

**Strategy to Avoid Excessive Oxygen using
Autonomous Oxygen Titration Intervention**

Short Title: SAVE-O2 AI

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the Medical Technology Enterprise Consortium (MTEC) Terms and Conditions of Award. The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SYNOPSIS

Study Title	Strategy to Avoid Excessive Oxygen (SAVE-O2) using Autonomous Oxygen Titration Intervention
Short Title	SAVE-O2 AI
Study Phase	Phase III
Device Description	The PRO100 device is an oxygen titration device developed by the company O2matic. The PRO100 device allows clinicians to set an oxygen titration (SpO2) range, then continuously and automatically administers and titrates the patient's oxygen flow rate to achieve the target SpO2 range. Operating on a closed-loop/autonomous oxygenation principle and supplied by a commercially available pulse oximeter for SpO2 input and a standard oxygen source, this device will continuously monitor the patient's SpO2 and adjust the O2 flow rate between 0 and 15 liters per minute (lpm) until the patient achieves oxygenation within the SpO2 range, is fully weaned from supplemental oxygen, or requires higher flow oxygen support. This approach may reduce the risk of complications from hypoxemia and hyperoxemia.
Brief Summary	Ensuring adequate oxygenation is a primary goal in surgical and medical patients to treat and prevent morbidity associated with hypoxemia. However, excessive oxygen administration resulting in hyperoxemia is common, leading to unnecessary utilization of supplemental oxygen, which is a particularly limited resource in austere settings. Building on the previous Strategy to Avoid Excessive Oxygen (SAVE-O2) clinical trials ¹ (Trauma: NCT045349559; Burn: NCT04534972), we seek to determine effective strategies to implement a targeted normoxemia approach to avoid both hyperoxemia and hypoxemia and reduce supplemental oxygen use, using the PRO100 closed loop/autonomous oxygen system. This research is critical for both military and civilian care settings in determining the effectiveness of an autonomous oxygen system to use to 1) reduce harm associated with both hypoxemia and hyperoxemia and 2) reduce excess use of oxygen .
Methodology	This study is a multicenter randomized controlled trial to determine the effectiveness of a closed loop/autonomous oxygen titration system (O2matic PRO100) to maintain normoxemia (goal range SpO2 90-96%, target 93%) during the first 72 hours of acute injury or illness, compared to standard provider-driven methods (manual titration with SpO2 target of 90-96%). The target population will focus on adults with major trauma, acute care surgery, burn, and respiratory illness, who are hospitalized and receive supplemental oxygen, but not high flow oxygen or mechanical ventilation. We will enroll up to 300 patients at four level 1 trauma centers in the United States within 36 hours of hospitalization and randomize to receive autonomous versus manual oxygen titration for up to 72 hours. We have chosen a consensus-based normoxemia target based on thresholds defined in our prior work^{2,3}, which included experts from our proposed sites. Regardless of randomization group, normoxemia range will be SpO2 90-96% with a target of 93%. The intervention will start upon randomization within 36 hours of hospitalization and will continue for the first 72 hours after randomization, or hospital discharge, escalation to high flow nasal oxygen/mechanical ventilation, or death, if sooner. The goal is to increase time within the normoxemia range and reduce the use of supplemental oxygen.
Primary Objectives	(1) <u>Determine the effectiveness of an autonomous oxygen titration system to improve normoxemia and reduce hypoxemia and hyperoxemia in acutely injured and ill patients receiving supplemental oxygen.</u> We will compare patient-hours spent in normoxemia (SpO2 90-96%), hypoxemia (SpO2 <88%), and hyperoxemia (SpO2 >96%) among patients randomized to autonomous vs manual oxygen titration. (2) <u>Determine the impact of an autonomous oxygen titration system on overall utilization of supplemental oxygen.</u> We will compare the total volume of supplemental oxygen administered to patients randomized to autonomous vs manual oxygen titration during the 72-hour intervention period.
Primary Endpoints	The primary endpoint is proportion of time spent within the targeted normoxemia range, defined as a SpO2 range of 90-96% (target 93%), as measured by continuous non-invasive pulse oximetry, during the first 72 hours after randomization.

Secondary Endpoints	1. Amount of supplemental oxygen administered, defined as total estimated oxygen volume during the first 72 hours after randomization. 2. Proportion of time spent in hypoxemia (SpO₂ <88%) during the first 72 hours after randomization. 3. Proportion of time spent in hyperoxemia (SpO₂ >96%) during the first 72 hours after randomization. 4. Time to Room Air, defined as the time from hospital presentation to the first episode of no supplemental oxygen (room air), censored at discharge or death.
Exploratory Endpoints	1. Supplemental O₂ free days (SOFD) defined as number of days alive and not on supplemental oxygen during the index hospitalization, censored at hospital discharge. Patients who are discharged without supplemental oxygen or with prior volume of baseline (pre-hospitalization) home oxygen are assumed to remain without additional supplemental oxygen to day 28. Patients who are discharged on supplemental oxygen, if above any prior baseline home oxygen therapy, are assumed to have additional supplemental oxygen to day 28. 2. All-cause mortality to day 28, defined as a dichotomous vital status (survived or died) at hospital discharge or day 28, whichever is first. 3. Respiratory failure, defined as receipt of high flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation, to day 28 or hospital discharge, whichever is first, excluding time in the operating room. 4. Hospital-free days to day 28 (HFD28) defined as the number of days alive and outside the hospital between the initial ED visit and 28 days later, censored at hospital discharge. This outcome is a composite of in-hospital mortality and length of hospital stay and has a range of 0 days (worst outcome) to 28 days (best outcome). Patients discharged to any location prior to day 28 are assumed to survive to day 28 and will be assigned 28 minus hospital length of stay hospital-free days. 5. Duration of time receiving no supplemental oxygen (room air) during the first 72 hours after randomization.
Study Population	Eligible patients will include adults (age 18 years or older) hospitalized from the Emergency Department (ED) with major trauma, burn patients, acute care surgery, or acute respiratory illness. We anticipate the study population to be representative of that of the area around the enrolling hospitals without specific selection of subjects based on sociodemographic characteristics.
Number of Subjects	Up to 300 patients will be enrolled in this study
Number of Centers	Four (4) hospitals in the United States will participate in this study. Each hospital will aim to enroll approximately 75-100 patients.
Duration of Subject Participation	Each patient will receive the intervention for up to 72 hours and will be followed to day 28 or hospital discharge, whichever is first, for secondary endpoints.
Inclusion Criteria	In order to be eligible to participate in this study, an individual must meet all of the following criteria: • Age 18 years or older • Hospitalized or will be hospitalized from Emergency Department for major trauma, burn, acute care surgery, or acute respiratory illness • Able to be randomized within 36 hours of hospital arrival • Receiving supplemental oxygen 1-10 liters per minute for documented or presumed hypoxemia (must be higher than baseline for those on chronic oxygen therapy) • Signed and dated informed consent from patient or legally authorized representative (LAR)
Exclusion Criteria	An individual who meets any of the following criteria will be excluded from participation in this study: • Anticipated hospital discharge within 24 hours • Imminent plans to discontinue supplemental oxygen • Imminent plans to administer high flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation

	• Clinical team unwilling or unable to follow the prescribed oxygen titration method in either randomized group • Known prisoner • Known pregnancy • Known contraindicated conditions for use of the PRO100 device: carbon monoxide poisoning, incapable of handling airway secretions, increased methemoglobin, cyanide poisoning, cluster headaches, undrained pneumothorax, sickle cell crisis, paraquat poisoning or a history of bleomycin poisoning, patients for whom the SpO₂ signal is not stable
Statistical Methodology	The primary analysis will be as-randomized (i.e., intention to treat). The primary outcome, proportion of time spent in normoxemia, is a continuous, patient-level measure ranging from 0 to 1. The difference in mean proportion of time spent in normoxemia will be compared between the two treatment arms using a two-sample t test. With two-sided alpha of 0.05 and a planned sample size of 300 total participants, there estimated power of >90% to detect an absolute difference in mean proportions of 0.1. Secondary outcomes will be compared between arms using statistical methods appropriate to each type of outcome (e.g., two-sample test of proportions to compare respiratory failure rates between arms).

LIST OF ABBREVIATIONS

AC = Alternating Current Power
AE = Adverse Events
AIS = Abbreviated Injury Scale
APACHE = Acute Physiology and Chronic Health Evaluation
ARDS = Acute Respiratory Distress Syndrome
BMP = Basic Metabolic Panel
CA = Competent Authority
CBC = Complete Blood Count
CCC = Clinical Coordinating Center
CFR = Code of Federal Regulations
CI = Confidence Interval
CMP = Clinical Monitoring Plan
COMIRB = Colorado Multiple Institutional Review Board
COPD = Chronic Obstructive Pulmonary Disease
COVID-19 = Coronavirus Disease of 2019
DCC = Data Coordinating Center
DoD = Department of Defense
DSMB = Data and Safety Monitoring Board
DSMP = Data and Safety Monitoring Plan
eConsent = Electronic Consent
eCRF = Electronic Case Report Form
ED = Emergency Department
EHR = Electronic Health Record
FDA = U.S. Food and Drug Administration
FHIR = Fast Healthcare Interoperability Resource
FiO₂ = Fraction of Inspired Oxygen
GCP = Good Clinical Practice
HFD28 = Hospital Free Days to Day 28
HFNO = High Flow Nasal Oxygen
ICC = Interclass Correlation Coefficient
ICH = International Conference on Harmonisation
ICU = Intensive Care Unit
IDE = Investigational Device Exemption
IEC = Independent Ethics Committee
IMV = Invasive Mechanical Ventilation
IRB = Institutional Review Board
ISS = Injury Severity Score
LAR = Legal Authorized Representative
LFT = Lipid Fat
LPM = Liters Per Minute
MST = Monk Skin Tone

SAVE-O2 AI

MRI = Magnetic Resonance Imaging

MTEC = Medical Technology Enterprise Consortium

NCT = National Clinical Trial

NIV = Non-Invasive Ventilation

O2 = Oxygen

OHRP = Office for Human Research Protections

OR = Operating Room

ORHO = Office of Human Research Oversight

PaO2 = Partial Pressure of Oxygen in Arterial Blood

PCLC = Physiological Closed-Loop Control

PDF = Portable Document Format

PHI = Protected Health Information

PI = Principal Investigator

PT/PTT/INR = Prothrombin Time/Partial Thromboplastin Time/International Normalized Ratio

QC = Quality Control

SAE = Serious Adverse Event

SAP = Statistical Analysis Plan

SAVE-O2 = Strategy to Avoid Excessive Oxygen

sIRB = Single IRB

SOFD = Supplemental Oxygen Free Days

SOP = Standard Operating Procedure

SpO2 = Oxygen saturation via pulse oximetry

TBSA = Total Body Surface Area

TCCC = Tactical Combat Casualty Care

UAP = Unanticipated Problem

U.S. = United States

VUMC = Vanderbilt University Medical Center

WOCBP = Women of Childbearing Potential

1. INTRODUCTION

1.1 Background and Significance

Ensuring adequate oxygenation is a primary goal in acute care to treat and prevent morbidity associated with hypoxemia in ill and injured patients. However, excessive oxygen and hyperoxemia is common in both civilian and military patients leading to unnecessary utilization of supplemental oxygen, a limited resource in austere settings. In our prior **Strategy to Avoid Excessive Oxygen (SAVE-O2)** clinical trials in critically injured and major burn patients, we found that titration to oxygen saturation of 90-96% (normoxemia) safely reduced use of supplemental oxygen and exposure to hyperoxemia, without increasing hypoxemia and improved the primary outcome of supplemental oxygen free days.³ The U.S. Department of Defense has recently explored the use of **closed loop/autonomous oxygen titration systems** for mechanically ventilated patients.⁴⁻⁶ Their initial research indicates an autonomous oxygen titration system is a reliable and cost-effective option for this patient population in low resource environments.^{4,5,7} Most hypoxemic patients receive oxygen at lower flow rates through a nasal cannula or face mask and do not require use of mechanical ventilation.⁸⁻¹¹ However, limited evidence exists on the use of autonomous oxygen titration systems for non-mechanically ventilated patients in acute care.

The **O2matic PRO100** (Herlev, Denmark) currently offers a viable solution as a closed loop/autonomous oxygen titration device. PRO100 operates on AC power, has a small weight and dimension, delivers up to 15 liters per minute, and is specifically designed for non-mechanically ventilated patients. It is compatible with most commercially available portable and standard oxygen systems. The PRO100 system allows providers to set a specific goal SpO2 range, while the device continuously and automatically titrates the flow of supplemental oxygen, based on closed loop principles. Continuous and automated titration can achieve oxygenation target, while optimizing the use of finite oxygen supplies with limited human oversight – freeing providers to perform other tasks. Preliminary data demonstrated that the PRO100 system reduced both hypoxemia and hyperoxemia in patients with COVID-19 pneumonitis and hypoxemic respiratory failure,¹¹ as well as hospitalized and home patients with chronic obstructive pulmonary disease (COPD).^{12,13} This device is cleared for use in 32 countries, including in the European Union, Australia, and New Zealand.

Pursuing the goal of targeting normoxemia, we look to determine effective ways to implement this approach within the use of a closed loop/autonomous oxygen titration system. Employing the PRO100 system will decrease the need for active oxygen titration by personnel, particularly during future multi-domain, large scale combat, and distributed maritime operations. Confronted with these environments, prolonged care paradigms will be common and combat medics and other front-line providers will have substantial limitations relative to the number of anticipated casualties. Therefore, this research is critical to determine the effectiveness of a portable autonomous oxygen system to use in low-resource environments to 1) **reduce potential harm** associated with both hypoxemia and hyperoxemia and 2) **reduce excess use of oxygen**.

1.2 Risk/Benefit Assessment

1.2.1 Known Potential Risks

The intervention arm will focus on utilizing an autonomous oxygenation system by targeting normoxemia to reduce exposure to potentially harmful hyperoxemia. There may be a small risk of increased exposure to hypoxemia episodes during autonomous oxygen titration, but this will be closely monitored. The research team will assist with device set up, quality checks, and reporting to treating physician and Primary Investigator (PI) to minimize the risk of exposure to both hypoxemia and hyperoxemia.

There is a risk associated with randomization because the randomized assignment will drive the method of oxygen titration. This risk will be minimized because the primary clinical team may override the randomization assignment if in the best interest of the study participant's care.

There is also a risk for loss of confidentiality, including inappropriate disclosure of identifiable health information. However, we have taken steps to prevent this occurrence, including use of REDCap for data management, only providing access to investigators and research staff directly involved in the project, providing access to identifiers only at the local site level, and removing identifiers from the data set at the earliest possible opportunity. If data needs to be transferred outside of REDCap, we will use institutional approved method for file transfer and de-identification of data prior to transfer.

1.2.2 Known Potential Benefits

The autonomous oxygenation intervention has potential to benefit individual patients by reducing potential harm associated with both hypoxemia and hyperoxemia. Autonomous titration also may reduce provider burden associated with manual oxygen titration in non-mechanically ventilated patients and reduce the overall use of supplemental oxygen. Results from this trial will help to provide additional data on the impact of reducing supplemental oxygen use, reducing exposure to hypoxemia and hyperoxemia, and provide insight on the use of an autonomous oxygen titration system on utilization of supplemental oxygen. Additionally, the trial will provide information into user-insight from the provider perspective of time spent titrating patient oxygen using an autonomous system versus manual titration. Overall, this research has the potential to improve the care of hospitalized civilian and military patients with acute illness and injury.

1.2.3 Assessment of Potential Risks and Benefits

Federal regulations at 45 CFR 46.111 (a)(2) require “the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.” Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits. The PRO100 device has been cleared for clinical use for hospitalized patients in 32 countries, including in the European Union, Australia, and New Zealand, based on prior research.

2. TRIAL SUMMARY

2.1 Objectives

We propose the following two objectives:

- (1) Determine the effectiveness of an autonomous oxygen titration system to improve normoxemia and reduce hypoxemia and hyperoxemia in acutely injured and ill patients receiving supplemental oxygen. We will compare patient-hours spent in normoxemia (SpO₂ 90-96%), hypoxemia (SpO₂ <88%), and hyperoxemia (SpO₂ >96%) among patients randomized to autonomous vs manual oxygen titration.
- (2) Determine the impact of an autonomous oxygen titration system on overall utilization of supplemental oxygen. We will compare the total volume of supplemental oxygen administered to patients randomized to autonomous vs manual oxygen titration during the 72-hour intervention period.

2.2 Hypothesis

We hypothesize that the use of an autonomous oxygen titration system will be more effective at maintaining normoxemia and reducing time spent in hypoxemia/hyperoxemia than standard manual titration in non-mechanically ventilated patients and will reduce the overall use of supplemental oxygen.

2.3 Preliminary Research

Oxygen therapy has undisputed importance in the care of critically ill medical and trauma patients to treat and prevent morbidity associated with hypoxemia.^{4,5} Emerging evidence suggests that hyperoxemia may be harmful for both mechanically ventilated and non-mechanically ventilated patients, emphasizing the urgency to determine oxygen titration needs in specific high-risk populations, such as major trauma and burn patients, throughout combat casualty care. Previous observational and clinical trials have demonstrated an association between hyperoxemia exposure and mortality,¹⁴⁻¹⁷ in-hospital pulmonary complications,¹⁸ and non-respiratory organ failure.¹⁹ In burn patients, reactive oxygen species and free radicals are particularly important as they are detrimental to burn wound healing and conversion from partial to full thickness burns.²⁰⁻²³

Early clinical trials of medical patients support the safety of a targeted normoxemia approach, where normoxemia is defined as a target oxygen saturation (SpO₂) of 88-96%.^{15,24,25} Recent large clinical trials in primarily medical (non-trauma/surgical) patients have demonstrated safety and similar clinical outcomes across a range of SpO₂ targets.²⁶⁻²⁸ However, limited data exist for trauma, burn, and surgical patients.

Accordingly, we convened a Delphi consensus panel of 31 nationally and internationally recognized military and civilian experts in trauma surgery, emergency medicine, critical care, and military operational medicine convened to create a targeted normoxemia strategy.² This panel developed a consensus-based definition of normoxemia: SpO₂ 90-96% or PaO₂ 60-100 mmHg. Utilizing this definition of targeted normoxemia, investigators within the SAVE-O2 network performed an observational study of study of critically injured patients at two level I trauma centers and one level II trauma center in Colorado between October 2015 and June 2018. Results suggested that during periods of

hyperoxemia, higher oxygen administration (FiO₂) was associated with a greater risk of mortality.²⁵ This was followed by a pre/post quasi-experimental pilot study to demonstrate the safety and feasibility of targeting normoxemia in this patient population.³ Building off this pilot work, investigators from the SAVE-O2 network performed a multicenter pragmatic clinical trial implementing a multimodal education and informatics intervention of targeted normoxemia (SpO₂ 90-96%), centered around limiting excessive supplemental oxygen administration and reducing exposure to potentially harmful hyperoxemia.¹ Preliminary results demonstrate that implementation of targeted normoxemia was safe, improved the primary outcome of supplemental oxygen free-days, and was associated with improvements in secondary outcomes (hospital-free days, mortality). However, the implementation relied on manual oxygen titration by front-line providers, which still led to higher than recommended use of supplemental oxygen in the trial.

Building from these preliminary results, the investigators of the SAVE-O2 AI study seek to combine the concept of normoxemia with a closed loop/autonomous oxygen titration system to reduce hyperoxemia in critically ill and injured patients. A closed loop/autonomous oxygen titration system is a physiological closed-loop control (PCLC) system. PCLC combines physiologic patient monitoring through sensors (pulse oximeter) with computational algorithms to continuously monitor a patient's health and deliver optimized therapeutic actions. The focus of the current study is the **O2matic PRO100** (Herlev, Denmark), as described in Section 1.1.

In general, PCLC systems are currently being pursued as a solution to a variety of broad medical challenges affecting patient quality of life, hospital financial burdens, rehabilitation, and emergency and intensive care. Autonomous oxygen titration systems also have the potential to reduce provider workload and associated resource cost while maintaining patient quality of care. A cost-effective analysis of an autonomous oxygen titration system versus manual oxygen-titration technology in one acute care hospital in Quebec, QC, Canada (n=47) found the autonomous device generated 20.7% savings per-patient costs at 180 days. Patients in the intervention arm experienced fewer days receiving supplemental oxygen than those in the control group.²⁹ An open-label randomized parallel group trial in New Zealand (n=20) found the number of FiO₂ adjustments by nursing staff was comparable in the manual versus autonomous oxygen titration groups, suggesting that the autonomous system may have the same or similar amount of titration input as clinical staff.³⁰

Other clinical studies have investigated the use of a closed loop oxygen titration system in mechanically ventilated patients. These include pediatric patients, medical intensive care unit (ICU) patients, and those with Acute Respiratory Distress Syndrome (ARDS). In these studies, time spent within the desired oxygenation range was significantly higher in the automatic titration group than in the manual titration group.^{6,33,34} The use of a closed loop/autonomous oxygen titration system in mechanically ventilated patients may, therefore, be a reliable and cost-effective solution in austere environments to reduce hyperoxemia. However, limited evidence exists to guide the use of autonomous oxygen titration devices in non-mechanically ventilated patients.

One recent clinical trial in Spain evaluated the use of a closed-loop oxygen system for acute hypoxemic respiratory failure patients receiving high flow nasal oxygen.⁷ In this single-center, single-blinded, randomized crossover study (n=45), patients randomized to the closed-loop oxygen control system spent more time in the optimal SpO₂ range compared to those who received manual titration (96.5 [93.5 to 98.9] % vs. 89 [77.4 to 95.9] %; $p < 0.0001$) (difference estimate, 10.4 (95% confidence interval 5.2 to 17.2)). Additionally, patients spent less time in suboptimal ranges, both above (0.6 [0.1 to 1.1] % vs. 1.0 [0.1 to 4.0] %; $p = 0.0053$) and below (2.3 [0.8 to 5.2] % vs. 4.2 [1.1 to 16.4] %; $p = 0.0004$) the cut-offs for the optimal SpO₂ range. Patient oxygen consumption during time above the optimal SpO₂ range was significantly lower in the closed-loop oxygen group. Sandal et al. similarly compared the use of a closed loop oxygenation system versus manual titration for pediatric patients receiving high flow nasal oxygen at a single Pediatric ICU in Turkey (n=23).³² Patients in the closed-loop oxygen group spent more time in the optimum SpO₂ range compared to those in the manual oxygen titration group [91.3% (IQR 78.4-95.1%) vs. 63.0% (IQR 44.4-70.7%)], mean difference [28.2% (95%-CI 20.6-37.8%); $P < 0.001$]. The median number of manual adjustments was lower with closed-loop oxygen control [0.0 (IQR 0.0-0.0) vs. 0.5 (IQR 0.0-1.0); $P < 0.001$].

Several other recent clinical trials from Canada and Europe evaluated the use of closed loop/autonomous oxygen titration systems in COPD patients, including the O2Matic PRO100. Results show patients using automatically titrated O₂ flow spent a greater amount of time within a predefined oxygen range,³³ had increased walking distance,^{34,13} spent less time in hypoxemia,^{35,12} and experienced a shorter duration of hospitalization³⁶ compared to patients receiving manual oxygen titration and pulse dose oxygen therapy.

3. STUDY DESIGN AND OUTCOMES

3.1 Overall Study Design

This study will be a **multicenter randomized controlled trial** to determine the effectiveness of using a closed loop/autonomous oxygen system (O2matic PRO100) to maintain normoxemia (oxygen saturation 90-96%, target SpO₂ 93% during the first 72 hours of acute injury or illness, compared to standard provider-driven methods (manual titration). Given the nature of the intervention, we will not blind the primary clinical team, patient, or implementation research team. However, the outcomes assessment is primarily electronic and will be blinded to the randomized group.

The target population will focus on major trauma, acute care surgery, burn, and acute respiratory illness patients who are hospitalized and receiving supplemental oxygen, but not invasive mechanical ventilation. We will enroll up to 300 patients at four level 1 trauma centers within 36 hours of hospitalization and randomize to receive autonomous versus manual oxygen titration for up to 72 hours. All four sites are geographically distant, level 1 trauma centers with previously established data collection systems. The trial will have two stages: the first stage will be for feasibility with a DSMB review after 40-50 patients have been enrolled. The second stage will be for efficacy. Both stages will evaluate safety. See also section [7.4 Interim Analysis](#).

We will employ a consensus-based and data-informed normoxemia target based on thresholds defined in our prior work, which included experts from our proposed sites: oxygen saturation (SpO₂) 90-96% and, when available, arterial oxygen pressure (PaO₂) 60-100 mmHg. Regardless of randomization group, oxygen saturation will target 90-96% with the goal SpO₂ of 93%. The intervention will start after informed consent and randomization and will continue for 72 hours after randomization. We aim to improve time spent in normoxemia, while decreasing time spent in hypoxemia and hyperoxemia and the overall use of supplemental oxygen.

3.1.1 Interventions in Both Arms

Enrolled participants in both trial arms will have a SpO₂ target of 93% with an acceptable range of 90-96%. This is based on prior work, suggesting this is a safe target in acutely ill patients and potentially improves outcomes in non-mechanically ventilated trauma patients.¹ In the current study, the randomized study intervention focuses on the method of implementing this oxygenation target (manual vs automated oxygen titration). All other aspects of clinical care, including frequency of vital sign assessments, level of care, use of specific oxygen devices (e.g., nasal cannula or face mask) and escalation to high flow oxygen devices or mechanical ventilation will be determined by the primary clinical team, per usual care. The recommended maximum flow rate will be 8 lpm for standard (non-humidified) nasal cannula and 15 lpm for humidified nasal cannula and face mask.

3.1.2 Usual Care (Manual Titration) Arm

Patients randomized to the usual care arm will receive usual care, manual oxygen titration, removal of supplemental oxygen, and escalation per hospital protocol, based on the site's usual SpO₂ assessments. The SpO₂ monitor for the O2matic PRO100 will also be connected to the patient in observation mode for data collection purposes only (not used for titration decisions). The recommended SpO₂ target will be 93% with an acceptable range for the protocol of 90-96%, which will be communicated daily to the clinical team during the intervention period. Oxygen titration, weaning/discontinuation, escalation to high flow oxygen devices or mechanical ventilation, and specific oxygen delivery devices used will occur per usual clinical practice, including the frequency of vital sign/SpO₂ assessments.

3.1.3 Intervention (Automated Titration) Arm

Patients randomized to the intervention arm will receive supplemental oxygen via nasal cannula or face mask and will have supplemental oxygen titrated using an autonomous oxygen titration system for the first 72 hours after randomization, or hospital discharge (whichever sooner). If the patient's provider wishes to keep the patient on a standard (non-humidified) nasal cannula on a higher flow rate (exceeding the 8 lpm recommendation) or to use a face mask on a flow rate (under the 8 lpm recommendation), that is appropriate and will not be considered a protocol deviation; however, the study team will program the PRO100 device to provide a maximum oxygen flow rate of 8 lpm if non-humidified nasal cannula is being used. If the patient requires > 8lpm, the PRO100 device will be programmed to provide a maximum oxygen flow rate of 15 lpm and recommend the patient receive oxygen via face mask or humidified oxygen though larger bore nasal cannula in order to reduce unfavorable outcomes related to administration of non-humidified high flow nasal oxygen. The patient will be monitored and vital signs documented by the site's usual SpO₂ assessments, but oxygen titration should occur automatically through the O2matic PRO100 device during the intervention period, unless there is a safety concern.

The recommended SpO₂ target will be 93% with a range programmed into the PRO100 device at 92-94%. Specifically, the device targets the lower programmed SpO₂ value +1 (i.e., 93% in this case). Overall, the acceptable SpO₂ range for the protocol is 90-96%. If a patient requires >15 lpm or other signs of advancing respiratory failure, they will be taken off the autonomous oxygen system and transitioned to higher flow oxygen devices or mechanical ventilation per usual clinical care. If the patient is not receiving any supplemental oxygen per the device's autonomous titration, the clinical team may remove the oxygen delivery device (e.g., nasal cannula) from the patient, but the patient should remain connected to the PRO100 device for the duration of the intervention period for data collection and to monitor for new supplemental oxygen needs.

3.1.4 Other Study Procedures

For enrolled participants in both trial arms, we will scan the inner forearm to quantify skin pigmentation using the Nix Spectro 2 (5 mm) device, a non-invasive spectrophotometer used for color matching in a multitude of commercial uses including cosmetics and medical/life sciences. The Nix Spectro 2 (5 mm) uses 8x broad spectrum white, violet, and ultraviolet light to evaluate spectral data across the visible spectrum (400-700 nm). The colorimetry data provided by the Nix device will be documented using RGB, HEX, and CIELAB values. The patient's skin values will first be recorded in the Nix Toolkit app on a password protected device (iPad, computer, etc.) used by the research coordinators. Research personnel will manually enter those values into REDCap by subject ID number, and the original value documented in the app will be immediately deleted. No patient identifying information will be entered into the Nix Toolkit app. For additional device specifications, please see [Appendix B](#).

3.2 Device Information

The **O2matic PRO100** (Herlev, Denmark) device currently offers a viable solution as a closed loop/autonomous oxygen titration device. The PRO100 device is a trend-based automated oxygen regulator that delivers oxygen through standard devices such as nasal cannula and facemask. This light-weight device operates on AC power and is specifically designed for non-mechanically ventilated patients. It is compatible with most commercially available portable and standard oxygen systems. The PRO100 system allows providers to set a specific oxygen saturation (SpO₂) range, with a minimal allowed range of 3% between minimum and maximum values. The device then continuously and automatically titrates the flow of supplemental oxygen, based on closed loop principles, to achieve the SpO₂ range while optimizing the use of limited oxygen supplies and time/attention of providers. Safety alarms are set to notify providers based on specific SpO₂ and oxygen volume parameters. Preliminary data demonstrated that the PRO100 system reduced both hypoxemia and hyperoxemia in patients with COVID-19 pneumonitis and hypoxemic respiratory failure.⁸ This device is cleared for use in 32 countries. For additional device specifications see [Appendix A](#).

3.3 Randomization

Randomization assignments are 1:1 to intervention or usual care at the patient level and treatments are assigned at randomization. Randomization will be implemented using an electronic system (REDCap) and the variable permuted block technique; treatment assignments in this two group trial will utilize a block size between four and eight. Employing the permuted block technique ensures balance across the intervention and control groups at regular enrollment intervals within each site, thus reducing the possibility of unequal distribution across arms for which the participant is eligible. Additionally, randomization will be stratified by site and patient subgroup (trauma/burn/surgical vs medical) to optimize balance across these key characteristics.

3.4 Table of Events

Table of Events					
Day	0	1	2	3	28 or Hospital Discharge
Eligibility & Baseline Data					
Assess eligibility	X				
Informed consent	X				
Baseline data collection	X				
Study Intervention Data					
Randomization	X				
Implementation of study intervention	X	X	X	X	

Device data	X	X	X	X	
Hospital Data					
Oxygenation data	X	X	X	X	X
Secondary outcomes and safety assessment	X	X	X	X	X
Adverse event and unanticipated problem monitoring	X	X	X	X	X
Hospitalization summary data					X

3.5 Study Outcomes

3.5.1 Primary Endpoint

The primary endpoint is proportion of time spent within the targeted normoxemia range, defined as an oxygen saturation (SpO₂) of 90-96% (target 93%), as measured by continuous non-invasive pulse oximetry, during the first 72 hours after randomization, censored at hospital discharge, escalation to high flow nasal oxygen/mechanical ventilation, or death if prior to 72 hours.

3.5.2 Secondary Endpoints

- (1) **Amount of supplemental oxygen administered**, defined as total estimated oxygen volume during the first 72 hours after randomization.
- (2) **Proportion of time spent in hypoxemia** (SpO₂ <88%) during the first 72 hours after randomization.
- (3) **Proportion of time spent in hyperoxemia** (SpO₂ >96%) during the first 72 hours after randomization.
- (4) **Time to Room Air**, defined as the time from hospital presentation to the first episode of no supplemental oxygen (room air), censored at discharge or death.

3.5.3 Exploratory Endpoints

- (1) **Supplemental O₂ free days (SOFD)** defined as number of days alive and not on supplemental oxygen during the index hospitalization, censored at hospital discharge. Patients who are discharged without supplemental oxygen or with prior volume of baseline (pre-hospitalization) home oxygen are assumed to remain without additional supplemental oxygen to day 28. Patients who are discharged on supplemental oxygen, if above any prior baseline home oxygen therapy, are assumed to have additional supplemental oxygen to day 28.
- (2) **All-cause mortality to day 28**, defined as a dichotomous vital status (survived or died) at hospital discharge or day 28, whichever is first.
- (3) **Respiratory failure**, defined as receipt of high flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation, to day 28 or hospital discharge, whichever is first, excluding time in the operating room.
- (4) **Hospital-free days to day 28 (HFD28)** defined as the number of days alive and outside the hospital between the initial ED visit and 28 days later, censored at hospital discharge. This outcome is a composite of in-hospital mortality and length of hospital stay and has a range of 0 days (worst outcome) to 28 days (best outcome). Patients discharged to any location prior to day 28 are assumed to survive to day 28 and are assigned 28 minus hospital length of stay hospital-free days.
- (5) **Duration of time receiving no supplemental oxygen** (room air) during the first 72 hours after randomization.

4. STUDY POPULATION AND ENROLLMENT

4.1 Population

Eligible patients will include adults (age 18 years or older) hospitalized from the Emergency Department with major trauma, burn patients, acute care surgery, or acute respiratory illness. For the purpose of this clinical trial, acute respiratory illness will be defined as primary or secondary lung processes that lead to hypoxemia, such as: respiratory tract, pulmonary embolism, pleural effusion, pulmonary edema, COPD exacerbation, asthma exacerbation,

pulmonary contusion, aspiration, or other cause of acute hypoxemic respiratory insufficiency/failure. Altered mental status or sedation as the primary cause of hypoxemia will not qualify as acute respiratory illness. There will be no specific selection of subjects based on sex, race or ethnicity, age, or socioeconomic status; efforts will be made to enroll a diverse cohort. We anticipate the study population to be representative of that of the area around the enrolling hospitals.

4.2 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Age 18 years or older
- Hospitalized or will be hospitalized from Emergency Department for major trauma, burn, acute care surgery, or acute respiratory illness
- Able to be randomized within 36 hours of hospital arrival
- Receiving supplemental oxygen 1-10 lpm for documented or presumed hypoxemia (must be higher than baseline for those on chronic oxygen therapy)
- Signed and dated informed consent from patient or legally authorized representative (LAR)

4.3 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Anticipated hospital discharge within 24 hours
- Imminent plans to discontinue supplemental oxygen
- Imminent plans to administer high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation
- Clinical team unwilling or unable to follow the prescribed oxygen titration method in either randomized group
- Known prisoner
- Known pregnancy
- Known contraindicated conditions for use of the PRO100 device: carbon monoxide poisoning, incapable of handling airway secretions, increased methemoglobin, cyanide poisoning, cluster headaches, undrained pneumothorax, sickle cell crisis, paraquat poisoning or a history of bleomycin poisoning, patients for whom the SpO2 signal is not stable

4.4 Justification for Exclusion Criteria

We aim to study the impact of early interventions within a pre-hospital and hospital setting and thus exclude people who are admitted to the enrolling hospital Emergency Department after 36 hours of injury. In addition, the goal is to have enough duration of time on protocol to assess differences between randomized groups. We will also exclude patients for whom oxygen titration with the PRO100 device is contraindicated.

4.5 Assessment of Eligibility and Exclusion Criteria

For patients who appear to meet inclusion criteria during pre-screening, a paper/electronic pre-screening form will be completed to determine eligibility and track exclusions. The (paper/electronic) pre-screening form will be accessed and stored in the electronic pre-screening database. If the patient appears to meet all eligibility criteria, the site investigator or research coordinator will approach the treating clinician and clinical team either in person, phone, electronic health record (EHR) secure chat, or other accepted local method to ask permission to approach the patient or LAR to confirm eligibility, discuss potential study recruitment, and proceed with informed consent.

For excluded patients, including refusal by the treating clinician/clinical team or patient/LAR, a small number of de-identified pre-screening variables will be collected including: month and year the patient met pre-screening criteria, age, sex, race/ethnicity (if available), and reason(s) the patient was excluded.

4.6 Recruitment Process and Screening Procedures

We will recruit study-eligible patients (or LARs) from the participating hospital Emergency Department or inpatient unit. Recruitment will occur within 36 hours of hospital arrival per eligibility criteria. Research staff will use the EHR to

screen potentially eligible patients using the include/exclusion criteria listed above. Upon identification of a patient meeting all inclusion and no exclusion criteria, patients will be approached by study research personnel (either site investigator or research staff) to obtain written informed consent prior to initiation of any study activities.

4.7 Process of Obtaining Informed Consent

Consent forms describing in appropriate detail the study interventions, study procedures, and risks will be given to the participant and/or their LAR. Consent forms will be IRB approved and the subject/LAR will be asked to read and review the document. A verbal explanation will also be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates and think about it prior to agreeing to participate. The patient/LAR will sign the informed consent document prior to any study procedures being conducted. The patient/LAR will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the enrolled participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. A witness signature will be included on the consent form when appropriate. However, a signature of the study personnel completing the consent is included and required. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If a subject is determined to not have capacity for consent due to the nature of their injury/injuries or other mental impairment, the LAR will be identified and approached for consent. If and when the study participant regains capacity during the hospitalization, attempts will be made to approach the participant for continued study participation. *Specifically at the University of Colorado*, a proxy consent may be used if no LAR is identified in the patient's EHR. The process of obtaining proxy consent is outlined in [Colorado Revised Statute 15-18.5-103](#) and the [Colorado Proxy Decision-Makers for Medical Treatment Act](#). Most notably, under section 15-18.5-103(2), a court or the attending physician must make a determination that an adult patient lacks decisional capacity to provide informed consent, and it must be documented in the patient's medical record. Second, section 15-18.5-103(3) states that the "interested parties" must decide who among them will make decisions regarding the care of the patient. The "interested parties" are defined as "the patient's spouse, either parent of the patient, any adult child, sibling, or grandchild of the patient, or any close friend of the patient." The medical record must document the specific procedures that are followed in this determination of a proxy decision-maker.

In addition to the traditional paper consent process, we will utilize a 21 CFR Part 11 compliant electronic consent (eConsent) process in REDCap, as an available consent method. The consent procedures outlined above will be used as part of the eConsent process rather than paper consent. At the end of the conversation, the patient/LAR will be asked to complete the eConsent Survey via REDCap using the patient/LAR or study-provided device. The research team and witness signatures will also be documented via REDCap. If the subject lacks decisional capacity and the LAR is not physically present in the ED for consent, the LAR will be contacted via telephone to discuss the study. The same process for informed consent, including explanation of the consent process, study, and opportunity for questions, will occur via telephone. The LAR, if in agreement to participate, will be sent a REDCap link for eConsent. If the LAR does not have access to REDCap, we will attempt remote consent, where the consent is emailed to the LAR for review, the study team will review via telephone the consent process and study procedures. If the LAR agrees to participation, they will sign the consent and email the signed consent back to the study team. For both paper and electronic Consent, subject/LAR will be offered a copy of their signed consent form.

The information for the informed consent discussion will be provided in an informed consent document (or electronic equivalent) that has been approved by the single IRB (sIRB) and in a language comprehensible to the potential participant, using an interpreter if necessary. We will have fully translated consent forms for commonly encountered languages at enrolling sites, or a short-form consent for less commonly encountered languages, and a qualified interpreter will be employed. Use of an interpreter and the interpreter's identity will be documented on the paper/electronic consent.

4.8 Vulnerable Subjects

Prisoners will not be enrolled due to their protected status and difficulty obtaining follow-up for the primary outcome after hospital discharge. Children will not be enrolled because this device has not been tested nor approved for individuals under 18 years of age.

Pregnant women will not be enrolled due to uncertainty of oxygen targets for pregnant women and their fetuses.

This trial may include participants who have diminished or no capacity to consent but for whom a LAR may provide consent. Patients without the capacity to consent for themselves may have a potential for direct benefit by participating in this trial, therefore, consent capacity will be determined by the treating physician based on the standard clinical assessment of capacity and communicated to the study team; if it is determined that the patient lacks the capacity to consent at enrollment, consent will be obtained from the LAR before any study-related procedures begin. The participant's capacity will be monitored throughout the study by working with the treatment team. If the participant regains the capacity to consent, they will be approached by the study team for reconsent, including being informed of their participation in the study and having an opportunity to withdraw from further participation in the study. Consent from a LAR for a person lacking decision-making capacity will conform to local legal requirements.

4.9 Strategies for Recruitment and Retention

Individual sites will be responsible for developing strategies for recruitment. Such strategies may include EHR patient reports, listings of eligible patients, or in-person patient-clinical team encounters. Patients admitted to participating sites who meet eligibility criteria may be reviewed by the study team for recruitment until study enrollment goals have been met.

4.10 Duration of Study Procedures

Duration of study participation is for 28 days maximum from randomization, or hospital discharge, whichever is sooner. Please reference [3.4 Table of Events](#) for additional information regarding timing of study procedures.

5. STUDY INTERVENTION

5.1 Study Intervention Description

The study intervention will begin within 36 hours of patient arrival to the hospital and within two hours of patient randomization. The study intervention will continue for the first 72 hours after randomization and will be monitored by the study investigators, study staff, and the patient's care team.

Enrolled participants in both trial arms will have a SpO₂ target of 93% with an acceptable range of 90-96%. The randomized study intervention focuses on the method of implementing this oxygenation target (manual vs automated oxygen titration). All other aspects of clinical care, including frequency of vital sign assessments, level of care, use of specific oxygen devices (e.g., nasal cannula or face mask) and escalation to high flow oxygen devices or mechanical ventilation will be determined by the primary clinical team, per usual care. The study will recommend a maximum of 8 lpm when using a standard (non-humidified) nasal cannula. Oxygen flow rates up to 15 lpm can be used with a face mask or nasal cannula with humidified oxygen. For all participants who require >15 lpm or has other signs of advancing respiratory failure, they will be transition to usual care intervention (e.g., HFNO, NIV, IMV).

Patients randomized to the usual care arm will receive manual oxygen titration per usual care, and patients randomized to the intervention arm will have supplemental oxygen titrated using the autonomous oxygen titration system for the first 72 hours after randomization, or escalation to HFNO/NIV/IMV or hospital discharge if sooner than 72 hours. See section [3.1.2 Usual Care \(Manual Titration\) Arm](#) and [3.1.3 Intervention \(Automated Titration\) Arm](#) for further description of the study arms.

Upon randomization, research or clinical staff will input the randomly assigned patient ID number that will be associated with the patient's oxygenation information stored on the device. The clinical and research staff at each site will program the PRO100 device for the appropriate target SpO₂ range and alarms based on that patient's randomization. Regardless of randomization arm, the PRO100 device and SpO₂ monitor will be connected to the patient. In the usual care arm, the device will be placed in 'observation mode' and clinical staff will titrate usual care (wall oxygen) manually. In the intervention arm, the PRO100 device will be set to the autonomous oxygen titration mode, and the research team will set the specified interval of supplemental oxygen and the SpO₂ threshold (recommended SpO₂ goal 93%, set range 92-94%). A trend will be established within 10 seconds of an input signal from the patient's pulse oximeter; the device "expects" an input signal and can alarm immediately if there is no signal (may be programmed to alarm after 1, 5, 15, or 30 minutes depending on patient circumstance). Once this trend is established, the PRO100 device will automatically titrate until the desired oxygenation range is reached. The speed of titration is based on current patient flow rate and distance from SpO₂ target, therefore, a lower flow rate and shorter distance to SpO₂ target will prompt slower titration intervals than a higher flow rate and greater distance to SpO₂ target.

The PRO100 device is equipped with several programmable alarms, based on SpO₂ values outside of the target range despite specific flow rates. The key flow rates recommended in this study will be:

- At 8 lpm – indicating the patient needs to graduate from non-humidified nasal cannula to another device (face mask, non-rebreather, or high flow nasal cannula with humidified oxygen)
- At 12 lpm – indicating the patient is approaching the oxygenation ceiling designated for this study
- At 15 lpm – indicating the patient has reached the oxygenation ceiling designated for this study. Above this threshold, the patient will need to be removed from the intervention and begin oxygen use/titration based on hospital protocol

The treating clinical team (primarily nurses and respiratory therapists) will implement the autonomous oxygen titration intervention or usual care (manual oxygen titration). The intervention is not binding, and clinical decisions can always override the recommendations when it is in the best interest of the patient. If the clinical team is unwilling to accept the oxygenation strategy – for either arm – the patient will not be enrolled in this study. The implementation at each site will involve physician, advanced practice provider, nursing, and respiratory therapy champions and engagement from clinical leadership to emphasize and prioritize the intervention.

Between randomization and hospital discharge or end of study intervention (72 hours after randomization), study personnel will review the electronic health record daily for potential sustained hypoxemic and/or hyperoxemic events. When there are relative contraindications, treating clinicians will determine whether an alternative intervention would be appropriate or whether the risk-benefit ratio favors continuing the study intervention with the known potential interaction. If the treating physician deems an additional therapeutic intervention may be helpful for the patient (i.e., nebulizer treatments), the intervention will be halted until the treatment is complete and the study intervention will resume. If the patient must enter the Magnetic Resonance Imaging (MRI) suite or Operating Room (OR), the study intervention will halt until the patient returns to the inpatient unit, at which time the study intervention will resume.

At the site level, we will conduct clinical site monitoring to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), applicable regulatory requirement(s), and within established safety guidelines.

To ensure proper and timely reporting of all adverse events, all study personnel will follow a clear communication plan. Unexpected adverse events potentially associated with study interventions will be reported to the site PI within 24 hours of awareness and recorded in a case report form in the study record. The overall study PI will, in turn, report all Adverse Events (AEs) potentially related to study procedures to the Clinical Coordinating Center (CCC) and sIRB 5 working days of occurrence in accordance with IRB policy. AEs and unanticipated problems (UPs) will be reported to the Data and Safety Monitoring Board (DSMB), sIRB, Department of Defense Office of Human Research Oversight (DoD ORHO), and U.S. Food and Drug Administration (FDA) in accordance with their reporting policies. The overall PI and the local site PI will be responsible for ensuring participants' safety on a daily basis.

5.2 Study Intervention Compliance

Individual site research staff will monitor study intervention compliance by directly observing the use of the device in the intervention group and will confirm with clinical staff that they are not using the device if the patient is randomized to the usual care group. Reminders about the study intervention, SpO₂ targets, and on-study materials will be provided to the clinical team for enrolled participants at least twice daily during the intervention period. The site research staff will monitor patient vital signs via EHR, monitor any AEs through EHR note review and direct communication with the clinical staff, and will document and follow-up on any instance the device is overridden. If the device is disconnected, the patient has been removed from the intervention, or if the device has been overridden, research personnel will document timing and reasoning associated with the non-compliant event.

5.3 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

5.3.1 Discontinuation of Study Intervention

The study intervention may be discontinued for the following:

- (1) The patient is consistently hypoxemic and requires a higher level of oxygen (15 lpm);
- (2) The patient has acute hypercarboxemia that requires higher levels of respiratory support (e.g., non-invasive or invasive mechanical ventilation);

- (3) The patient is adequately and consistently oxygenated on room air and the device is no longer needed (monitoring may still occur with PRO100 and hospital monitors);
- (4) The patient must receive a clinical intervention that is contraindicated with the use of the oxygen monitoring device;
- (5) It is deemed by the attending physician or study investigator that the patient is no longer eligible for the intervention due to oxygenation needs (such as invasive mechanical ventilation) or other clinical needs;
- (6) The patient or LAR withdraws the patient from the study.

5.3.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participating in this study at any time upon request. An investigator may terminate participation in the study if any situation occurs such that continued participation in the study would not be in the best interest of the participant or the integrity of the study.

Discontinuation of the intervention, regardless of the reason, e.g., patient or physician request, or adverse event, does not constitute study withdrawal. Patient data will still be collected as planned and analyzed as intention to treat unless the participant also withdraws consent for continued follow-up.

5.3.3 Study Termination or Suspension

The study intervention be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Circumstances outside of interim analyses that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants in a strategy, such as excess mortality or serious adverse treatment effects;
- Insufficient compliance to the protocol requirements;
- Insufficient accrual in a study arm.

If the study intervention stops for safety, noncompliance, or data quality, it may resume once such concerns about safety, protocol compliance, or data quality are addressed and satisfy the requirements of appropriate oversight bodies including but not limited to the sIRB, the DSMB, and the FDA.

Decisions to stop the study intervention based on the accruing data are not considered premature termination or suspension. They will be guided by the decision thresholds described in the statistical analysis plan and augmented by details in relevant Appendices. Such decisions will generally be weighed by the DSMB. Reasons for stopping based upon the data will include safety (DSMB review of AEs) or demonstration of inferiority.

6. STUDY PROCEDURES

6.1 Study Intervention

See Section [5.1 STUDY INTERVENTION DESCRIPTION](#).

6.2 On-Study Monitoring

6.2.1 Clinical Evaluations

Between randomization and hospital discharge or end of study intervention, study personnel will review the electronic health record daily for potential sustained hypoxemic and/or hyperoxemic events. When there are relative contraindications treating clinicians will determine whether an alternative medication would be appropriate or whether the risk-benefit ratio favors continuing the medication with the known potential interaction.

6.2.2 Baseline Variable Collection

Baseline is defined as the patient's status at randomization. Physiological measurements and laboratory results obtained from clinically available data in the 24 hours prior to randomization may contribute to baseline data. The following information will be obtained to reflect the patient's baseline status:

- (1) Confirmation of informed consent for trial participation
- (2) Confirmation of inclusion/exclusion eligibility criteria for trial participation

- (3) Admission data: date and time of presentation, origin (home, skilled nursing facility, rehabilitation/long-term-acute care hospital, nursing home, outside hospital, outside ICU), location at enrollment (ED, hospital ward, ICU)
- (4) Primary reason for hospital admission (trauma, acute care surgery, burn, acute respiratory illness)
- (5) Date and time of ED arrival
- (6) Date and time of hospital admission
- (7) Date and time of hospital discharge
- (8) Date and time of randomization
- (9) Sociodemographic (such as age, sex, race, ethnicity, height, weight, socioeconomic status, payer)
- (10) Comorbidities
- (11) Volume of supplemental oxygen received at randomization
- (12) Vital signs
- (13) Mechanism of injury
- (14) Shock Index
- (15) Mode of Arrival
- (16) Height and Weight
- (17) Skin Pigmentation (Fitzpatrick Skin Classification, Monk Skin Tone (MST) Scale, Nix Spectro 2 (5 mm) device)
- (18) Mechanism of injury and severity variables for trauma and burn patients
- (19) Laboratory assessments as part of routine clinical care
- (20) Organ failure severity assessment

6.2.3 Assessments Between Hospital Presentation and Hospital Discharge (to day 28)

- (1) During the study intervention and the following 72 hours or until study intervention is discontinued:
 - a. Start and stop time of device connection/removal;
 - b. Starting supplemental oxygen dose;
 - c. PRO100 SpO2 values every minute during the intervention period;
 - d. PRO100 alarms and fallback modes;
 - e. Daily vital signs
- (2) Adverse Events that are:
 - a. Serious and definitely related, probably or possibly related, or of uncertain relationship
 - b. Unexpected and definitely related, probably or possibly related, or of uncertain relationship
- (3) All charted SpO2 and PaO2 values and oxygen administration data
- (4) Hospital monitor SpO2 values every minute until hospital discharge (to day 28)
- (5) Secondary outcomes and safety assessments
- (6) Date and time of first receipt of high-flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation
- (7) Date and time of last receipt of high-flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation
- (8) Discharge disposition

6.2.4 Assessments Following Hospital Discharge

Patients will be followed through day 28 following randomization or hospital discharge, whichever is first. There will be no follow-up after hospital discharge.

7. DATA MANAGEMENT AND STATISTICAL ANALYSIS PLAN

This section describes the statistical approach for the comparison of intervention versus its concurrent and eligibility matched usual care comparator group. The principal analyses will be intention-to-treat, based upon randomization assignment. Unless otherwise noted, all hypothesis testing and confidence intervals will be two-sided at the $\alpha = 0.05$ level of significance.

7.1 Clinical Coordinating Center

The CCC at the University of Colorado Denver, led by Adit Ginde, MD, MPH (overall Principal Investigator), will oversee all aspects of the trial and site activities. The CCC will coordinate directly with enrolling sites to launch data collection and randomization and develop/implement standardized training procedures, in conjunction with site investigators and coordinators. In addition, the biostatistical core will be housed at the Clinical Coordinating Center. Direct identifiers will be shared with the DCC at VUMC for monitoring and compliance. The only PHI that will be shared with the University of Colorado CCC will be dates and times (limited dataset), as these data are needed for data analysis.

7.2 Data Coordinating Center

The Data Coordinating Center (DCC) at Vanderbilt University Medical Center, led by Alex Cheng, PhD, will provide specialized REDCap-related data planning, implementation, and management services to the CCC at the University of Colorado and trial implementation sites. For this project, the DCC will utilize established REDCap database environments developed during the SAVE-O2 clinical trials. The DCC will focus specifically on socialization and implementation of digital forms related to this project, data mapping and data extraction strategies between EHR and REDCap environments, and correspondence with involved parties for questions and concerns throughout the study's lifespan. API sync using SMART on FHIR may be used to upload data from some sites to the DCC REDCap. The DCC will work closely with the University of Colorado biostatistical core in developing on-study data reports and the data analysis plan.

A fully identified dataset will be transmitted to and stored at the study's DCC at Vanderbilt University Medical Center (VUMC) 21 CFR Part 11-compliant REDCap system for purposes of monitoring and compliance. These data will also be accessible to the independent study monitor. A limited dataset, which is de-identified except for dates and times, will be made available to the University of Colorado CCC for statistical analysis, and scientific reporting. This dataset will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by VUMC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived in secure servers at VUMC and University of Colorado.

7.3 Statistical and Analytical Plans

There will be a formal Statistical Analysis Plan (SAP). This SAP will provide detailed descriptions of all primary, secondary, and sensitivity analyses, all interim and final decision thresholds, and all required documentation to ensure the reproducibility of statistical analyses. The SAP will be finalized prior to the first formal interim analysis performed by the DSMB halfway through the study intervention; as this interim analysis will primarily focus on safety, there will be no formal adjustment to significance levels of final analyses. The finalized SAP will take precedence and override the statistical considerations described in this section of this protocol (i.e., Statistical Considerations).

7.4 Interim Analysis

The DSMB will have the ability to analyze all safety data at any time during the study and stop the study indefinitely for safety reasons. The safety report will include a summary of all baseline demographics and physiological variables as well as on-study variables, and all adverse events by randomized groups. The first stage of the trial will be for feasibility. After 40-50 participants have been enrolled, the DSMB will evaluate initial data and progress to determine whether to proceed. The second stage of the trial will be for efficacy. Both trial stages will also focus on safety.

In addition, a formal interim analysis for safety will be complete after 150 total participants are accrued. The incidence of hypoxemia is the primary measure of safety in this study. We will test the null hypothesis that there is no difference

in proportion of time spent in *hypoxemia* between the two treatment groups. Specifically, let η_1 be the mean proportion of time in hypoxemia in the control condition and let η_2 be the corresponding mean in the intervention arm. We will test $H_0: \eta_1 = \eta_2$ vs. $H_1: \eta_1 < \eta_2$. If we reject the null at the 1% level of significance, then the trial may be stopped for safety. No interim analysis for efficacy will be conducted, and the trial will not be stopped for efficacy or futility. Further details will be provided in the SAP. Potential protocol modifications will be discussed between the trial investigators and DSMB as part of the review.

7.5 Sample Size Determination

The primary outcome being a proportion between 0 and 1 will be analyzed as a continuous measure. Using two-sample t test, we compute the power for $n = 150$ patients per arm, shown in the table below. We assume a mean in the control group of $\mu_1 = 0.6$; the mean proportion of time in the target range among patients assigned to standard of care by L'Her et al. (2021)³⁷ was found to be 0.621. The effect size (difference in mean between the two treatment arms, $\delta = \mu_2 - \mu_1$) was varied between 0.1 and 0.15; this is substantially smaller than the effect size shown of 0.319 shown in L'Her et al. (2021)³⁷. An estimated standard deviation for this outcome of $\sigma \approx 0.183$ can also be computed from results reported in L'Her et al. (2021)³⁷; we therefore examine a range of standard deviations between 0.2 and 0.5, to account for possibly increased variability in the outcome distribution.

μ_1	μ_2	$\delta = \mu_2 - \mu_1$	σ	Power
0.6	0.7	0.1	0.2	99.1%
0.6	0.75	0.15	0.2	100.0%
0.6	0.8	0.2	0.2	100.0%
0.6	0.7	0.1	0.3	82.1%
0.6	0.75	0.15	0.3	99.1%
0.6	0.8	0.2	0.3	100.0%
0.6	0.7	0.1	0.4	57.9%
0.6	0.75	0.15	0.4	89.9%
0.6	0.8	0.2	0.4	99.1%
0.6	0.7	0.1	0.5	40.8%
0.6	0.75	0.15	0.5	73.6%
0.6	0.8	0.2	0.5	93.2%

From this table, we see that there is >99% power for an effect size of 0.1 as long as the standard deviation of the outcome is ≤ 0.3 . Our base estimate is that the standard deviation outcome will be 0.2 based on prior data (L'Her et al); there is 99.1% power for an effect size of 0.1 under this assumption.

Due to the importance of subgroup analysis to the research goals, we have also computed power for the two-sample t test as applied to subgroups of various sizes. The methods are identical to those described above for the primary analysis, except that the sample size available is reduced to the size of the subgroup in question.

Subgroup size	Sample size per arm	μ_1	μ_2	$\delta = \mu_2 - \mu_1$	σ	Power
150	75	0.6	0.7	0.1	0.2	86.0%
150	75	0.6	0.75	0.15	0.2	99.5%
150	75	0.6	0.8	0.2	0.2	100.0%
120	60	0.6	0.7	0.1	0.2	77.5%
120	60	0.6	0.75	0.15	0.2	98.3%
120	60	0.6	0.8	0.2	0.2	100.0%
90	45	0.6	0.7	0.1	0.2	65.0%
90	45	0.6	0.75	0.15	0.2	94.0%

90	45	0.6	0.8	0.2	0.2	99.7%
60	30	0.6	0.7	0.1	0.2	47.8%
60	30	0.6	0.75	0.15	0.2	81.5%
60	30	0.6	0.8	0.2	0.2	96.8%
30	15	0.6	0.7	0.1	0.2	26.2%
30	15	0.6	0.75	0.15	0.2	50.9%
30	15	0.6	0.8	0.2	0.2	75.3%

This table shows that we have good (>80%) power even for subgroups as small as 60 (20% of the total sample size) when the effect size is 0.15 or larger.

7.6 Population for Analysis

The analytic sample will include all patients randomized. Analysis will be intention-to-treat.

7.7 Analysis of Outcomes

The analytic approach is summarized below. Full details will be described in the separate Statistical Analysis Plan.

7.7.1 Analysis of Primary Endpoint

The primary analysis will be as-randomized (i.e., intention to treat). The primary outcome, proportion of time spent in normoxemia, is a continuous, patient-level measure ranging from 0 to 1. The outcome data will be summarized descriptively by treatment arm, using mean and median as measures of central tendency, and standard deviation (SD) and interquartile range (IQR) as measures of spread; visual summaries (e.g., histograms) will also be examined. The difference in mean proportion of time spent in normoxemia will be compared between the two treatment arms using a two-sample t test. The formal statistical null hypothesis to be tested is $H_0: \beta_1 = 0$, that is, there is no difference in mean proportion of time in the target range is the same between control and intervention groups; the alternative hypothesis is $H_1: \beta_1 \neq 0$. The anticipated sample size is sufficiently large that the Wald test of this coefficient in a linear regression model should be valid even if the primary outcome is not normally distributed. However, sensitivity analyses specifying a mean-variance relationship of the form $Var(Y) = \phi\mu(1 - \mu)$ may be undertaken to determine if the quasibinomial nature of our primary outcome variable has any meaningful impact on our results.

7.7.2 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed using statistical methods appropriate to their type. Descriptive statistics including mean/median, SD/IQR will be calculated, overall and stratified by treatment arm. Amount of supplemental oxygen administered, being a continuous outcome, will be formally analyzed similarly to the primary endpoint, using a two-sample t test to compare the mean between the two treatment arms, with the estimated difference in means presented along with 95% confidence interval. Proportion of time spent in hypoxemia/hyperoxemia will likewise be analyzed in the same manner as the primary endpoint. Time to room air will be analyzed in the competing risks framework³⁸, as this time-to-event outcome occurs only in the absence of death or discharge from hospital. This framework will be used to calculate the median time to room air in each group along with 95% confidence interval for this quantity.

7.7.3 Adherence and Retention Analyses

Adherence and retention will be analyzed descriptively. The proportion of participants for whom the protocol of their randomized treatment arm was followed will be calculated, defining adherence; this will be stratified by treatment arm. Retention, although less relevant as our primary outcome is defined within the first 72 hours of a patient's hospital stay, will be calculated as the proportion of patients engaged on study who complete the data collection period without withdrawal, stratified by treatment arm. We anticipate that this will be close to 100%.

7.7.4 Missing Data

Missing data is expected in the primary endpoint since this is collected directly from two independent monitoring devices, either or both of which may fail to provide valid measurements at any time during data collection. Our analytic approach will leverage all available information from both devices: at each time point (defined to be 1 minute intervals), we will average the SpO2 values from the two devices if both are available; otherwise the sole available measurement will be taken if only one is available, and if neither device has provided a valid measurement at that time, then that time

will not be included in the calculation of the primary endpoint. Sensitivity analyses will be performed using only measurements from each device separately.

Missing covariate values are not anticipated to be a substantial issue in analysis, so no imputation is planned. If necessary, an additional category of “missing” will be added to covariates instead.

7.7.5 Safety Analyses

Safety signals will be captured by secondary and exploratory endpoints and adverse event reporting. In particular, proportion of time spent in hypoxemia will be monitored to ensure that patients are not exposed to undue risks during the conduct of the trial. This will be quantified by mean proportion of time spent in hypoxemia within each treatment arm. We will analyze rates of respiratory failure, defined the proportion of patients receiving high flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation, stratified by treatment arm. We will also analyze adverse events and serious adverse events, stratified by treatment arm, and grouped by organ system category.

7.7.6 Baseline Descriptive Statistics

Baseline descriptive statistics will be calculated for variables including but not limited to age, sex, race/ethnicity, skin pigmentation, type of patient (trauma/burn/surgical vs medical), comorbidities, home oxygen use, and supplemental oxygen flow rate at baseline. This will include mean and SD for continuous variables and frequency and percent for categorical variables. Statistics will be presented for the sample overall and stratified by treatment arm. Comparisons between treatment arm will be made to ensure balance has been achieved by randomization.

As an overall approach, we will analyze primary and secondary endpoints using a regression modeling framework, with specific distributions chosen depending on the type of outcome (e.g., binary, count, ordinal, time-to-event). The primary analysis will be as-randomized (i.e., intention to treat), so the primary exposure variable in these regression models will be a binary indicator of randomized treatment arm (equal to 1 for experimental and 0 for control). A threshold of $p = 0.05$ will be considered statistically significant and will be reported for the primary endpoint. Other secondary and exploratory endpoints will be reported as effect estimates with 95% confidence intervals.

7.7.7 Subgroup Analyses

We will stratify all described analyses by certain pre-specified subgroups. Depending on the particular analysis, this may involve testing interactions between covariates defining these subgroups and the treatment effect. Alternatively, we may instead conduct separate analyses of the treatment effect within each level of these subgroups. In either case, the goal is to describe heterogeneity of treatment effects (HTE). The subgroups we plan to use include age, sex, race/ethnicity, skin pigmentation (Fitzpatrick Skin Classification, MST scale, Nix Spectro 2 (5 mm) colorimetry values), body mass index, COPD, volume of supplemental oxygen received at randomization, primary reason for hypoxemia, and baseline illness severity (SOFA scores). Further details will be outlined in the Statistical Analysis Plan.

7.7.8 Exploratory Analyses

Exploratory endpoints will be analyzed according to their type. Supplemental O₂-free days and hospital-free days to day 28 will be treated as a continuous variable and compared between treatment arms using a t test, but, as these are composite outcomes, will also be subjected to the Wilcoxon test in case of important deviations from t-test assumptions. All-cause mortality to day 28 will be analyzed in the competing risks framework, as it occurs only in the absence of discharge alive from hospital. Respiratory failure is a binary endpoint, so will be compared between arms using a two-sample test of proportions. Duration of time receiving no supplemental oxygen will be quantified as a patient-level proportion of time and analyzed in the same manner as the primary outcome.

8. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

8.1 Ethical Standard

All studies conducted under this Master Protocol will adhere to the highest ethical standards. The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice and other relevant regulations. Further, studies will be conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

8.2 IRB/Ethics Committee/Competent Authority

This trial will be initiated only after all required legal documentation has been reviewed and approved by the Colorado Multiple Institutional Review Board (serving as the sIRB)/ Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments to both the protocol and informed consent form.

8.3 Posting of Clinical Trial Consent Form

The informed consent form approved by the sIRB for all sites will be posted on the clinicaltrials.gov website after the clinical trial protocol is finalized and the first patient is enrolled.

8.4 Regulatory Oversight

The Colorado Multiple Institutional Review Board (COMIRB) will serve as the sIRB for the University of Colorado. The additional enrolling sites will cede review to the COMIRB sIRB. COMIRB will be sIRB for the entire study. OHRO will function as the military oversight for this clinical trial. The CCC will submit quarterly and annual reports outlining data and enrollment goals and any safety concerns.

The FDA will provide oversight and approval for the IDE application process. Once approved, the FDA will rely on the trial primary investigator and CCC to submit the following reports:

- *Sponsor Reports* such as: unanticipated adverse device effects ([IDE AE program 812.150](#)), withdrawal of IRB approval, withdrawal of FDA approval, current and any change list of investigators [[21 CFR 812.150\(b\)\(4\)](#)], annual reports, recalls and device disposition, final report, failure to obtain informed consent, significant risk device determination
- *Investigator Reports* such as: unanticipated adverse device effects ([IDE AE program 812.150](#)), withdrawal of IRB approval, withdrawal of FDA approval, progress reports, deviations from the investigational plan, failure to obtain informed consent, final report

8.5 Informed Consent Process

Informed consent is a process initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's participation. Informed consent should follow both local institutional policy and national regulatory guidance. Informed consent will be obtained from the patient or from a LAR if the patient lacks decision-making capacity. This study will utilize both traditional paper-based approach and an electronic/e-consent option.

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

8.5.1 Consent/Assent and Other Information Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. A paper consent document, which will translate into the eConsent document – containing the following consent materials are submitted with this protocol:

- (1) Patient signature block with date;
- (2) LAR signature block with date;
- (3) Coordinator attestation signature block with date;
- (4) Witness signature block with date (if needed).

8.5.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB approved and the participant will be asked to read and review the document. The study investigator or study research coordinator will explain the research study to the participant and/or LAR and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's/LAR's comprehension of the purposes, procedures, and potential risks of the study and of

their rights as research participants. Participants/LARs will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants/LARs should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant/LAR will eSign the informed consent document prior to any procedures being done specifically for the study. Participants/LAR must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The participants/LARs will have an opportunity to download their signed eConsent document for their records; if they are unable to download the document, study personnel will print out a paper copy of their signed consent document. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

8.5.3 Electronic/eConsent approach

- (1) The electronic informed consent document is opened on a research device or a link for the electronic informed consent document is sent to the patient's or LAR's device.
- (2) Research staff will discuss the informed consent document with the patient or LAR either in person or by telephone or videophone. This step confirms subject/LAR identity.
- (3) If the patient or LAR decides to consent to participate, the patient or LAR signs the electronic informed consent document. This signature may be either:
 - a. an actual signature (often tracing a finger on the screen) OR
 - b. a username and password specific to the individual signing
- (4) Research staff and the witness, provide signatures within the electronic database (e.g., REDCap) confirming their participation in the informed consent process.
- (5) The image of the signature page may be printed and bundled with a copy of the blank informed consent document for research records.

If a hospital device is provided to facilitate electronic or paper-based consent, that device will be disinfected according to institutional protocols and removed by research staff or clinical staff during the next entry into the patient's room.

This approach complies with relevant regulations and sub-regulator guidance at 45 CFR 46.117, 45 CFR 164.512, 21 CFR 11 Subpart C (11.100–11.300), <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/use-electronic-informed-consent-questions-and-answers/index.html>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent>.

The information for the informed consent discussion will be provided in an informed consent document (or electronic equivalent) that has been approved by the sIRB and in a language comprehensible to the potential participant, using an interpreter if necessary. We will have fully translated consent forms for commonly encountered languages at enrolling sites, or a short-form consent for less commonly encountered languages, and a qualified interpreter will be employed. Use of an interpreter and the interpreter's identity will be documented on the paper/electronic consent.

8.5.4 Paper-based approach

- (1) The informed consent document is delivered to the patient or LAR.
 - a. If the patient or LAR is on-site, the informed consent document may be delivered to the patient or LAR either by research staff or by clinical staff.
 - b. If the LAR is off-site, the informed consent document may be emailed, faxed, or otherwise electronically transferred to the LAR (method dictated by institutional policy).
- (2) Research staff discuss the informed consent document with the patient or LAR in-person if they are on-site or by telephone or videophone if they are not on-site. This step confirms subject/LAR identity.
- (3) If the patient or LAR decides to consent to participate, the patient or LAR signs the paper copy of the informed consent document.

- (4) If on-site, a photocopy of the signature page will be scanned by the research staff. If the LAR is off-site, a photograph is taken of the signature page by the LAR of the informed consent document and uploaded into the electronic database (e.g., REDCap).
 - a. If using the LAR's device (such as a personal cellular phone), a survey link can be sent to their device to allow direct upload of the image into the electronic database (e.g., REDCap).
 - b. If using a staff device, it must be approved to store Protected Health Information (PHI) by the local institution. In that case, research personnel can take a photograph of the signature page of the informed consent document. The photograph can then be uploaded into the electronic database. If a staff device is taken into the patient's room to take a photograph it must be able to be disinfected according to local institutional practices.
- (5) Research staff and the witness provide signatures within the electronic database (e.g., REDCap) confirming their participation in the informed consent process.
- (6) The patient or LAR retains the paper consent document. The image of the signature page may be printed and bundled with a copy of the blank informed consent document for research records.

8.6 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Demonstration of efficacy that would warrant stopping;
- Insufficient compliance to protocol requirements;
- Data that are not sufficiently complete and/or evaluable;
- Determination that the primary endpoint has been met;
- Determination of futility.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, sIRB and/or the FDA.

8.7 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the research investigators, their staff, and the sponsor(s) and their interventions. While this study intervention will not be collecting biological or genetic samples, this confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the sIRB, regulatory agencies or device company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored within a password protected server at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing sIRB, Institutional policies, or sponsor requirements.

A fully identified dataset will be transmitted to and stored at the study's DCC at Vanderbilt University Medical Center (VUMC) 21 CFR Part 11-compliant REDCap system for purposes of monitoring and compliance. These data will also be accessible to the independent study monitor. A limited dataset, which is de-identified except for dates, will be made available to the University of Colorado CCC for statistical analysis, and scientific reporting. This dataset will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by VUMC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived in secure servers at VUMC and University of Colorado.

8.8 Future Use of Stored Data

After the study is completed, a fully de-identified, archived dataset will be transmitted to and stored within the University of Colorado secure data repository for use by other researchers. The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained and individuals who would like access the data will need to contact the CCC and DCC for permission. Databases are backed up by the database administrator in conjunction with any updates or changes to the database. At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures. Permission to transmit data to the DCC at VUMC will be included in the informed consent.

When the study is completed, access to study data will be provided through the University of Colorado secure data repository.

8.9 Data Handling and Record Keeping

We will collect, manage, and store human subject's data using a REDCap database that has been previously established during the SAVE-O2 clinical trials. REDCap is a secure and encrypted web application designed to support data capture for research studies, providing user-friendly, web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes University of Colorado Denver and was initiated at Vanderbilt University. The database will be hosted at the Vanderbilt University DCC and shared with the University of Colorado for on-study reporting and data analysis. Direct identifiers will be shared with the DCC at VUMC for monitoring and compliance. The only PHI that will be shared with the University of Colorado CCC will be dates (limited dataset), as these data are needed for data analysis.

8.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets and IP logs will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical and patient-reported data will be entered into a 21 CFR Part 11-compliant data capture system provided by the DCC at VUMC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

8.9.2 Study Records Retention

Per FDA regulation 312.62C, study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

8.9.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. It is expected during routine care that oxygen monitoring and administration devices will be intermittently removed by patients or the clinical team and during transitions of care. We will not consider the following to be protocol deviations: unintentional removal of the PRO100 device or pulse oximeter(s) resulting in gaps in SpO₂ monitoring for <8 hours per episode and <24 hours cumulative during the 72 hour intervention period. These episodes will be recorded but will not be reported as protocol deviations. Other reporting such as adverse events would be as specified in the protocol.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. The site PI/study staff is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

All deviations must be addressed in study source documents, reported to COMIRB and local site IRB within 5 days of identification, OHRO, DSMB, and the FDA during continuing review submission. Serious noncompliance, UAPs, or safety events will follow expedited report procedures under 21 CFR Part 11.

8.10 21 CFR Part 11 Compliance

8.10.1 Record Locking

This trial will utilize the REDCap record-locking feature, that will allow the users to lock a participant record. A complete audit trail of the locked records will be kept in the data instrument's history log. Users will receive a prompt when locking an entire record. They will be asked to review a Portable Document Format (PDF) copy of the entire record to confirm it is the correct record and/or file. Once the PDF has been reviewed and confirmed, the record will be locked. All records that are locked using record-level locking will have a duplicate copy of the PDF file automatically stored on a secure file server outside of REDCap. The record-locking feature complies with all the requirements described in 21 CFR Part 11 for FDA trials and has been validated at VUMC.

8.10.2 eConsent

Informed consent should follow both local institutional policy and national regulatory guidance. One option in this trial is to utilize the REDCap eConsent feature. The DCC at VUMC has developed an eConsent framework within the REDCap platform allowing research participants to rapidly review and sign consent documentation for delivery via web, tablet, or smartphone. Electronic consent forms can leverage standard REDCap survey features including multi-lingual language capacity for information rendering and capture. Upon completion, the system documents the 'consent transaction' and stores final, "frozen" consent PDFs in REDCap, allowing researchers to retrieve information on the consent type, status, and version at any time. Consents are also stored in a separate secure document system for redundancy and permanent archival. The REDCap eConsent framework has been 21 CFR Part 11 validated at VUMC.

9. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND UNANTICIPATED PROBLEMS

9.1 Definition of Adverse Event (AE)

An adverse event (AE) will be defined as any untoward medical occurrence associated with use of the study device or study procedures, whether or not the event is related to the study device or study procedures (21 CFR 312.32 (a)). If a diagnosis is clinically evident (or subsequently determined), the diagnosis, rather than the individual signs and symptoms or lab abnormalities, will be considered as the AE if it meets criteria for recording.

9.2 Definition of Serious Adverse Event (SAE)

An AE will be considered to be a **serious adverse event (SAE)** if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- (1) Death;
- (2) A life-threatening adverse event;
- (3) Inpatient hospitalization or prolongation of existing hospitalization;
- (4) A persistent or significant incapacity;

- (5) Substantial disruption of the ability to conduct normal life functions;
- (6) Important medical event that requires an intervention to prevent any of 1-5 above.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Definition of an Unexpected Adverse Event

An adverse event will be considered “unexpected” if the nature, severity, or frequency is neither consistent with:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol-related documents, such as the investigator brochure, IRB-approved research protocol or informed consent document or collected systematically as outcomes of the research protocol; nor
2. The expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

9.4 Definition of a Related Adverse Event

Causality is the likelihood that the event is caused by the study intervention. Causality will be assessed by a site investigator by considering the following factors:

- Definitely Related
 - reasonable temporal relationship
 - follows a known response pattern
 - clear evidence to suggest a causal relationship
 - there is no alternative etiology
- Probably Related
 - reasonable temporal relationship
 - follows a suspected response pattern (based on similar interventions)
 - no evidence of a more likely alternative etiology
- Possibly Related
 - reasonable temporal relationship
 - little evidence for a more likely alternative etiology
- Unlikely Related
 - does not have a reasonable temporal relationship
 - AND/OR
 - there is good evidence for a more likely alternative etiology
- Not Related
 - does not have a temporal relationship
 - AND/OR
 - definitely due to an alternative etiology

Note: Other applicable factors (e.g., de-challenge, re-challenge) should also be considered for each causality category when appropriate. Causality assessment is based on information available at the time of the assessment of the AE. The investigator assessing the event may revise the causality assessment as additional information becomes available.

For SAEs, the sponsor will make an independent determination on causality. If either the investigator or the sponsor assesses the event as “related” (definitely, probably, or possibly related), it will be considered related for the purpose of determining whether an event is reportable to health authorities.

9.5 Adverse Event Recording and Reporting

The following types of adverse events will be recorded and reported through day 28 or hospital discharge, whichever is first:

- Adverse events that are serious and definitely related, probably or possibly related, or of uncertain relationship.
- Adverse events that are unexpected and definitely related, probably or possibly related, or of uncertain relationship.

Adverse events that do not meet the above criteria will not be recorded. Adverse events that the lead investigator at a site assesses to meet the above criteria for recording and reporting will be entered into the adverse event electronic case report form in the trial database. The lead investigator at the site will record an assessment of each characteristic for the adverse event, including seriousness, unexpectedness, and relatedness. For any adverse event that is serious AND unexpected, and definitely related, probably or possibly related, or of uncertain relationship, the site investigator will report the adverse event to the coordinating center within 24 hours of becoming aware of the adverse event. For any other adverse event requiring recording and reporting, the site investigator will report the adverse event to the coordinating center within 72 hours of becoming aware of the adverse event. The coordinating center will coordinate with the site investigator to obtain information about the adverse event regarding each characteristic for the adverse event, including seriousness, expectedness, and relatedness. The site investigator will be responsible for making final determinations regarding seriousness and unexpectedness. The coordinating center will be responsible for making final determinations regarding relatedness. The sponsor will also make an independent determination regarding relatedness.

For adverse events that meet the above criteria for recording and reporting, the coordinating center will notify the DSMB, the IRB, and the sponsor in accordance with the following reporting plan:

Fatal or life-threatening (and therefore serious), unexpected, and definitely related, probably or possibility related, or of uncertain relationship. Report to the DSMB, IRB, and sponsor within 7 days after notification of the event.

Serious but non-fatal and non-life-threatening, unexpected, and definitely related, probably or possibly related, or of uncertain relationship. Report to DSMB, IRB, and sponsor within 15 days of notification of the event.

All other adverse events meeting criteria for recording and reporting. Report to DSMB, IRB, and sponsor in regularly scheduled reports.

The coordinating center will distribute the written summary of the DSMB's periodic review of reported adverse events to the IRB in accordance with NIH guidelines: (<http://grants.nih.gov/grants/guide/notice-files/not99-107.html>).

The study sponsor is responsible for evaluating adverse event reports and shall report the results of such evaluation to the FDA.

9.6 Clinical Outcomes that may be Exempt from Adverse Event Recording and Reporting

In this study of hospitalized patients with advanced illness at high risk for death and other adverse outcomes due to their underlying advanced illness, clinical outcomes, including death, will be systematically collected and analyzed for all patients. The primary, secondary, and exploratory outcomes will be recorded and reported as clinical outcomes and not as adverse events unless treating clinicians or site investigators believe the event is Definitely Related or Probably or Possibly Related to the study intervention or study procedures. This approach – considering death and other outcomes as clinical outcomes rather than adverse events and systemically collecting these clinical outcomes for analysis – is common in trials among patients with advanced illness. This approach ensures comprehensive data on death and other outcomes for all patients, rather than relying on sporadic adverse event reporting to identify these important events.

The following events are examples of study-specific clinical outcomes that would not be recorded and reported as adverse events unless treating clinicians or site investigators believe the event was Definitely Related or Probably or Possibly Related to the study intervention or study procedures:

- Death (all deaths occurring prior to hospital discharge or 28 days will be recorded);
- Duration of ICU admission;
- Duration of hospitalization
- Receipt of high flow nasal oxygen or mechanical ventilation

9.7 Serious Adverse Event Reporting

Adverse events that are serious and definitely related, probably or possibly related, or of uncertain relationship will be reported by the site investigator to the coordinating center within 72 hours of becoming aware of the event. For any adverse event that is serious AND unexpected, and definitely related, probably or possibly related, or of uncertain relationship, the site investigator will report the adverse event to the coordinating center within 24 hours of becoming aware of the adverse event. Adverse events that are serious but deemed unlikely related or unrelated to the study intervention will not be reported as adverse events.

9.8 Unanticipated Problems

9.8.1 Definition of Unanticipated Problems (UAP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition includes an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the study device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

9.8.2 Unanticipated Problem Reporting

The site investigator will report unanticipated problems to the coordinating center within 72 hours of becoming aware of the event. The UAP report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UAP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UAP.

To satisfy the requirement for prompt reporting, UAPs will be reported using the following timeline:

- UAPs that are SAEs will be reported to the IRB and to the study sponsor within 72 hours of the coordinating center becoming aware of the event.
- Any other UAP will be reported to the IRB and to the study sponsor within 5 working days of the coordinating center becoming aware of the problem.

All UAPs should be reported to appropriate institutional officials (as required by an institution’s written reporting procedures), the supporting agency head (or designee), and the OHRP within 5 working days of the IRB’s receipt of the report of the problem from the investigator.

10. SAFETY OVERSIGHT

10.1 Data and Safety Monitoring Plan (DSMP)

The below data safety and monitoring plan is commensurate with the risks as well as the size and complexity of the study. With input and approval from the Sponsor and COMIRB, a DSMB will be assigned to this study. The principal role of the DSMB is to assure the safety of patients in the trial. They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the steering committee and sponsor with respect to:

- Participant safety and risk/benefit ratio of study procedures and interventions;
- Initial approval of the protocol and subsequent amendments (with specific attention to study population, intervention, and study procedures);
- Adherence to the protocol requirements;

- Completeness, quality, and planned analysis of data;
- Ancillary study burden on participants and main study;
- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance.

The DSMB will consist of members with expertise in acute/critical care, biostatistics, and clinical trials. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The coordinating center, principal investigators, and unblinded study biostatistician will be responsible for the preparation of all DSMB and adverse event reports. The DSMB will develop a charter and review the protocol and patient notification forms during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter. The DSMB will have the ability to recommend that the trial end, be modified, or continued unchanged.

The below plan outlines that appropriate oversight and monitoring of the conduct and progress of the study to ensure that important information that may affect the safety and welfare of subjects is collected, recognized, and acted upon quickly while still ensuring the validity and integrity of the data. This monitoring plan includes structured AE and SAE determination, monitoring and reporting. AEs and UAPs will be reported to the DSMB, COMIRB, and the DoD OHRO, in accordance with their reporting policies. The PI globally and the site PI at the local level will be responsible for ensuring participants' safety on a daily basis.

11. CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the CCC team at the University of Colorado.
- Remote, centralized monitoring will be conducted at each site after the first five patients have been enrolled at that site. Then, monitoring will be conducted yearly to evaluate key study variables, evaluate key outcome variables, review patient consent forms and eligibility.
- Study and site PI(s) and lead site coordinators will be provided copies of monitoring reports within 14 days of visit.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits will be conducted by the research staff at the CCC to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP

12. QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion, and study device quality checks. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and device data are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

13. STUDY FINANCES

13.1 Funding Source

This study is funded by the Department of Defense through an Other Transactional Authority (MTEC). O2matic PRO100 devices will be rented by the Clinical Coordinator Center for the trial (University of Colorado). O2matic, the industry partner, will have no role in the decision to publish, data analysis, or interpretation of the data.

13.2 Costs to the Participant

There will be no cost to the participant.

14. PUBLICATION AND DATA SHARING POLICY

14.1 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the MTEC has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

15. REFERENCES

1. Dylla, L., Douin, D.J., Anderson, E.L. *et al.* A multicenter cluster randomized, stepped wedge implementation trial for targeted normoxia in critically ill trauma patients: study protocol and statistical analysis plan for the Strategy to Avoid Excessive Oxygen (SAVE-O2) trial. *Trials* 22, 784 (2021).
2. Douin DJ, Schauer SG, Anderson EL, et al. Systematic review of oxygenation and clinical outcomes to inform oxygen targets in critically ill trauma patients. *J Trauma Acute Care Surg.* 2019;87(4):961-977.
3. Dylla L, Anderson EL, Douin DJ, et al. A quasi experimental study of targeted normoxia in critically ill trauma patients. *J Trauma Acute Care Surg.* 2021;91(2S Suppl 2):S169-S175.
4. Jernigan PL, Hoehn RS, Blakeman TC, et al; Portable mechanical ventilation with closed-loop control of inspired fraction of oxygen maintains oxygenation in the setting of hemorrhage and lung injury. *J Trauma Acute Care Surg.* 2015;79(1):53-59.
5. Pannu SR, Exline M, Klammer B, et al; Early titration of oxygen during mechanical ventilation reduces hyperoxemia in a pilot, feasibility, randomized control trial for automated titration of oxygen levels. *Crit care Explor.* 2022;4(6)e0704
6. Johannigman J, Branson R, Blakeman TC, Rodriguez D. *Closed Loop Control of Oxygen Delivery and Oxygen Generation.* Wright-Patterson AFD, OH: Air Force Research Laboratory; 2017. AFRL-SA-WP-SR-2017-0024.
7. Roca O, Caritg O, Santafé M, et al; Closed-loop oxygen control improves oxygen therapy in acute hypoxemic respiratory failure patients under high flow nasal oxygen: a randomized cross-over study (the HILOOP study). *Critical Care.* 2022;26:108.
8. Committee on Tactical Combat Casualty Care (CoTCCC). *Tactical Combat Casualty Care (TCCC) Guidelines for Medical Personnel.* Joint Trauma System; 2021.
9. Hudson IL, Blackburn MB, Staudt AM, et al; Analysis of casualties that underwent airway management before reaching role 2 facilities in the Afghanistan conflict 2008-2014. *Mil Med.* 2020;185(Suppl 1):10-18.
10. McMullan J, Ward Hart K, Barczak C, Lindsell C, Branson R. Supplemental oxygen requirements of critically injured adults: an observational trial. *Mil Med.* 2016;181(8):767-72.
11. Hansen EF, Bech CS, Vestbo J, Andersen O, Kofod LM. Automatic oxygen titration with O2matic® to patients admitted with COVID-19 and hypoxemic respiratory failure. *Eur Clin Respir J.* 2020;7(1):1833695.
12. Hansen EF, Hove JD, Bech CS, Jensen JS, Kallemose T, Vestbo J. Automated oxygen control with O2matic® during admission with exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis.* 2018;13:3997-4003.
13. Kofod LM, Westerdahl E, Kristensen MT, Brocki BC, Ringbæk T, Hansen EF. Effect of Automated Oxygen Titration during Walking on Dyspnea and Endurance in Chronic Hypoxemic Patients with COPD: A Randomized Crossover Trial. *J Clin Med.* 2021;10(21):4820.
14. Girardis M, et al. Effort of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit. The Oxygen-ICU randomized clinical trial. *JAMA* 2016;316:1583-1589.
15. de Jonge E, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008;12:R156.
16. Van den Boom W, Hoy M, Sankaran J, et al; The search for optimal oxygen saturation targets in critically ill patients: Observational data from large ICU databases. *Chest.* 2020;157(3):566-573. doi:10.1016/j.chest.2019.09.015
17. Baekgaard JS, Isbye D, Ottosen CI, et al. Restrictive vs liberal oxygen for trauma patients-the TRAUMOX1 pilot randomised clinical trial. *Acta Anaesthesiol Scand.* 2019;63(7):947-955. doi:10.1111/aas.13362
18. Hirase T, Ruff ES, Ratnani I, Surani SR. Impact of Conservative Versus Conventional Oxygenation on Outcomes of Patients in Intensive Care Units: A Systematic Review and Meta-analysis. *Cureus.* 2019;11(9):e5662. Published 2019 Sep 15. doi:10.7759/cureus.5662
19. Singh, V, et al. The Pathogenesis of Burn Wound Conversion. *Ann Plast Surg.* 2007 Jul;59(1):109
20. Cancio, LC, et al. Guidelines for Burn Care Under Austere Conditions: Surgical and Nonsurgical Wound Management. *J Burn Care Res.* 2017 Jul/Aug;38(4):203.

21. Palimeri, TL, et al. Measuring Burn Injury Outcomes. *Clin N Am*. 2014; 94:909
22. Kao, Y, et al. Fluid Resuscitation in Patients with Severe Burns: A Meta-analysis of Randomized Controlled Trials. *Acad Emerg Med*. 2018 Mar;25(3):320
23. Carlo WA, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-1969.
24. Stockinger ZT, et al. Prehospital supplemental oxygen in trauma patients: its efficacy and implications for military medical care. *Mil Med* 2004;169:609-612.
25. Douin DJ, Anderson EL, Dylla L, et al. Association Between Hyperoxia, Supplemental Oxygen, and Mortality in Critically Injured Patients. *Crit Care Explor*. 2021;3(5):e0418. Published 2021 May 14. doi:10.1097/CCE.0000000000000418
26. Semler MW, Casey JD, Lloyd BD, et al. Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation. *N Engl J Med*. 2022;387(19):1759-1769. doi:10.1056/NEJMoa2208415
27. ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Mackle D, Bellomo R, et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. *N Engl J Med*. 2020;382(11):989-998.
28. Schjørring OL, Klitgaard TL, Perner A, et al. Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. *N Engl J Med*. 2021;384(14):1301-1311.
29. Harper J, Kearns N, Bird G, et al. Automatic versus manual oxygen titration using a novel nasal high-flow device in medical inpatients with an acute illness: a randomised controlled trial. *BMJ Open Respir Res*. 2021;8(1):e000843. doi:10.1136/bmjresp-2020-000843
30. Sturrock S, Williams E, Dassios T, Greenough A. Closed loop automated oxygen control in neonates-A review. *Acta Paediatr*. 2020;109(5):914-922. doi:10.1111/apa.15089
31. Morozoff E, Smyth JA, Saif M. Applying Computer Models to Realize Closed-Loop Neonatal Oxygen Therapy. *Anesth Analg*. 2017;124(1):95-103. doi:10.1213/ANE.0000000000001367
32. Sandal O, Ceylan G, Topal S, et al. Closed-loop oxygen control improves oxygenation in pediatric patients under high-flow nasal oxygen-A randomized crossover study. *Front Med (Lausanne)*. 2022;9:1046902. Published 2022 Nov 16. doi:10.3389/fmed.2022.1046902
33. Soydan E, Ceylan G, Topal S, et al. Automated closed-loop FiO₂ titration increases the percentage of time spent in optimal zones of oxygen saturation in pediatric patients-A randomized crossover clinical trial. *Front Med (Lausanne)*. 2022;9:969218. Published 2022 Aug 25. doi:10.3389/fmed.2022.969218
34. Vivodtzev I, L'Her E, Vottero G, et al. Automated O₂ titration improves exercise capacity in patients with hypercapnic chronic obstructive pulmonary disease: a randomised controlled cross-over trial. *Thorax*. 2019;74(3):298-301. doi:10.1136/thoraxjnl-2018-211967
35. Lellouche F, Bouchard PA, Roberge M, et al. Automated oxygen titration and weaning with FreeO2 in patients with acute exacerbation of COPD: a pilot randomized trial. *Int J Chron Obstruct Pulmon Dis*. 2016;11:1983-1990. Published 2016 Aug 24. doi:10.2147/COPD.S112820
36. Lellouche F, L'Her E, Bouchard PA, Brouillard C, Maltais F. Automatic Oxygen Titration During Walking in Subjects With COPD: A Randomized Crossover Controlled Study. *Respir Care*. 2016;61(11):1456-1464. doi:10.4187/respcare.04406
37. L'Her E, Jaber S, Verzilli D, et al. Automated closed-loop versus standard manual oxygen administration after major abdominal or thoracic surgery: an international multicentre randomised controlled study. *Eur Respir J*. 2021;57(1):2000182. Published 2021 Jan 5.
38. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics*. 1978;34(4):541-554.
39. Little, R.J. and Rubin, D.B., 2019. *Statistical analysis with missing data*. John Wiley & Sons.

Appendix A – O2Matic PRO100 Device Specifications

Physical

Weight	1850 g
Dimensions	205x265x95 mm
Display size	7"
Display resolution	800 x 480
Connection	DB9, USB
Alarm volume	56 dB

Electrical

Main	100-240 VAC, 50/60 Hz
DC input	12 VDC
Power consumption	12 VA
Battery type	Lithium Polymer
Battery Capacity	1,5 hours

Classifications

Type of protection	Class II and internally powered
Degree of protection	Type BF – Applied part
Ingress protection	IPX0
Method of sterilization	None
Suitability of use	Oxygen rich environment
Mode of operation	Continuous

Environmental

Operating temperature	5°C – 35°C
Storage temperature	-20°C – 60°C
Operating humidity	10% – 90%
Storage humidity	10% – 90%
Operating altitude	0 - 2000 meters
Input pressure	up to 100 PSI (6 bar)

Performance

SpO2 reading	70% - 100% ± 2
Heart rate	40 – 240 ± 5
Flow rate	0 – 15l/min
Alarm delay	< 20 secs

General

Expected service life	5 years
Language	English

Table A1 - Input validation:

Validation Type	Validation Rate
Heart rate alarm upper limit input range	85 – 200 BPM
Heart rate alarm lower limit input range	40 – 80 BPM
SpO2 alarm limit input range	80 – 100 %
Oxygen flow - Automatic mode	0 – 15 l/min
Oxygen flow – Manual mode	0 – 15+ l/min*
Oximeter Signal Alarm delay	0 – 300 secs

*In manual mode flow it is possible to open up the valve at maximum. When doing this the O2matic device shows 15+ l/min and shows a warning of “inaccurate flow.” The actual output is based on current oxygen source. At 4 bars pressure input the O2matic PRO delivers 30 l/min.

Table A2 - Alarm specifications:

Alarm Specification Type	Specification
Alarm signal generation delay	Less than 2 secs
Display update	30 ms
Decibel (dB)	56
Danger SpO2 alarm	3 % under low
Critical SpO2 alarm	Less than 80 %

Table A3 - Default settings table

Default Type	Default Value
Pause screen timer	30 mins
Mute button timer	120 secs
Oximeter Signal Alarm delay	60 secs
Mode	Automatic

Table A4 – Factory set profiles

Name	Min SpO2	Max SpO2	Min O2 Flow	Max O2 Flow	Initial O2 Flow	Max Pulse Rate	Flow response
COPD	88	92	0	6	2	130	NORMAL
HYPOXEMIA	94	98	0	15	5	130	NORMAL
ACTIVITY	90	94	0	15	5	150	FAST

Table A5 – Flow response settings

Flow response	Rate
Normal	20 %
Fast	100 %

Settings file

Parameter	Description	Input range
LowIntensityAlarmTimer	Delay for Low Intensity Alarm in minutes.	Between 60 and 300 secs
MuteButtonTimer	Duration of muted effect.	Between 60 and 300 secs
HomeTimer	Time before return to home from inactivity.	Between 60 and 300 secs
SampleDuration	Seconds between each session log.	Between 1 and 30 secs
NoSignalAlarmDelay	Seconds before a no signal alarm.	Between 0 and 300 secs
LowIntensityAlarmDelay	Seconds before low intensity alarm.	Between 0 and 300 secs
TimeSpentUnderAcceptableSpO2	Seconds before long period low intensity alarm.	Between 60 and 300 secs
ki	Flow Response rate.	Between 0,25 and 1
Debug	Debug.	Only for service use

Nix Spectro 2 (5 mm)

Product specifications – v3.2



Form factor

Dimensions	45 mm X 60 mm X 60 mm (1.77" X 2.36" X 2.36")
Materials	Durable, matte black powder coated metal enclosure
Haptics and visuals	Vibration and RGB feedback for charging, connection, and measurement state
Features	Scratch-resistant glass lens Dust and water-resistant Hard point for braided aircraft cable attachment

Performance

Measurement speed	1 reported scan/second
Optical resolution	True 31 channel measurement (diffraction grating with 288 pixel diode array)
Spectral visible range	400 – 700 nm, 10 nm resolution reporting
Repeatability	0.05 ΔE_{00} on white (D65, 10°, to mean of 10 measurements every 3 s on white, at a temperature of 23 °C)
Inter-instrument agreement	0.35 ΔE_{00} average, 0.7 ΔE_{00} max. (deviation from Nix Sensor Ltd. standard unit at a temperature of 23 °C on 12 CERAM CCS-II tiles (D65, 10°))
Temperature range	10 °C – 35 °C
Humidity	0% – 80% non-condensing

Optics

Measurement geometry	45°:0° ring illumination optics
Measurement port diameter	16 mm (0.63") diameter
Illumination spot size	6 mm (0.24") diameter
Measurement aperture	5 mm (0.20") diameter
Light source	High CRI, broad spectrum LED light source (white, violet and UV)
Optional Adapters	Liquids, powders, gels, and soft surface adapters available

Nix Spectro 2 (5 mm)

Product specifications

Calibration

Each unit individually factory calibrated
Integrated/automatic temperature compensation
In-field normalization: manual on included external ceramic reference

Density data

Evaluated according to ISO 5-3:2009
Density status: A, E, I, T
Note: Particular density data availability may differ based on application used.

Battery life + charging

USB-C charging of internal lithium polymer battery
90 day (3 month) standby time per charge (device advertising on BLE)
1,000+ scans per charge

Packaging + accessories

Impact-resistant, waterproof carrying case, ideally suited for field operations
USB-C charging cable
Ceramic reference tile
Inspection certificate
Nix lanyard
Microfiber carrying pouch
Microfiber cloth

Reflectance measurement

Measurement conditions:
M0 – UV included – ISO 13655:2017
M1 – D50 – ISO 13655:2017
M2 – UV excluded – ISO 13655:2017
Note: Particular reflectance measurement mode availability may differ based on application used.

Colorimetry data

Evaluated according to ASTM E308-18
CIEXYZ, CIELAB, LCH(ab), RGB, CMYK, and more
Illuminant: A, C, D50, D55, D65, D75, F2, F7, F11
Observer: 2°, 10°
Note: Particular colorimetry data availability may differ based on application used.

Software development kit

Features device connectivity routines, commands to request measurements, and utilities to perform color conversions.
For an up-to-date list of features and supported platforms, visit:
nixsensor.com/nix-software-development-kit/

Connectivity

Bluetooth Low Energy
Legacy USB CDC Serial

Warranty + expected product lifespan

12 months from date of sale, warranty for manufacturer's defects (does not cover user damage).

Premium service plan available for purchase.
For details, visit:
nixsensor.com/premium-service-plan/