) Study and less than 5% missing data for the primary outcome,[1] we anticipate that at least 34 patients per 2-month cluster (612 patients over 36 months of enrolment) will complete the T-MoCA at 12 months. The SD of the T-MoCA is 2.8.[51] Assuming an intracluster correlation of 0.01, we will have 80% power to detect a difference of 0.90 points in T-MoCA score between any two treatment groups, a change considered to be clinically meaningful.[52–54]

Sensitivity analyses of primary outcome

Patients undergoing mechanical ventilation for critical illness have a high severity of illness and are at high risk of death prior to 12-month assessment. Patients who die prior to the 12-month follow-up will have missing cognitive outcomes, complicating analyses between the three treatment arms and leading to bias should the mortality rates differ between oxygen target groups overall or among subgroups of patients. Similarly, there are also patients who may be too cognitively impaired to complete the cognitive assessments but have secondary outcome data completed by their authorised surrogates. To address these potential sources of bias, we will conduct additional sensitivity analyses to evaluate the robustness of our findings. For our cognitive outcomes, we will repeat the analysis assigning patients who are unable to complete a cognitive assessment due to cognitive impairment, a T-MoCA score of 0 and patients who die prior to follow-up as having the worst possible cognitive outcome by assigning a score of −1.[55] Because a lower score on the cognitive assessment is consistent with worse cognition, a composite endpoint with a score of −1 for death maintains the ordering assumption needed for this approach and allows for an intention-to-treat analysis using all study participants. The multivariable model will be reanalysed with the same covariates except for pre-illness dementia and education, which were not collected in non-survivors. We will also complete additional sensitivity analyses, including a complete case analysis, an unadjusted analysis and an analysis using the complete SOFA score (including respiratory component). All sensitivity analyses will be conducted for the primary outcome only.

Analysis of secondary outcomes

We will assess SpO_2 targets' effect on 12-month global cognition as characterised by the Global Cognition Composite Score, and individual cognitive domains: executive function, attention, verbal fluency, immediate and delayed memory, and abstraction (table 1).

We will also examine the effect of the different oxygen targets on delirium/coma-free days, basic and independent activities of daily living, quality of life, employment status and nursing home placement (table 2).

The analysis plan will be similar to the primary analysis. If there are insufficient events for the 12-month categorical outcomes (employment status, quality of life and rehospitalisation), we will reduce the number of covariates in the multivariable models to avoid overfitting, or we will conduct a descriptive (univariate) analysis.

Heterogeneity of treatment effect

We will examine whether certain prespecified baseline variables modify the effect of study group assignment on the primary outcome. We will evaluate for effect modification using the same model used for the primary outcome. Independent variables will include study group assignment, the potential effect modifier and potential interaction terms (eg, study group×baseline variable of interest). We will present categorical variables analysed as potential effect modifiers using forest plots and continuous variables as partial effects plots.

We will evaluate the following variables as modifiers of any effect of oxygen target on the primary outcome:

1. Age
2. Race/ethnicity
3. Baseline dementia status (yes/no)
4. Education
5. Baseline severity of illness (non-respiratory SOFA score)
6. Cardiac arrest
7. Comorbidities

Trial status

CO-PILOT is an ongoing ancillary study of long-term cognitive outcomes among patients randomised to higher, intermediate and lower SpO_2 targets as part of the ongoing PILOT trial. Patient enrolment in CO-PILOT began on 1 July 2019 and will end on 31 August 2022.

ETHICS AND DISSEMINATION

Institutional Review Board approval

The CO-PILOT Study was approved by the Institutional Review Board (IRB) of Vanderbilt University Medical Center (IRB# 190315).

Dissemination plan

Study 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 study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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