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Optimization of Inspired Oxygen during Mechanical Ventilation (OPTI-OXYGEN): rationale and design of a pragmatic randomised controlled trial

Sonal R Pannu,[1,2] Jonathan Peters ,[3,4] Jamie Zimmer,[3] Guy N Brock,[5] Matthew Exline,[1,2] Jeffrey C Horowitz,[1,2] Taylor B Thompson,[6] Todd W Rice,[7] Elliott D Crouser[1,2]

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For numbered affiliations see end of article.

Correspondence to
Jonathan Peters;
jp537421@ohio.edu

ABSTRACT

Introduction Targeted oxygenation protocols in mechanically ventilated patients are critical in avoiding the deleterious effects of hypoxaemia and hyperoxaemia. Peripheral oxygen saturation (SpO2) is a practical metric that commonly drives oxygen titration protocols and guidelines but has inaccuracies attributable to patient variability that can lead to occult hypoxaemia. Conversely, arterial oxygen saturation (SaO2) offers accuracy but is costly and invasive. We aim to develop a novel approach to targeted oxygenation that collectively uses the accuracy of SaO2 and the feasibility of SpO2 to mitigate occult hypoxaemia and prevent hyperoxaemia.

Methods and analysis The Optimization of Inspired Oxygen during Mechanical Ventilation trial is a pragmatic stepped wedge, open label, cluster-randomised controlled trial of an algorithm-based SpO2-SaO2 electronic alert-based oxygen titration protocol. The intervention arm includes targeted oxygenation via an electronic SpO2-SaO2 driven alert protocol. The control group will be subjected to oxygen titration according to standard practice. Within the intervention arm, patients will be assigned to groups with different SpO2 targets based on the degree of SpO2-SaO2 difference. In the 'Conserve O2' group, where SpO2<SaO2 by 1–5% or SpO2>SaO2 by 1–2%, electronic alerts will be used to titrate FiO2 to a target SpO2 of 90–94%. In the 'Boosted O2' group, where SpO2>SaO2 by 3–5%, electronic alerts will be used to titrate FiO2 to a target SpO2 of 93–97%. Patients with an SpO2-SaO2 difference >5% in either direction will be monitored but not assigned to either group. The sample size to determine efficacy is 1620 subjects, randomised over 60 weeks. The primary outcome is the proportion of time during mechanical ventilation spent within the target range, SpO2 of 90–94% (Conserve O2) or SpO2 of 93–97% (Boosted O2) at any FiO2. Secondary outcomes include the proportion of time with SpO2 >94% or SpO2 >97% with FiO2 ≤0.4 within each respective algorithm, the proportion of time with SpO2 <90% or SpO2 <93% within each respective algorithm, length of intensive care unit and hospital stay, hospital mortality, ventilator and vasopressor free days, new onset of arrhythmia when SpO2 <90%, and change to comfort care status (DNRCC) and time to DNRCC after enrolment.

Ethics and dissemination The protocol was approved by The Ohio State University Institutional Review Board (Protocol # 2023H0016) and is registered at ClinicalTrials.gov (NCT 05923853). Progress and safety of the trial are monitored by an independent Data and Safety Monitoring Board. Study results will be published in peer-reviewed medical journals. This study is being carried out with a waiver of consent as participation in the study presents no more than minimal incremental risk compared with routine clinical care for mechanically ventilated critically ill adults outside of the study.

Trial registration number NCT05923853.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our approach to targeted oxygenation uniquely addresses known limitations in peripheral oxygen saturation measurements.
⇒ The study allows for individual assessment of peripheral oxygen saturation-arterial oxygen saturation differences and personalises oxygenation strategies accordingly.
⇒ The use of a real-time automated algorithm generating electronic alerts prompting oxygen titration is a novel strategy in critical care.
⇒ Reflecting real-world clinical complexity, the pragmatic design of this study increases generalisability of the findings to everyday critical care practice.
⇒ We are accepting some degree of occult hyperoxaemia while balancing the complexity of the oxygen titration algorithm.

INTRODUCTION

Targeted oxygenation is critical in mechanically ventilated patients to avoid extremes of hypoxia and hyperoxaemia, both associated with worse patient-oriented outcomes.[1–7] Consequently, clinical practice guidelines continue to recommend targeted fractional inspired oxygen (FiO2) titration to avoid excessive or insufficient oxygenation in acutely ill patients.[8] Our previous work

employing electronic health record (EHR)-based algorithms leveraging peripheral oxygen saturation (SpO2) by continuous pulse oximetry to optimise supplemental FiO2 during mechanical ventilation has been shown to reduce hyperoxaemia and facilitate liberation from mechanical ventilation.[9 10] Our choice of SpO2 as the driver of oxygen titration stems from its widespread acceptance in intensive care unit (ICU) weaning protocols, clinical practice guidelines and inclusion in the new global definition of acute respiratory distress syndrome (ARDS).[8 11–13] Moreover, SpO2 is an integral bedside marker used in the assessment of physiologic readiness for extubation from mechanical ventilation.[14 15] Also, given the correlation of SpO2/FiO2 ratio with arterial oxygen tension (PaO2)/FiO2 ratio, as well as its non-invasive nature, continuous availability and ease of applicability in resource-limited areas, it is now widely incorporated as a diagnostic and prognostic marker of hypoxaemia.[16 17]

Nonetheless, SpO2 remains a flawed measure as pulse oximetry is known to have limitations including limited accuracy with darker skin tones.[13 18] Renewed recognition of this inherent flaw in the technology has stemmed from recent studies which have shed light on the disparities that arise because of differences between haemoglobin saturation as measured by pulse oximetry and that in the arterial blood gas (SaO2). These studies have revealed that occult hypoxaemia is associated with delayed treatment, increased severity of organ failure and increased hospital mortality.[19–24] During critical illness, in addition to skin pigmentation, SpO2-SaO2 differences are also influenced by low flow states, that is, shock and vasopressor use, hypoxaemia, acidemia, atypical haemoglobin and sensor types. Moreover, in addition to these factors, SpO2-SaO2 bias may vary during the course of hospitalisation, compounding the challenge of accurately administering oxygen to mechanically ventilated patients.[25–27]

Given that both hypoxaemia and hyperoxaemia can be detrimental to patient outcomes and must be addressed for optimised oxygen dosing, an approach that integrates the accuracy of SaO2 with the pragmatic ease of SpO2 may hold the key to the comprehensive assessment and optimal administration of supplemental oxygen in critically ill patients. Here, we present the methodology for the Optimization of Inspired Oxygen during Mechanical Ventilation (OPTI-OXYGEN) trial, a pragmatic stepped wedge randomised clinical trial to determine the efficacy of an adaptive SpO2-SaO2-based oxygen titration protocol based on an automated algorithm with electronic alerts. We propose a novel strategy to prospectively screen for differences between paired SaO2 values via co-oximetry and SpO2 via pulse oximetry and to optimise oxygenation to mitigate occult hypoxaemia while employing an automated algorithm to prevent hyperoxaemia. We hypothesise that the use of this SpO2-SaO2-based automated oxygen titration protocol will improve accuracy of targeted oxygenation and reduce both occult hyperoxaemia and hypoxaemia during mechanical ventilation as compared with a traditional physician-based approach.

MATERIALS AND METHODS

Design and oversight

OPTI-OXYGEN is a single-centre, stepped wedge, cluster-randomised, pragmatic trial conducted at The Ohio State University Hospitals (University Hospital, Ross Heart Hospital and University Hospital East) and The James Cancer Hospital. The five participating ICUs include specialised medical, medical oncology, surgical (general surgery and trauma) and coronary critical care units along with a mixed medical-surgical ICU, which total 152 beds.

The protocol was approved by the Ohio State University (OSU) Institutional Review Board (IRB) (Protocol #2023H0016) and is registered at ClinicalTrials.gov (NCT 05923853). SPIRIT guidlines for clinical trials were utilized in the development of this trial (online supplemental file 1). Progress and safety of the trial are monitored by an independent Data and Safety Monitoring Board (DSMB).

Participants

All adult patients (≥18 years of age) requiring mechanical ventilation admitted to the participating ICUs will be screened for eligibility. Exclusion criteria include patients intubated only for procedures such as bronchoscopy, oesophagogastroduodenoscopy or colonoscopy, and patients for whom hyperoxaemia may be desired as treatment. Other exclusion criteria include pregnancy, prisoner status, pneumothorax, carbon monoxide poisoning and patients requiring hyperbaric oxygen therapy. Patients with pneumothorax, carbon monoxide poisoning and hyperbaric oxygen therapy may need liberal oxygenation for therapeutic indications; therefore, frequent titrations in these patients may not be justified. Patients who are actively pregnant, as defined by the presence of positive urine or serum pregnancy test, or the patient's personal history of current pregnancy, will be excluded primarily because the effects of varying supply of oxygen in the fetus is not known. Please see additional details in the study procedures.

Randomisation and blinding

Each of these units is divided into clusters of 8–12 beds with a total of 14 clusters in the study. Each ICU will be randomised electronically by the statistician, with nested randomisation of clusters within the ICU. All intubated patients meeting inclusion criteria in a particular cluster will be in the control or intervention arm per the randomised assignment of that cluster. In the first 'step', every cluster will be assigned to the control arm. Using the randomisation scheme, each cluster will sequentially transition from the control arm to the intervention arm every 4 weeks, marking a 'step'. The study will have a total of 15 'steps' (figure 1). Once a cluster transitions to the intervention arm, that cluster will stay as intervention for the remainder of the trial. When a cluster is in the control arm, eligible patients will continue to receive usual care per the established ICU mechanical ventilation protocol

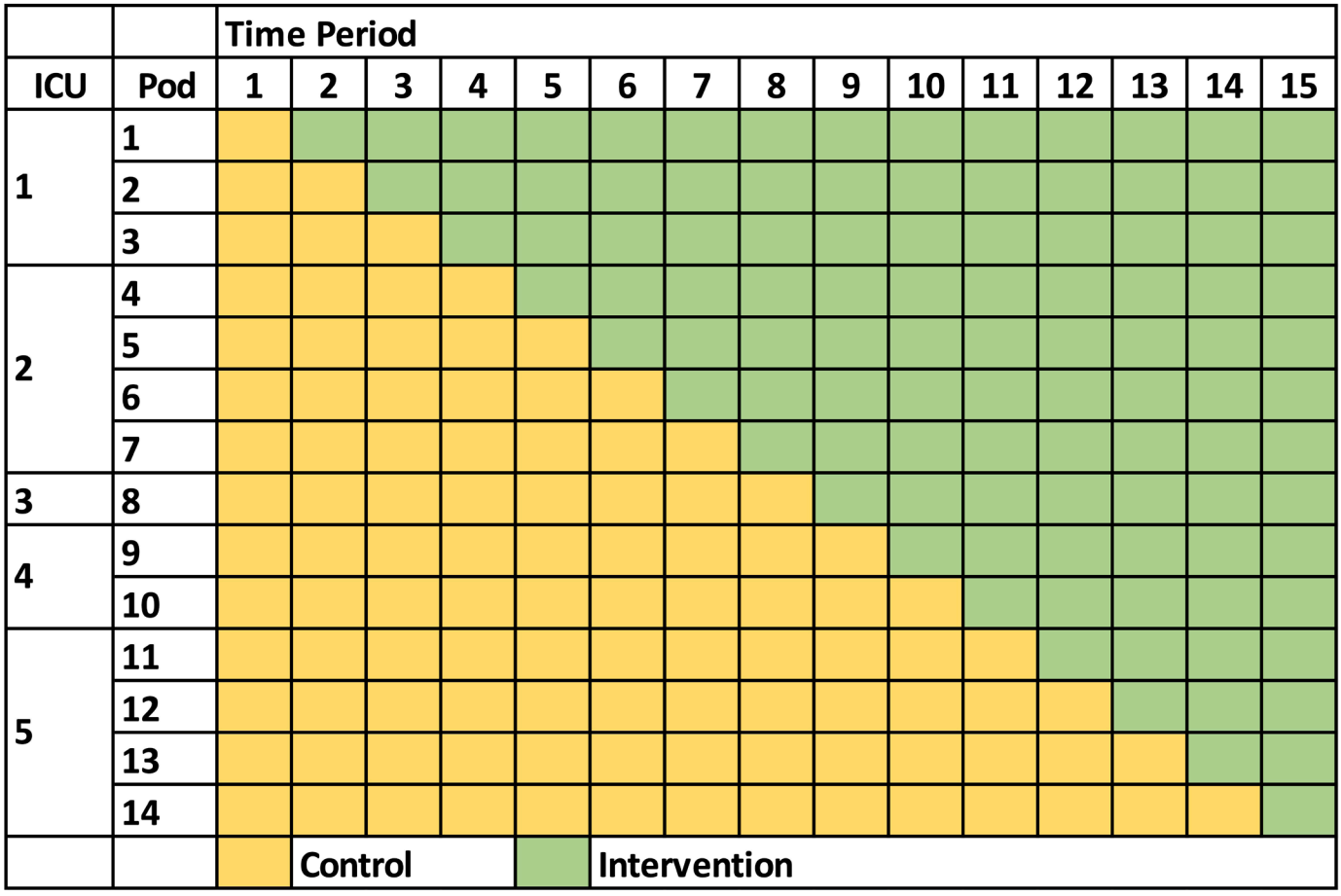

Figure 1 Optimization of Inspired Oxygen during Mechanical Ventilation stepped wedge design. Five intensive care units, each with 1-4 pods of 8-12 beds, will be randomly assigned to fourteen steps starting at four weeks and every four weeks thereafter. The total duration of enrollment is 60 weeks. ICU, intensive care unit.

(online supplemental appendix C). When a cluster switches to the intervention arm, eligible patients will be assigned to a conservative or liberal oxygenation protocol or excluded based on the range of the difference between SaO2 from the arterial blood gas (ABG) and the corresponding SpO2 on pulse oximetry. Patients will remain in the study until they are liberated from mechanical ventilation or discharged from the hospital, whichever occurs earlier.

Our design is a complete stepped wedge, cluster-randomised, unblinded study. There are 14 clusters, each with 8–12 beds. All clusters start in the control group at the beginning of the trial. Given this is a stepped wedge design, randomisation is not occurring at the patient level but rather at the cluster level. Randomisation is nested so that first, ICUs (five total) are randomised then pods (clusters) within ICUs (one to four pods within each ICU) are randomised. Every 4-week step, there will be a sequential transition of one ICU pod from control to intervention. The last 48 hours of each 4-week step will be a washout period for the ICU pod transitioning from control to intervention, with no new control patients enrolled during these last 48 hours.

Respiratory therapists and study coordinators are unblinded in this study and will be informed if their pod is control or intervention. Due to the nature of the interventions, blinding respiratory therapists as to which arm the ICU pod is assigned would be impossible. Study investigators and statisticians are blinded to study data.

Study procedures, intervention arm

Our team at The Ohio State University has developed a real-time automated algorithm which continuously analyses FiO2 and SpO2 data at 1 min intervals to generate electronic alerts when pre-specified FiO2 and SpO2 criteria are met. The development of electronic alerts and their efficacy have been published previously.[28] For this study protocol, this automated algorithm is designed to have conservative and liberal oxygen therapy groups, referred to as 'Conserve O2' and 'Boosted O2', respectively. In the Conserve O2 group, our aim is to maintain SpO2 range within 90–94% at any FiO2, while the goal of the Boosted O2 group is SpO2 ranging between 93 and 97% at any FiO2. When 80% of the data points in a 45 min window are above the target range for the respective arm, a hyperoxaemia alert will be generated. In Conserve O2, that means when SpO2 >94% with FiO2 ≥0.4, while in Boosted O2 it means SpO2 >97% when FiO2 ≥0.4. No alerts are sent when FiO2 <0.4. The lower

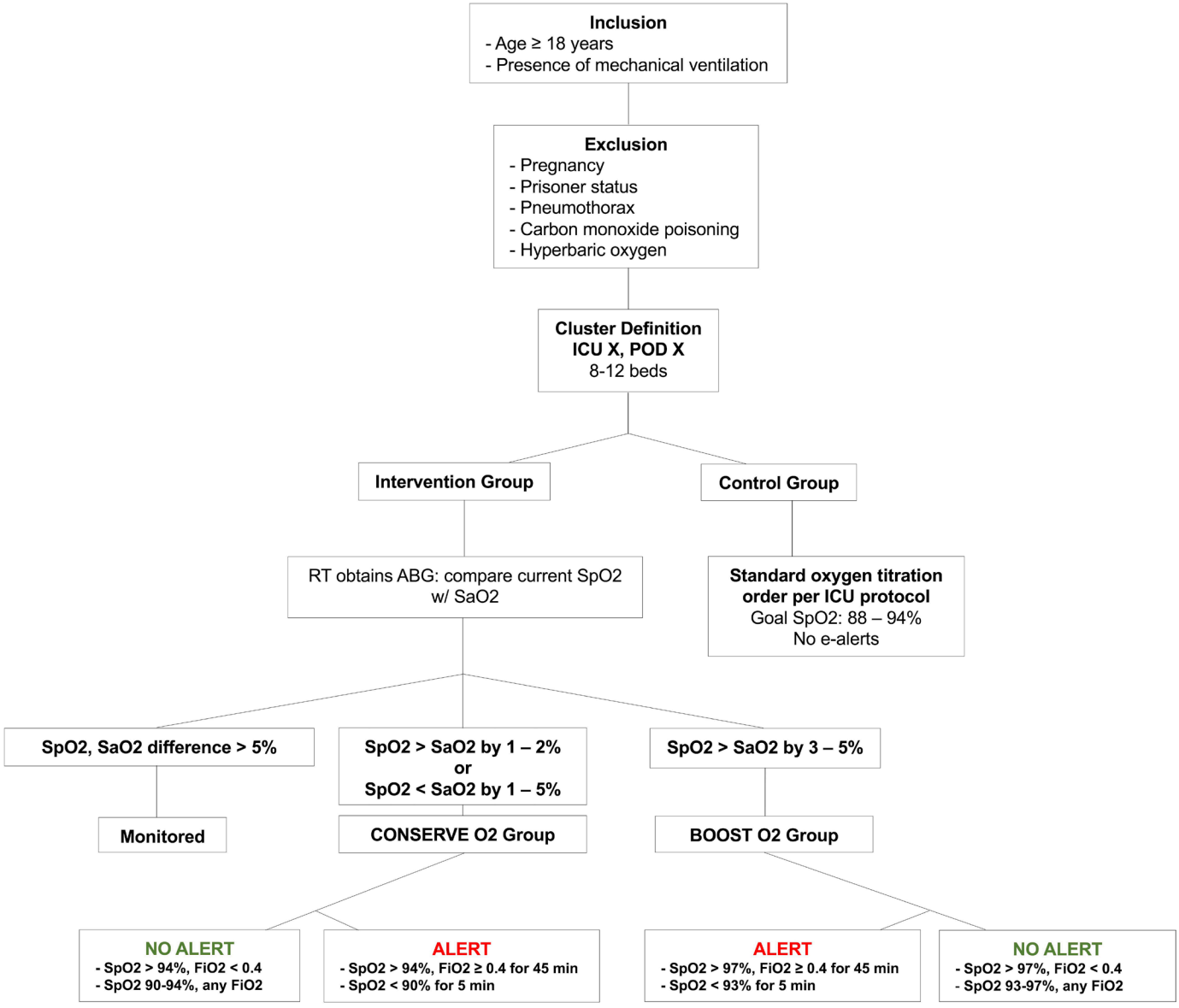

Figure 2 Trial enrolment and intervention flow. This figure shows the events of the trial from enrollment to intervention and control pod assignments. ABG, arterial blood gas; FiO2, fraction of inspired oxygen; ICU, intensive care unit; RT, respiratory therapist; SaO2, arterial oxygen saturation; SpO2, peripheral oxygen saturation.

limit for hypoxaemia is 90% for the Conserve O2 group and 93% for Boosted O2.

In all eligible intubated patients, SaO2 on co-oximetry will be correlated to SpO2 on pulse oximetry using an ABG drawn closest after time of endotracheal intubation, but not more than 24 hours later. The ABG used to assess SpO2-SaO2 difference is obtained when the study patient does not show active respiratory or haemodynamic instability. In the study protocol, this is defined as SpO2 ≥90% and no or low vasopressor requirements, that is, norepinephrine equivalent dose <0.2 µg/minute. Based on the SpO2-SaO2 difference, study patients will be assigned to the Conserve O2 or Boosted O2 groups or excluded (figure 2). Hidden or occult hypoxaemia exists when SpO2 overestimates SaO2, that is, SpO2 >SaO2. In the study protocol, if SpO2>SaO2 by ≤2%, patients will be assigned to the Conserve O2 group. On the other hand, if SpO2>SaO2 by 3–5% and the extent of hidden hypoxaemia is higher, study patients will be assigned to the Boosted O2 group. When SpO2 underestimates SaO2, that is, SpO2<SaO2, patients are at risk of hidden hyperoxaemia. In this protocol, when SpO2<SaO2 by ≤5%, patients will be assigned to the Conserve O2 group. Study patients who have a SpO2-SaO2 difference >5% in either direction will be monitored but will not be assigned to either oxygenation group. Their primary providers will be informed about the difference, so oxygenation decisions can be made by them, independent of the study protocol.

Once assigned to either group, electronic alerts based on respective targets will be initiated (figure 3). Both Conserve and Boosted algorithms communicate with the EHR, analysing FiO2 from the ventilator and SpO2 from the bedside monitor every minute. Alerts with the study patient's room number are sent to Cisco phones or

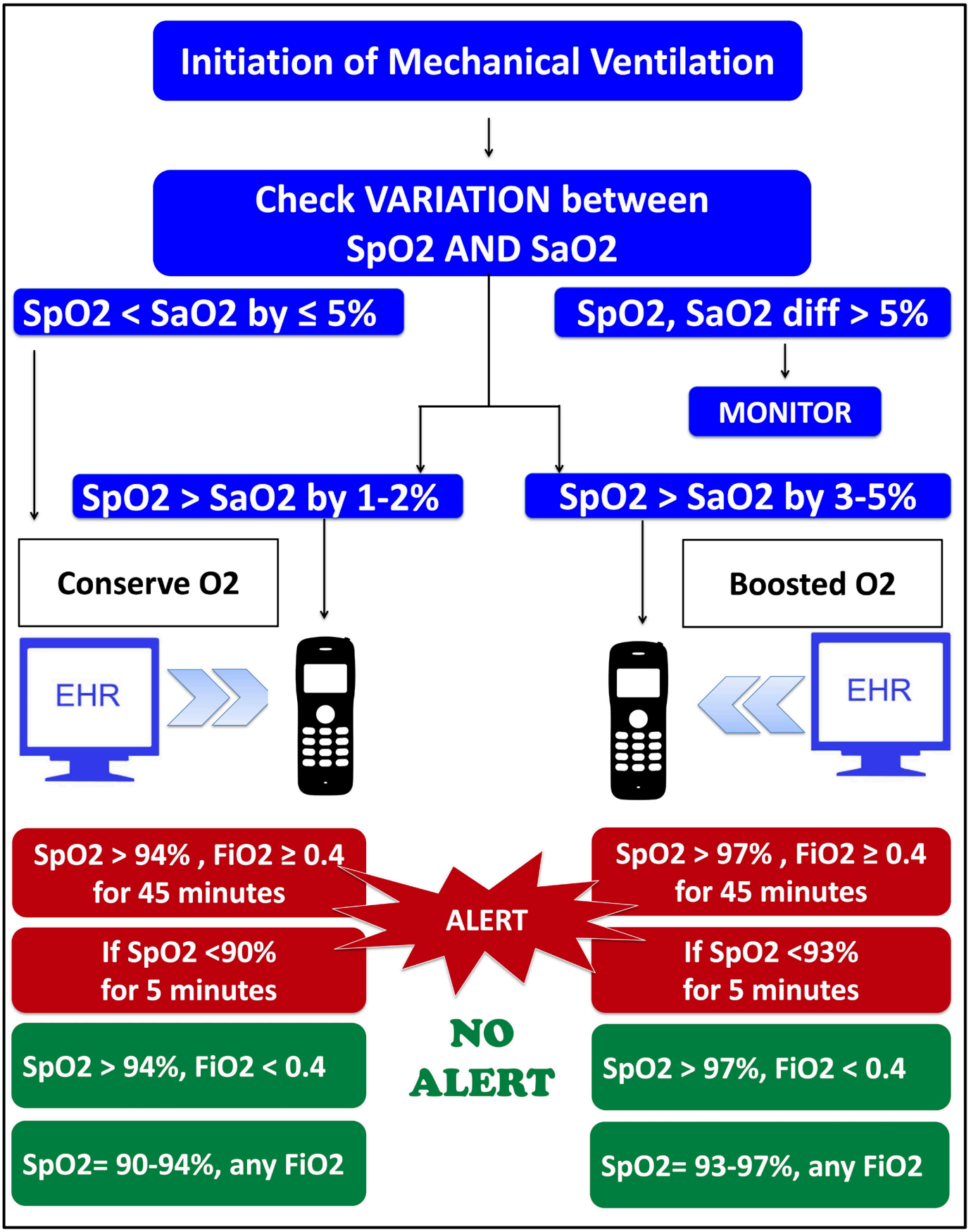

Figure 3 Intervention arm flow diagram. This figure shows the assignment of patients from the intervention pod to Conserve O2 or Boosted O2 groups based on the difference between SpO2 and SaO2 levels. EHR, electronic health record; FiO2, fraction of inspired oxygen; SaO2, arterial oxygen saturation; SpO2, peripheral oxygen saturation.

	CONSERVE O2	BOOSTED O2
HYPEROXIA ALERT→	SpO2 > 94% & FiO2 ≥ 0.4 for > 45 min	SpO2 > 97% & FiO2 ≥ 0.4 for > 45 min
ACTION→	If FiO2 ≥ 0.7 → reduce FiO2 by 0.2	
	If FiO2 < 0.7→ reduce FiO2 by 0.1	
NO ALERT→	SpO2 > 94% & FiO2 < 0.4 or SpO2 90-94, any FiO2	SpO2 > 97% & FiO2 < 0.4 or SpO2 93-97%, any FiO2
HYPOXIA ALERT→	SpO2 < 90% for 5 min, any FiO2 value	SpO2 < 93% for 5 min, any FiO2 value
ACTION→	Increase FiO2 by 0.2 → call Physician	
	PEEP management per ICU mechanical ventilation protocol	

Figure 4 Decision support tool. The decision support tool is used for FiO2 titration. It is in the form of a laminated card provided to respiratory therapists and provides instructions for titration. FiO2, fraction of inspired oxygen; ICU, intensive care unit; PEEP, positive end expiratory pressure; SaO2, arterial oxygen saturation; SpO2, peripheral oxygen saturation.

pagers carried by respiratory therapists for that specific ICU. An alert can only be generated at most every 45 min, and no more than four alerts are sent every 6 hours to prevent alert fatigue. Protocol compliance is monitored by changes in FiO2 each time an alert is generated. Respiratory therapists are given recommendations for FiO2 titration on a decision support card (figure 4). FiO2 titrations are expected as soon as possible following an alert, but no later than 45 min. All other aspects of mechanical ventilation are managed per the ICU mechanical ventilation protocol (online supplemental appendix C). Patients remain in the respective O2 groups until liberated from mechanical ventilation. All subsequent ABGs obtained by the care team are not mandated by the protocol and will not influence intervention arm assignment (ie, Boosted O2 or Conserve O2) regardless of any SpO2-SaO2 difference, but will be evaluated in a retrospective exploratory analysis.

Study procedures, control arm

For eligible patients in the control arm, FiO2 titration is done by a standard oxygen titration ordered in the EHR by physicians and followed by respiratory therapists (online supplemental appendix C). The ICU ventilator management protocol will guide patient care. Within the protocol, guidance for oxygenation is given to maintain SpO2 between 88 and 94%. Respiratory therapists are encouraged to review oxygen needs at least once every 4 hours. ABGs are not mandated by the ventilator management protocol and will be drawn as deemed necessary by the clinical team.

Waiver of consent

This study is being carried out with a waiver of consent as participation in the study presents no more than minimal incremental risk compared with routine clinical care for mechanically ventilated critically ill adults outside of the study. The Ohio State University IRB, which functions as an ethics committee responsible for reviewing human subject research, approved the waiver of consent. The two SpO2 target ranges examined in OPTI-OXYGEN are used in routine clinical care in the study ICUs and are all within the range recommended by at least one international guideline. In addition, the safety of an oxygen range of 90–97% (ranges used in OPTI-OXYGEN) and an extended range of 88–100% has been established by at least two randomised clinical trials. Moreover, to minimise any further risk, OPTI-OXYGEN uniquely addresses the inaccuracies of SpO2 measurements and increases patient safety by defining SpO2 ranges based on SaO2 measurements. The oxygen ranges used in OPTI-OXYGEN are the usual ranges patients are exposed to in the participating ICUs and used by the treating physicians in those ICUs. Therefore, patients would be expected to receive similar oxygen therapy in an unstructured manner if they were not in the trial. There is clinical equipoise, that is, we have inadequate prior data to suggest the superiority of one approach over the other.

Stakeholder engagement, education and adherence

Respiratory therapy leadership was engaged in protocol development, study design and implementation. Given the pragmatic nature of the study, inclusion, education and training of all ICU staff was intensive. This included

respiratory therapists, nurses, physicians, advanced practice providers and ICU directors for each of the involved units. The ICU or research director of each unit was identified as a local physician champion. The study was presented at each ICU's operation council meeting. Meetings with the respiratory leads of each ICU (medical, surgical, cardiac and the medical oncology unit) were conducted regularly over several months. Education materials were prepared and disseminated via in-person meetings, emails, electronic shared drive updates and newsletters to respiratory therapists. Similar meetings were conducted and information disseminated within the nursing teams. Study outlines and expectations were posted in respiratory and nursing break rooms. Over 100 respiratory therapists were trained for this trial prior to its initiation. Being primarily responsible for performing FiO2 titration, respiratory therapists are encouraged to discuss any concerns regarding oxygen titration with treating physicians and/or study investigators. Respiratory therapists must document and provide reasoning for protocol deviations in the EHR flowsheet.

The study coordinator conducts routine reviews of study progress and screens for protocol adherence or deviation. The respiratory leadership may additionally perform spot checks of therapist performance for protocol compliance.

Patient and public involvement

Patients and the public were not involved in the design or conception of this trial.

Adverse events and patient safety

The bedside nurse and respiratory therapist monitor patients after titration. The study is monitored by a DSMB and a medical monitor has also been appointed. The medical monitor, who is blinded and independent from the research team, is responsible for real-time monitoring of reports of serious adverse events and safety concerns and providing the DSMB with case-by-case reports of the serious adverse events. Attribution of adverse events is detailed in online supplemental appendix D.

Outcomes

The primary outcome is the proportion of time during mechanical ventilation spent within the target range, SpO2 of 90–94% (Conserve O2) or SpO2 of 93–97% (Boosted O2) at any FiO2. Secondary outcomes include the proportion of time with SpO2 >94% or SpO2 >97% with FiO2 ≤0.4 within each respective algorithm, the proportion of time with SpO2 <90% or SpO2 <93% within each respective algorithm, length of ICU and hospital stay, hospital mortality, ventilator and vasopressor free days, new onset of arrhythmia when SpO2 <90%, and change to comfort care status (DNRCC) and time to DNRCC after enrolment. A sensitivity analysis will be conducted of subjects with a SpO2-SaO2 difference >5%. In addition, data for self-reported race, skin tone (measured by Fitzpatrick scale and Monk scales), and variables associated with shock and acidemia during critical illness, along with SaO2, PaO2 and SpO2, will be collected to further corroborate correlation and predictors of bias between these measures of oxygenation. We will collect data related to primary comorbid conditions which have been shown to be valuable for developing precision and personalisation in oxygen titration to identify their trajectories and substratify their outcomes (eg, coronary artery disease, chronic obstructive pulmonary disease, acute ischaemic stroke, post-cardiac arrest and hypoxic ischaemic encephalopathy[29 30]). Any patient who is enrolled in the study and is re-intubated within 48 hours of extubation will continue in the same arm as before.[31] Reintubation within such a short time can be clinically considered as a part of the same disease process. However, if re-initiation of mechanical ventilation occurs after 48 hours, the same patient cannot be enrolled in the study again during that hospitalisation. Once a patient is discharged from the hospital, they will be excluded from any future enrolment. Time duration of hyperoxaemia in both arms is counted only when the patient is under study protocol.

Sample size and power

Power was based on previously published data demonstrating an increase in time with SpO2 in the expected target range using automated oxygen titration from 32%±13% (treatment) to 40%±14% (control) (effect size=0.57).[9] The effect size (ES) found in a previous pilot study conducted at OSU (Pilot Trial of Titration of Oxygen Levels) was 0.36.[10] Our design is a complete stepped wedge having 14 clusters with 4 week steps (15 total time periods) and an expected average of 5.70 subjects per cluster per 4-week time period (n=1620 over 60 weeks, ~3.85 patients per ICU pod cluster per 4 weeks). Assuming a reduction in percentage of excess exposure time of 3.9% and SD of 15% (ES=0.26), the study has 90% power (α=0.05, ICC=0.1, two-sided). Please see online supplemental appendix E for a detailed statistical analysis plan.

DISCUSSION

OPTI-OXYGEN is a pragmatic, multidisciplinary study implemented to advance targeted oxygenation by addressing SpO2 bias to mitigate occult hypoxaemia while also preventing uncontrolled hyperoxaemia. The vision of OPTI-OXYGEN is based on SpO2-SaO2 correlation in critically ill patients and adjusting goals accordingly for oxygen supplementation. Algorithmic feedback for FiO2 titration based upon 24-hour real-time screening is provided.

Below we discuss the rationale for key aspects of the OPTI-OXYGEN study design.

Simultaneous measurement of SaO2-SpO2 is a key design aspect of this study

Numerous studies conducted in healthy volunteers and critically ill patients have shed light on the disparities

between haemoglobin saturation as measured by SpO2 and SaO2. In addition to hypoxaemia, a significant factor contributing to these differences is self-reported race, a likely reflection of skin with darker pigmentation. This racial disparity in black patients associated with the predictive value of SpO2 in estimating PaO2 was initially reported in mechanically ventilated patients more than three decades ago by Jubran *et al*.[18] More recently, studies in healthy volunteers demonstrated that sensor type, gender and skin colour were predictive of SpO2-SaO2 errors, specifically in darker skinned patients.[32] In critically ill patients, Sjoding *et al* reported a statistically higher occurrence of occult hypoxaemia (SaO2 less than 88%) in black patients (17% (95% CI 12.2 to 23.3)) when SpO2 readings fell within the range of 92–96%, as compared with their white counterparts (6.2% (95% CI 5.4 to 7.1)).[20] This phenomenon was corroborated through secondary analyses of the Veterans Health Administration database evaluating 30 039 SpO2, SaO2 pairs in acutely ill patients. Among SpO2 values greater than or equal to 92%, probabilities of occult hypoxaemia were statistically higher in black (19.6% (95%CI 18.6% to 20.6%)) versus white patients (15.6% (95%CI 15% to 16.1%), p<0.001). Additionally, black patients had a higher probability of having a larger SpO2-SaO2 disparity on subsequent ABGs as compared with the initial SpO2-SaO2 difference.[24] In other studies, occult hypoxaemia was observed in all racial and ethnic subgroups with varying incidence. While more pronounced in black patients, the presence of hidden hypoxaemia was associated with delays in determining treatment eligibility, worse organ function score and higher hospital mortality in critically ill patients of all races.[21 22] Thus, discrepancies between SpO2 and SaO2 remain an important problem that needs to be addressed and accounted for in studies of oxygen titration in critically ill patients.[19 22] Notably, these data are limited to its retrospective nature and lack of simultaneous measurements. In addition, it may harbour contextual nuances, selection bias and missing data.[22 33] For instance, ABG assessments are typically conducted to ascertain oxygenation status amidst acute haemodynamic or respiratory compromise to guide critical clinical decisions. These scenarios are characterised by low perfusion, such as shock and hypoxaemia, which often accentuate the SpO2-SaO2 bias, and therefore, secondary analyses of clinically indicated ABGs may not fully reflect the bias accurately. In addition, there is a time lag between the two measurements, albeit as minimal as 5 or 10 min in these studies. Therefore, to minimise possible errors, a prospective analysis of SpO2-SaO2 bias is warranted with notation of the SpO2 at the exact time that the ABG is obtained.

It is important to highlight that the issue of disparities between SpO2 and SaO2 has not received sufficient attention in large prospective clinical trials focused on oxygenation targets, underscoring the need to specifically address this matter in current and future oxygenation trials.[25 34–36]

Recognising the gravity of this issue, the U.S. Food and Drug Administration (FDA) received a congressional inquiry and in February 2021 issued a safety communication to alert healthcare providers to the limitations and potential inaccuracies of pulse oximeters in certain circumstances. A significant development in this regard was the meeting of the Anesthesiology and Respiratory Therapy Devices Panel of the Medical

Device Advisory Committee in November 2022, discussing concerns that pulse oximeters may be less accurate in individuals with darker skin pigmentation.[37] Among their recommendations, the panel stressed the necessity of large datasets and prospective studies that simultaneously collect paired SpO2 and SaO2 data while systematically accounting for important confounding variables. The prospective paired steady SpO2-SaO2 correlation in OPTI-OXYGEN is designed to contribute to that knowledge gap with bedside assessments of pulse oximeter sensors, motion artefacts, objective skin tone measurements and other confounding factors as noted in online supplemental appendix B. OPTI-OXYGEN will aim to provide more robust evidence regarding the impact of skin pigmentation on real-world pulse oximetry.

Rationale for the Conserve O2 and Boosted O2 SpO2 and FiO2 ranges

Trimming excess FiO2 use and adherence to oxygen titration are necessary to reduce hyperoxaemia.[9] Reduction in hyperoxaemia is associated with improved mortality in critically ill patients, although not noted consistently in all oxygenation trials.[3 4] Effective FiO2 titration can lead to earlier ventilator liberation; however, assessment and prevention of hyperoxaemia must take the SpO2-SaO2 bias into account. While hidden hypoxaemia, where SpO2 overestimates the true SaO2, is central to this issue, the reverse (ie, SpO2 underestimating true SaO2 leading to occult hyperoxaemia) may also exist. Examining 105 467 paired observations from 7693 subjects, it was found that in 75% of cases, the errors were bidirectional. While occult hypoxaemia was less frequent within the oxygenation saturation range of 95–100%, the prevalence of hyperoxaemia (partial pressure of arterial oxygen >110 mm Hg) increased, affecting 42.3% of black and 46.0% of white patients.[38] In another analysis involving 1024 patients with 5557 paired measurements, it was observed that among patients with SpO2 values between 92% and 96%, black patients were more likely to experience both hypoxaemia (3.5% vs 1.1%; p=0.002) and hyperoxaemia (4.7% vs 2.4%; p=0.03) compared with white patients.[39] Consequently, a liberal approach to oxygenation aimed at just addressing occult hypoxaemia cannot serve as a viable solution, as it would result in uncontrolled hyperoxaemia. Therefore, cautious evaluation of hyperoxaemia must also be incorporated in oxygenation goals.

We addressed this issue in our study through the Conserve O2 and Boosted O2 groups. The range in Conserve O2 is SpO2 90–94% at any FiO2. Alerts are only

triggered when FiO2 leads to oxygen saturation goals over the upper limit of SpO2 in that respective group. For example, in the Conserve O2 group, alerts are sent when SpO2 >94% when FiO2 ≥0.4. We chose the upper level of 94% based on recommended safe upper SpO2 targets in acutely ill patients and based our current ventilator management protocol (online supplemental appendix C).[8 40] We defined the lower SpO2 range of 90%.[35] Since the maximum overestimation of SaO2 in the Conserve O2 group can be 2%, the most conservative estimated SpO2 levels would not be lower than 88–92%. The Boosted O2 range was developed to address higher risk occult hypoxaemia in patients who reflect a high positive bias of 3–5%. In these patients, an increased target SpO2 range of 93–97% was determined. With this more liberal target range, our most conservative estimate of SaO2 would also be 88–92%, while most patients would be expected to be within 90–94% only when on higher FiO2 levels. Once FiO2 is <0.4, no alerts for oxygen titration are sent in either group. In other words, once the FiO2 is <0.4, the upper SpO2 limit is not monitored. If desaturations or hypoxaemia occurs after this point, they are managed as clinically deemed necessary. For patients with occult hyperoxaemia, that is, where SpO2 underestimates SaO2, we created a single category of SpO2<SaO2 ≤5% and defined their oxygenation goals similar to the Conserve O2 group. We refrained from creating 'subgroups' for hyperoxaemia targets due to the possibly higher risk of hypoxaemia from 'tighter' hyperoxaemic ranges and to also help with minimising the complexity of the algorithm. Patients with a SpO2-SaO2 bias of greater than 5% in either direction are screened and monitored but excluded from Boosted O2 or Conserve O2 oxygen groups, due to the higher risk for occult hypoxaemia or hyperoxaemia in the study protocol. These patients are managed as clinically deemed necessary by the primary teams. Thus, the Boosted and Conserve O2 groups are designed to provide safe targeted oxygenation ranges to patients within a range of SpO2 and SaO2 bias noted in the literature (1–5%), while providing exploratory data on extreme variations (>5%) noted during acute illness.

Steadystate SpO2-SaO2 measurement

The assessment of SpO2-SaO2 difference may not be simplistic, since that difference may vary during hospitalisation in the same patient. In addition to hypoxaemia, the presence of shock (low flow state), vasopressors, acidemia, lactate levels and bacteremia could have effects on SpO2-SaO2 bias during critical illness.[27] The effects of predictors have been explored, but conclusive correlations have not been defined. To address these effects in our study, we plan to ensure attainment of a steady-state ABG, that is, adherence to specific criteria of SpO2 ≥90% and vasopressor utilisation <0.2 µg/kg/min of norepinephrine equivalents. We deemed this necessary for robust correlation between the SpO2 and SaO2 readings. SpO2 readings ≥90% in hospital settings exhibit 88.6% sensitivity and 95.1% specificity in detecting SaO2 >90%.[26] We decided to select vasopressor use as a prerogative for both shock and low perfusion states from vasoconstriction. The threshold of <0.2 µg/kg/min of norepinephrine equivalents was selected considering that alpha constriction is not typically activated within that dose range. Given that there is no conclusive data on any other predictors of SpO2-SaO2 difference in critically ill patients, we intend to conduct an exploratory analysis to determine SpO2-SaO2 bias, direction, magnitude and their longitudinal assessment with known confounding factors during the course of critical illness.

Realtime objective skin colour assessment

In OPTI-OXYGEN, we will be performing skin colour assessments in all enrolled patients to provide corroborative measurements with self-reported race and SpO2-SaO2 bias. These will be primarily done via skin colour classification scales and melanin index measurements via reflectance spectrophotometer. Measurements will be done by trained clinical research coordinators at the earliest possible time close to enrolment when SpO2 is at least 90%. Measurement sites are (1) at the closest location to the pulse oximeter sensor, (2) at the dorsal surface of the finger between the nail bed and the distal interphalangeal joint, and (3) at the centre of the forehead. These colour measurements are done with windows closed and ambient lights. The reflectance spectrophotometer is a handheld, portable measurement instrument designed for colourimetric measurements and calculating melanin index. The Monk Scale and Fitzpatrick Classification System will be used (online supplemental appendix B). The Fitzpatrick scale (6-shade scale) was initially developed for photochemotherapy (PUVA therapy) and is included as it is one of the most common classification systems for skin pigment.[40] The Monk Skin Tone is a 10-shade scale designed to be easy to use for development and evaluation of technology while presenting a more representative range of skin.[41] The scale is currently being implemented by Google research across a large range for inclusivity and skin tone representation. The Monk Scale is more inclusive than the Fitzpatrick Scale. Given there can be variation in the printed versions, trained clinical research coordinators make assessments on tablets as often as possible.[42] If a printed version is needed, the high quality version of the Monk Scale is used in OPTI-OXYGEN. Predictive and prognostic associations between skin tone scale and spectrometric analysis, with the direction and variability of SpO2-SaO2 bias as well as secondary hospital outcomes, will be included in the analysis. OPTI-OXYGEN will be able to provide a large, diverse dataset in critically ill hospitalised patients with standardised techniques for skin pigment quantification.

Limitations

Most ICU protocols are steering away from frequent arterial blood gas measurements, so the ability to correlate SpO2 and SaO2 over time in individual patients may be limited. The requirement of an ABG during a steady

state in all intubated patients may be contrary to the current practice. However, given the documented prevalence of occult hypoxaemia due to SpO2-SaO2 bias and consequential association with worse hospital outcomes, prospective correlation is necessary for both research and clinical identification of balanced oxygen supplementation. We remain cautious of the possibility that SpO2-SaO2 bias on the initial ABG may vary during the course of hospitalisation. However, we will be collecting data throughout the study to analyse and account for unexpected bias variations. Finally, in this study design, we are accepting some degree of occult hyperoxaemia while balancing the complexity of the algorithm.

The OPTI-OXYGEN approach: a framework for precision oxygen therapy

To our knowledge, this is the first study to incorporate SpO2 bias to correct oxygenation targets and provide optimised and personalised oxygenation goals in each patient while reducing hyperoxaemia. Personalisation of oxygenation goals may positively affect survival in critically ill patients.[5] OPTI-OXYGEN provides a methodology to implement personalised oxygenation targets. In addition, through the simultaneous measurement of SpO2 and SaO2 paired data within a real-world framework, this research contributes significantly to the development of a comprehensive prospective electronic dataset across a large tertiary care health system, helping in generating large collaborative datasets. OPTI-OXYGEN will contribute data to the FDA-approved Open Oximetry project (openoximetry.org) with the goal to create an open access online data repository and provide collaboration between bringing together oximetry experts, engineers, academic researchers, clinicians, community members, manufacturers and regulatory bodies. Such datasets are pivotal for examining the multifaceted influences on SpO2 bias, including skin tone, illness dynamics and device errors, thereby paving the way for more accurate oxygenation strategies. Our study addresses the urgent need for corrective measures in the clinical application of pulse oximetry, especially as we await longer-term solutions such as the development of new sensor technologies or the recalibration of existing devices. The potential recalibration of pulse oximeters to incorporate correction factors, alongside automated FiO2 titration, is a promising step towards the goal of targeted oxygen therapy. Therefore, OPTI-OXYGEN, with the large, high fidelity dataset, prospective bias measurement and incorporation of corrective factors in an automated algorithm, lays the groundwork for the use of artificial intelligence in oxygenation management.

Current status of this trial

This trial is currently active and enrolling. Enrolment began 15 January 2024. Data collection will conclude 15 March 2025 with anticipated data analysis concluding 30 September 2025.

Information can be found under Clinicaltrials.gov Identifier (NCT 05923853).

Author affiliations
[1]Division of Pulmonary, Critical Care and Sleep Medicine, The Ohio State University, Columbus, Ohio, USA
[2]Davis Heart and Lung Research Institute, The Ohio State University, Columbus, Ohio, USA
[3]Department of Respiratory Therapy, The Ohio State University, Columbus, Ohio, USA
[4]Ohio University Heritage College of Osteopathic Medicine Dublin Campus, Dublin, Ohio, USA
[5]Center for Biostatistics, The Ohio State University, Columbus, Ohio, USA
[6]Department of Medicine, Pulmonary and Critical Care Unit, Massachusetts General Hospital Institute for Patient Care, Boston, Massachusetts, USA
[7]Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

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ORCID iD
Jonathan Peters http://orcid.org/0000-0003-1322-986X

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