ZOLL Medical

FiO_2 Closed-Loop Control Using the ZOLL 731 Series Ventilator

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Investigational Plan

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ARDS	Acute Respiratory Distress Syndrome
CLC	Closed-Loop control
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organization
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMP	Data Management Plan
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FFR	Federal Financial Report
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
GUI	Genitourinary Medicine
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MC	Manual Control
MedDRA®	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
N	Number (of subjects)
O_2	Oxygen
PaO2	Partial Pressure Arterial Oxygen
PCLC	Physiologic Closed-Loop Control
PEEP	Positive End-Expiratory Pressure

PHI	Protected Health Information
PI	Principal Investigator
PID	Proportional Integral Derivative controller
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SaO2	Oxygen Saturation
SOP	Standard Operating Procedure
SpO_2	Saturation of Peripheral Oxygen
UAP	Unanticipated Problem

1. PROTOCOL SUMMARY

Title:

FiO_2 Closed-Loop Control Using the ZOLL 731 Series Ventilator.

Précis:

A randomized, multicentere trial involving critically-ill patients comparing conventional, manual control of inspired oxygen (FiO_2) within a target range, with a computer-controlled, closed-loop FiO_2 delivery using an FDA-cleared continuous ventilator.

Objectives:

The objective of this study is to demonstrate that physiologic closed-loop control (PCLC) is at least as safe and effective as manual control in keeping hemoglobin oxygen saturation (SpO_2) within the target range of 92 to 96%.

The primary efficacy outcome is the relative duration as defined by the total duration of minutes with SpO2 within the target range of 92 to 96% divided by 720 minutes (the planned duration of the study). Similarly the relative duration for the primary safety outcome is defined as the total duration of time that the SpO2 level at or above 88% divided by 720 minutes.

Hypothesis:

We plan to conduct a 2-state statistical test: non-inferiority followed by a superiority test. Demonstration of non-inferiority for both the effectiveness and safety endpoints is required for study success.

Primary effectiveness for non-inferiority: The use of PCLC to maintain oxygen saturation (SpO_2) within the target range of 92 to 96%, as measured by the relative duration, is not inferior to the manual control (MC).

Secondary effectiveness for non-inferiority: The use of PCLC to maintain orxygen saturation (SpO_2) within the targe range of 92 to 96% when $FiO_2 > 21\%$ and $SpO_2 \geq 92\%$ when $FiO_2 = 21\%$, as measured by the relative duration, is not inferior to the manual control (MC) group.

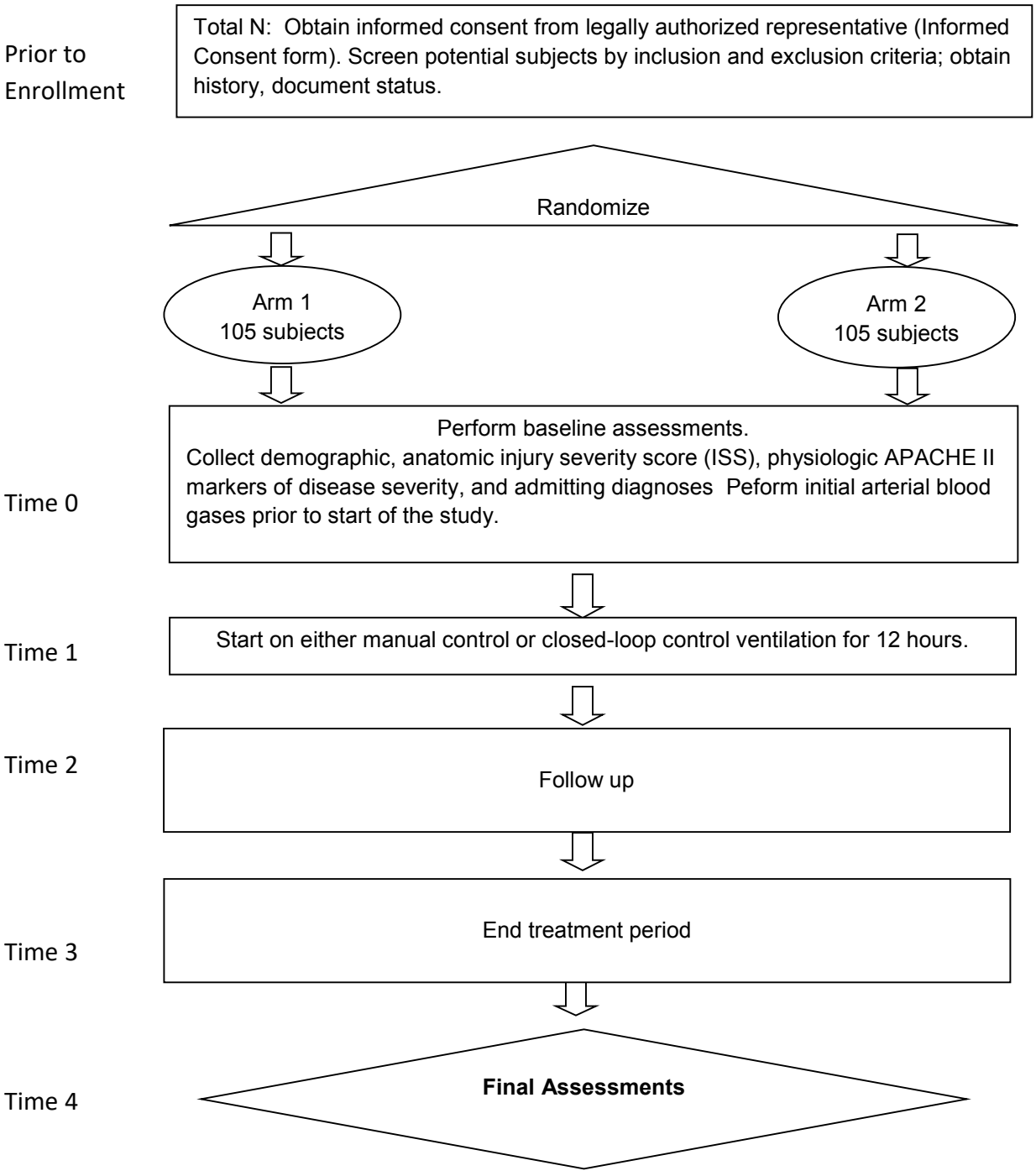
Primary effectiveness for superiority: The relative duration of time with SpO_2 within the target range of 92 to 96% is greater in the PCLC compared with manual control (MC) group.

Secondary effectiveness for superiority: The relative duration of time with SpO_2 within the target range of 92 to 96% when $FiO_2 > 21\%$ and

	$SpO_2 \geq 92\%$ when $FiO_2 = 21\%$, as measured by the relative duration, is greater in the PCLC compared with manual control (MC) group. **Primary safety**: The use of PCLC to maintain the SpO_2 level at or above 88%, as measured by relative duration of time, is not inferior to the manual control (MC).
Population:	The study population will consist of 210 critically-ill patients, male and female, between the ages of 18 - 65 who have been exposed to trauma and require mechanical ventilation and supplemental oxygen.

Number of Sites:	4 Sites 1. The University of Cincinnati Level 1 Trauma Center (Cincinnati, Ohio) 2. The Los Angeles County Medical Center Level 1 Trauma Center (Los Angeles, California) 3. University of Texas Health Science Center at Houston Level 1 Trauma Center (Houston, Texas) 4. Regions Hospital Level 1 Trauma Center (St. Paul, Minnesota)
Description of Intervention:	The trial will use [redacted] for automatic adjustment of FiO_2 to maintain the SpO_2 within a target range, based on continuous use of pulse oximetry. Intubated subjects will be randomized to either manual control of FiO_2 or closed-loop control of FiO_2, during a 12-hour period. The PCLC is designed to respond to acute hypoxemia (SpO2 <88%) within seconds while preventing hypoxemia and minimizing exposure to excessive inspired oxygen levels.
Study Duration:	15 months
Subject Participation Duration:	12 hours of study and 24 hours for follow-up.
Estimated Time to Complete Enrollment:	12 months

Schematic of Study Design:



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3. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

3.1 Background Information

The specific aim of this IDE clinical study is to test a ventilator closed-loop algorithm which will continuously adjust the level of inspired oxygen concentration (FiO_2) using physiologic closed-loop control (PCLC) to maintain a target level of hemoglobin oxygen saturation (SpO_2) based on readings from a pulse oximeter in critically ill patients in the Surgical ICU. Results from the study will be applicable to patients in the prehospital environment as well as during transport or during mass casualty events.

3.1.1 Device Description

The 731 Series ventilator used in the study is identical to the FDA-cleared device (K071526, K091238, K103318, K111473) except that the software has been revised to include FiO_2 physiologic closed-loop control algorithm. The ventilator has been cleared for use in the hospital and in the prehospital environment as well as during transport. In addition, the military has approved the device for use in all military ground and air transport vehicles.

This study will use a [redacted] for automatic adjustment of FiO_2 to maintain the SpO_2 at a target value (94% ±1%), see figure 1 and 2. It is also designed to respond to acute hypoxemia (SpO_2 <88%) within seconds and minimize exposure to excessive inspired oxygen. The proposed system is intended for prehospital and military use in far forward areas where O_2 supplies are limited. By reducing unnecessarily high FiO_2 the system will reduce exposure of the lungs to O_2 and save O_2 resources. Additionally, preventing hyperoxemia may mitigate the untoward effects of overwhelming oxidative stress.

The system to be studied uses pulse oximetry for continuous monitoring of oxygenation.[redacted]

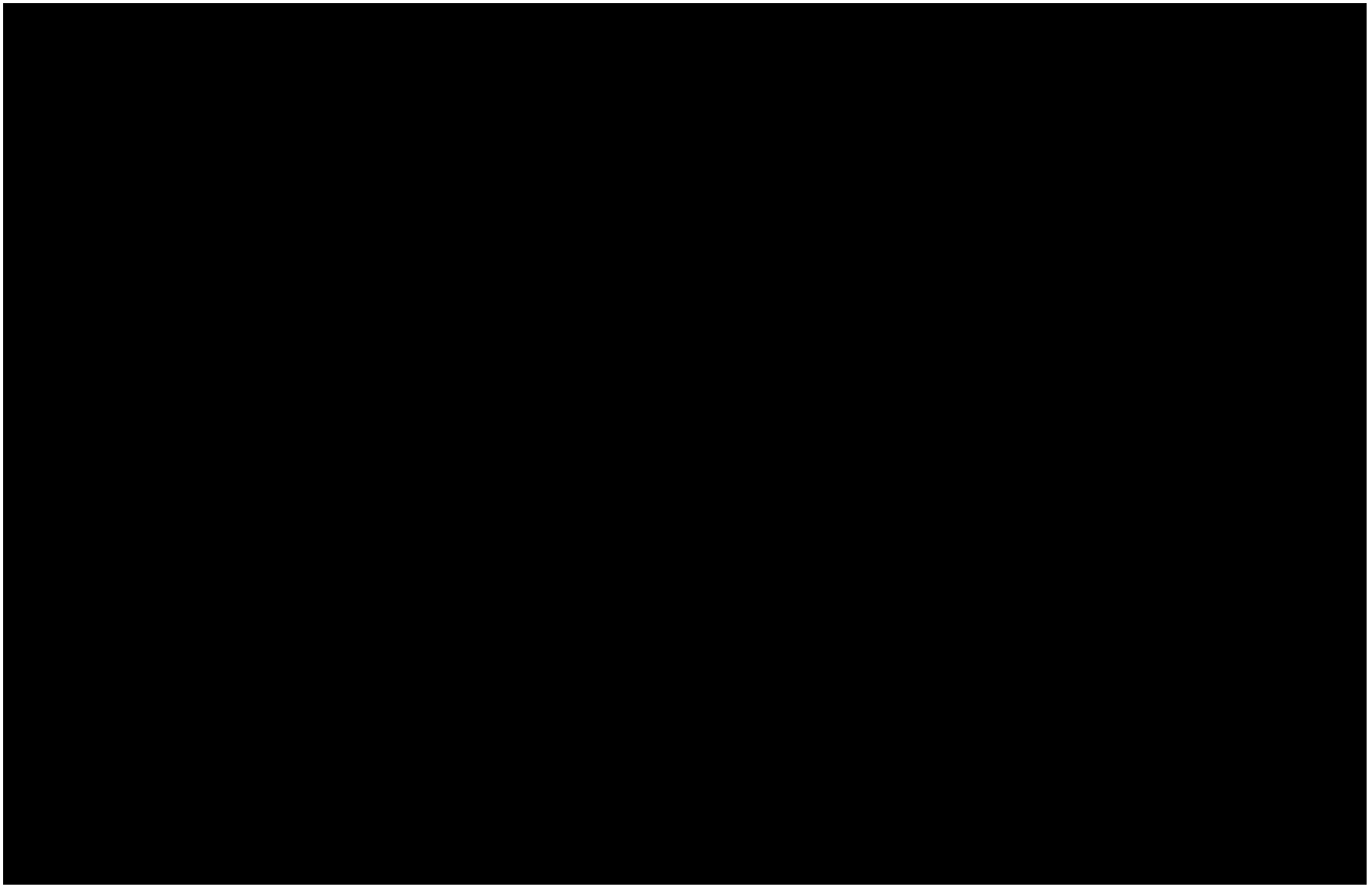
[redacted]

If the oximetry signal is lost, the algorithm is disabled and the FiO_2 remains constant (this is equivalent to the current practice) and both audio and visual alarms alert clinicians to the loss of SpO_2 signal and temporary pause of closed-loop control.

[redacted]

Figure 1

[redacted]



Accessories:

For the purpose of the study, each device shall be packaged with the standard 731 Series accessories which include: AC/DC power supply (p/n 024-0012-00), 6' AC power cord (US, p/n 708-0042-00), pulse oximeter connection cable (p/n 708-0037-00), test lung (p/n 820-0132-00) and high-pressure oxygen hose (p/n 825-0002-00). Single-patient use consumables: ventilator circuit (p/n 820-0106-00) and pulse oximeter sensor (p/n LNCS Adxt), shall be provided in bulk packs for use by the investigational team at no cost. All the these accessories have been reviewed and cleared with 731 Series Ventilator 510(k) submission.

In addition, a modified version of the user manual with specific labeling related to CLC shall be supplied with each device. A separate package shall contain the laptop, its power supply and the USB data connection cable.

Intended Use:

The intended use aligns with the intended use of the cleared 731 ventilators except that the patient population for PCLC use is in keeping with the study population.

The Model 731 ventilator is indicated for use in the management of infant through adult patients weighing ≥5 kg with acute or chronic respiratory failure or during resuscitation by providing continuous positive-pressure ventilation. The FiO2 physiologic closed-loop control functionality is intended only for use with patients 18 to 65 years of age who require mechanical ventilation as a result of trauma or acute surgical illness who would benefit from automatic control of their oxygenation. It is appropriate for use outside the hospital, during transport and in austere environments where they may be exposed to rain, dust, rough handling and extremes in temperature and humidity. In addition, the device is cleared for use in an MRI environment when specifically marked with the "MRI conditional" labeling. It is also not intended for use in explosive environments. With an appropriate third-party filter in place, they may be operated in environments where chemical and/or biological toxins are present (see External Filter Use in the Operation Manual). The Model 731 ventilators is intended for use by skilled care providers with knowledge of mechanical ventilation, emergency medical services (EMS) personnel with a basic knowledge of mechanical ventilation and by first responders under the direction of skilled medical care providers. The device has a full range of ventilation modes (AC, SIMV, CPAP with PS and NPPV-PPV).

For the purposes of the proposed investigation, the device will be labeled for investigational use and under the control of the investigational team.

3.2 Rationale and Report of Prior Investigations

For mechanically ventilated patients, maintenance of adequate oxygenation is a primary goal because hypoxemia can lead to cellular hypoxia, organ dysfunction, and/or death.[1, 2] At the same time, hyperoxemia should be avoided because of the potentially toxic effects of supplemental oxygen[3-5] and reported detrimental clinical impact of hyperoxemia.[6-8] With the current standard of care, clinicians manually adjust ventilator settings in order to maintain normoxemia; however, normoxia is not always achieved with manual adjustment.[9] Automated or physiologic closed-loop control (PCLC) of ventilation has potential advantages. With PCLC, physiological feedback is used to control the state or output of a dynamic system. Potential benefits of CLC are: 1) quicker continuous intervention compared to intermittent caregiver intervention, 2) consistent treatment based on physiology and proven algorithms, and 3) continued, appropriate treatment in the absence of a skilled caregiver. Medical applications of PCLC include anesthesia delivery, fluid delivery, and mechanical ventilation.[10-15] Use of PCLC of FiO_2 is most prevalent in the neonatal population where avoidance of hyperoxemia and hypoxemia are especially critical.[16, 17]

Automated or PCLC of ventilation may be especially valuable for remote operations and enroute care (ERC) because PCLC allows for optimal care regardless of location or care team. With military and civilian prehospital operations, patients are not always managed by physicians or care providers with advanced training. As a result, optimal care or even the standard of care may not be possible in prehospital and/or military environments. Even with highly trained personnel, ERC of critically injured patients is challenging. During transport healthcare providers are faced with space restriction, poor patient access, and vehicle motion/turbulence, which make the delivery of high quality patient care difficult. Healthcare providers also may risk their own safety during transport because, in order to properly access patients, they are often unrestrained.[18] Especially in the military setting, clinicians must balance the needs of multiple high acuity patients simultaneously during transport and thus may not have the capacity to continuously monitor and treat all patients.

While maintenance of adequate oxygenation and prevention of hypoxemia are the primary goals for patients requiring ventilation, oxygen consumption is an additional concern with military operations. During Critical Care Air Transport (CCAT) by the US Air Force Critical Care Air Transport Teams (CCATT), oxygen supplies account for nearly one-third of the mission weight. Mission planning commonly involves calculation of required oxygen needs and doubling of that value as a margin of safety. Uniform automated control of FiO_2 could result in a reduction in the amount of O_2 used to support patients during ERC by preventing inadvertent hyperoxia.

Our PCLC of FiO_2 system was developed to automatically monitor and manage life support ensuring adequate steady-state oxygenation, immediate response to acute desaturation events, and controlled use of oxygen for mechanically ventilated patients regardless of the treatment location or care team. This review provides a summary of prior investigations related to the use of automated control of the FiO_2 in mechanically ventilated patients and provides justification for the proposed study.

3.2.1 Summary of Investigations of other PCLC of FiO2 Systems

Preclinical FiO2 Physiologic Closed-Loop Control Systems

The first system of PCLC of FiO_2, which used SaO_2 as the physiological input, was described in 1975 by Mitamura et al.[19] Although the system was rudimentary, it was effective at maintaining SaO_2 in animals when changes in SaO_2 were minimal. In a series of three investigations, Tehrani and colleagues studied a microprocessor controlled system using proportional-integral-derivative control (PID) to automatically adjust FIO2 using pulse oximetry.[20-23] In this series of lung model and animal experiments the authors found that the controller was capable of restoring oxygen saturation to physiologic levels within 20-25 seconds.[20, 21] The authors concluded that the system was capable of correcting hypoxemia within seconds while preventing hyperoxia, eliminating artifacts, and minimizing oxygen exposure. While they cited the need for patient trials, none were accomplished. Raemer et al., also used a PID controller to adjust FiO_2 based on SpO_2 input in a series of animal experiments.[24] This system also used an artifact rejection algorithm and adjusted the FiO_2 gain based on the error signal (difference between actual and desired SpO_2) and minute ventilation. The response time to reach a stable SpO_2 after a change in FiO_2 was 50-70 seconds. Yu and colleagues also used computer simulation to demonstrate the performance of a FiO_2 control system and an animal experiment validated the model.[25]

Clinical FiO_2 Closed Loop and Open Loop Control Systems in Adults

Recently, an automatic control of FiO_2 system (Evita XL ventilator and Masimo SpO_2) was tested on 20 ICU patients and compared to 30 historical control patients treated by standard of care (manual FiO_2 adjustment by nursing staff).[26] The system was operated as an open-loop control system with a research nurse at the patient's bedside at all times. Two algorithms with different SpO_2/FiO_2 slopes were tested using a cross-over design. Both algorithms targeted SpO_2 of 92to 96% and acted to increase FiO_2 to 100% when SpO_2 fell below 85%. For the patients treated with the open loop FiO_2 control system, SpO_2 was in target range >95% of the time. The steeper SpO_2/FiO_2 slope was slightly better at maintaining SpO_2 in target range for the patients that were more hypoxemic (PaO_2/FiO_2<188). Compared to historical controls, patients treated with the open-loop FiO_2 control spent less time in hypoxemic and hyperoxemic states.

Another more complex system of PCLC ventilation, which includes PCLC of FiO_2 and PEEP as well as adaptive support ventilation (i.e. control of mandatory rate, inspiratory time, tidal volume, and inspiratory pressure), has been studied extensively. The safety of this PCLC system has been demonstrated in adult patients with normal lungs, ARDS, COPD, post cardiac surgery [12, 27-30] as well as during weaning from ventilator support of adult[13] and pediatric patients.[31] A lung model also showed good performance of the PCLC system in 4 clinical scenarios (normal lungs, brain injury, ARDS, COPD [32] This system has an ability to set target SpO_2. Lower setting of SpO_2 (90 to 92%) resulted in less oxygen use in ICU patients but had no impact on biochemical, physiological, or clinical outcomes. While there is ongoing research and use of FiO_2 PCLC in adults in Europe, the majority of FiO_2 control has focused on use in neonates where both hypoxia and hyperoxia create significant pathology for these patients.

PCLC systems have also been developed for devices that administer long-term oxygen therapy.[33, 34] These systems (AccuO2 and O_2 Flow Regulator) autonomously titrate the volume of oxygen delivered to a patient in response to changes SpO_2. In one study, 28 COPD patients were treated in a randomized cross-over design with a standard continuous-flow O_2 delivery system, the CR-50 O_2 conserving device, or the AccuO2 CLC system.[33] All three systems maintained SpO_2 near target range but the AccuO2 systems did so with less variability. Moreover, the AccuO2 system conserved more oxygen. In another study with a randomized crossover design, patients with chronic lung disease were treated during exercise using the PCLC O_2 Flow Regulator or manual oxygen flow titration by a respiratory therapist.[34] Overall, SpO_2 was higher and less time was spent below SpO_2 target when the O_2 Flow Regulator PCLC system was used.

FiO_2 Closed Loop Control Systems in Neonates

Automated control of FiO_2 has been studied most extensively in preterm infants. Control of oxygenation is particularly important for preterm infants because hypoxemia is associated with increased mortality whereas hyperoxemia can result in severe complications such as retinopathy, bronchopulmonary dysplasia, brain injury, and childhood cancer.[35-37] PCLC of FiO_2 was validated using simulation in 1985.[38] Beddis and Dugdale were amongst the first to study PCLC of FiO_2 in neonatal patients.[39-41] Using an indwelling umbilical PO_2 electrode the authors were able to demonstrate that the desired range of PaO_2 was achieved more frequently during closed-loop control compared with manual control (Beddis et al 88% PCLC vs. 72% manual; Dugdale et al 75% vs. 45%). Since those first studies, there have been numerous studies of PCLC systems of FiO_2 with SpO_2 as the physiological sensor.[16, 17, 42-52] The table below summarizes the literature. In all these randomized crossover studies, PCLC of FiO_2 was compared to either "optimal manual control," in which an investigator or research nurse was constantly present at the patient's side and fully dedicated to manual FiO_2 control, or "routine manual control" in

which the nurse on duty (responsible for 2 or 3 patients) was told to adjust FiO_2 as needed to maintain SpO_2 in the desired range. In all studies, the percent of time in target range was higher with PCLC compared with routine manual care and was similar or higher with PCLC compared with optimal manual care. Hyperoxia was also avoided with use of PCLC. The incidence of extreme hypoxia was comparable or lower with PCLC.

With a different study design, Wilinska and colleagues used the Avea ventilator FiO_2 PCLC system with Masimo pulse oximeter technology to treat preterm infants.[53] In this crossover study, the target SpO_2 range was alternated between 87-93% and 90-93% every 12 hours over 3 days. In this study with prolonged use of PCLC, manual FiO_2 adjustments were infrequent (<2 per day). Although the purpose of this study was to compare saturation with two different SpO_2 target ranges, it demonstrated the feasibility of prolonged use of PCLC of FiO_2.

Together, these clinical studies demonstrate that PCLC of FiO_2 has been safely used to treat extremely vulnerable and fragile preterm infants.

3.2.2 Summary of Investigations of our PCLC of FiO_2 System

Computer Simulation

Our PCLC of FiO_2 algorithm has been validated using computer simulation [redacted]

Preliminary Preclinical Trial

The initial preclinical trial of our PCLC of FiO_2 system, which was conducted in 2003-2004, is unpublished but described in the attached DARPA report (Darpa Final Report V2.pdf). [redacted]

[redacted]

The ventilator used for the PCLC porcine study was an Impact Instrumentation, Inc. Model 754 ventilator modified to accept command and control from an external laptop, which ran the algorithm and monitored a secondary pulse oximeter (MS-11, Masimo Corporation Irvine, CA) that provided the physiologic signal used by the controller. The initial ventilator settings were FiO_2 of 0.40, ventilation rate of 10 bpm, tidal volume of 10 ml/kg and PEEP of 0. Ventilation with PCLC of FiO_2 was stated in parallel with the fluid resuscitation. During the course of the experiment, the rate and tidal volume were adjusted by the resident to maintain E_TCO_2 >50 mm Hg. Positive end-expiratory pressure was increased to 5 cm H_2O towards the end of the experiment when SpO_2 could no longer be maintained with a FiO_2 of 100%.

As detailed in Figure 1 of the DARPA report, SpO_2 was maintained in the target range of 92 to 96% a total of 64% of the time and above 90% a total of 87% of the time. [redacted]

When excluding values with "FiO_2 rightfully at extremes," SpO_2 was within the target of 92 to 96% a total of 73% of the time and above 90% a total of 95% of the time [redacted]

[redacted]

[redacted]

In summary, this preliminary preclinical study demonstrated the feasibility of our PCLC FiO_2 algorithm as target SpO_2 was consistently achieved. [redacted]

Recent Preclinical Investigation in Animals with Lung Injury

In our most recent study we tested our PCLC system in a porcine model of combined hemorrhagic shock and acute lung injury.[56] We hypothesized that the PCLC would reliably maintain safe levels of oxygen saturation in both injured and uninjured animals.

[redacted]

[redacted]

The study examined the ability of the PCLC system to maintain oxygenation in a porcine model of hemorrhagic shock and acute lung injury. We found that the PCLC system responded to changes in SpO2 with appropriate increases and decreases in FIO_2 and maintained the target SpO_2 range comparably in both injured and uninjured animals.

Enroute Care, In Situ Data Collection

In an effort to understand the mechanical ventilation challenges faced during en route care and to demonstrate use of our ventilator and integrated pulse oximeter in this setting, we collected data from a series of ventilated warfighter patients during en route care.[59] Twenty-two patients were monitored as they were evacuated by USAF CCAT teams from Balad Air Base, Iraq to Landstuhl Regional Medical Center (LRMC), Germany during the time period of June to September 2006. Patients were managed following the standard of care and monitored both with the pulse oximeter from the critical care monitor and a pulse oximeter integrated into the Impact 754 ventilator. The preexisting RS-232 data port on the Impact 754 ventilator was used to download ventilator settings, and monitored values (i.e. HR and SpO_2) every 5 seconds to a separate laptop computer.

All 22 subjects survived transport from Iraq to Germany and the data set included 117 hours of continuous recording. For five patients, there were no recorded ventilatory changes in flight. Three desaturation events, <90%, were recorded lasting 35, 115, and 280 seconds. No interventions were recorded during the desaturation events with spontaneous resolution in all patients. The FiO2 ranged from 24 - 100% with an average of 49%. FiO_2 was the most common ventilatory change made by CCAT teams en route averaging 0.27 changes per hour. SpO_2 ranged from 85 - 100% with a mean of 98%.

Desaturation was defined as a recorded SpO_2 of less than 90%. The following three episodes were seen: 85% nadir for 35 seconds, 86% nadir for 115 seconds and an 89% nadir for 280 seconds. No interventions in mechanical ventilation were seen during these desaturation episodes with spontaneous resolution to a SpO_2 of ≥90% in all patients.

[redacted]

Overall the study was the first effort to collect data from patients on life support during enroute care. It may be that the human factors in the context of this difficult mission are the most important finding. Despite the care provider to patient ratio of no more than 2 patients/team (critical care physician, critical care nurse and respiratory therapist), 3 of 22 patients had desaturation events (14%) that were unwitnessed and untreated. This finding should not reflect negatively on the efforts or skill of the CCAT team but rather on the exceedingly difficult challenge of caring for these patients during en route care. It is this context that led us to propose that autonomous controller(s) could be beneficial when care providers are not available to monitor or manage the patient or when other mission needs (other patients or the safety of the care provider is in jeopardy).

Initial Clinical Trial

We subsequently applied for and received an IDE [redacted] to study FiO_2 PCLC in multi-trauma patients who required mechanical ventilation. The results from the first subset of patients were published[60] [redacted]

The PCLC system used for this study was similar to the system used for the initial preclinical study described [redacted]

A total of 95 mechanically ventilated trauma patients were enrolled in this randomized crossover study. In random order, patients were treated for 4 hours with the ventilator FiO_2 adjusted by a respiratory therapist according to standard practice and 4 hours with FiO_2 adjusted automatically by the PCLC system. During the control period, clinicians aimed to maintain SpO_2 of >94% and reduce FiO_2 to nontoxic levels (FiO_2 <0.50). During the automated control period, the PCLC system adjusted FiO_2 to a target SpO_2 of 94 ±2%. The study was conducted with a safety monitor at the bedside.

The primary safety endpoint, total duration of desaturation (SpO_2 <88%), was significantly longer with manual control compared with automated control (1.25 ±2.64 minutes vs. 0.55 ±1.37 minutes, p=0.0018). SpO_2 was maintained in the target SpO_2 range of 92 to 96% more often during the automated control period compared with the manual control period (p<0.001). Oxygen use was significantly lower during the automated control period (1.91 ±1.51 L/min) compared with manual control period (3.04 ±1.37 L/min, p<0.001).

There were no equipment failures or unanticipated adverse effects identified during the study. The only anticipated adverse events were related to the patients' critical illness (e.g. anxiety, agitation, pain, and dyspnea) and there was no difference between the groups. There was one serious event in which a patient was being bathed and the endotracheal tube became kinked. The SpO_2 fell and the FiO_2 was increased to 1.0 the patient recovered spontaneously and FiO_2 control following the protocol was continued with no adverse effect.

Table- Closed-loop control of FiO_2 Studies in Preterm Infants

				In Target Range (%)		
First Author	**Year**	**Study Population**	**Target SpO2 range**	**PCLC**	**Control**	**Control Type**
Bhutani [42]	1992	14 pre-term infants	94-96%	81	54	RMC
					69	OMC
Sun [44]	1997	16 pre-term infants	set ± 3%	72*	58	RMC
Claure [48]	2001	14 pre-term infants	88-96%	75	66	OMC
Urschitz [50]	2004	12 pre-term infants	87-96%	91	82	RMC
					91	OMC
Morozoff [45]	2009	7 pre-term infants	90-96%	73	57	RMC
Claure [46]	2009	16 pre-term infants	88-95%	58	42	RMC
Claure [47]	2011	32 pre-term infants	87-93%	40	32	RMC
Hallenberger [16]	2014	34 pre-term infants	site specific	72	61	RMC
van Kaam [49]	2015	80 pre-term infants	89%-93% or 91%-95%	62	57	RMC
Waitz [51]	2015	15 pre-term infants	86-96%	76	69	RMC
Lal [17]	2015	27 pre-term infants	90-95%	73	60	RMC

OMC- optimal manual control; RMC- routine manual care; PCLC- closed loop control; * open-loop control

Prior investigation by both our group and others demonstrates the feasibility of automated control of FiO_2 and that the investigation can be performed safely in the proposed clinical setting.

3.3 Potential Risks

The risks associated with this trial are minimal.

Subject risks:

All subjects will require intubation and mechanical ventilation. The ventilator used in the study performs identically to the FDA-cleared device (K071526, K091238, K103318, K111473). There are many risks associated with intubation and mechanical ventilation, quite apart from the investigational portion of this protocol. These are addressed in the Instructions for Use and User Manual for the 731 Series ventilator. The investigational portion of the protocol is the algorithm which automatically adjusts the FiO_2. During the study, SpO_2 will be monitored by two pulse oximeters, one used as the input for the FiO_2 control and the second as a redundant safety monitor.

Patients enrolled in the trial will have been subject to traumatic injuries or acute surgical illness requiring surgical intervention. The multitrauma found in the civilian setting is quite analogous to the trauma that can result from combat: penetrating and blunt as well as severe hemorrhage. These injuries along with acute surgical illness may include crush injuries, sepsis, and blood loss. are anticipated. In the feasibility study, we observed very few safety adverse events related to patient condition.

During the study, SpO_2 will be monitored by two pulse oximeters: one used for the output of the FiO_2 controller and the second as a redundant safety monitor. All subjects will continue to be monitored using standard intensive care protocol. Adverse events will be verified based on observation, bedside notes and the subject's medical record.

Appendix A provides the definitions for possible adverse events, including definitions for the seriousness, relatedness and device/procedure relatedness.

Increased oxygen desaturation due to progressive lung dysfunction and missed diagnosis or delayed treatment of a condition that causes desaturation (pulmonary embolism, pneumothorax, pneumonia) as a result of PCLC titrating are rare and given the use of the controller, the subjects oxygenation is maintained. [redacted]

Progressive lung dysfunction in this patient population may be difficult to diagnosis within the 12-hour study period. Increased neutrophilia, defencins, and other inflammatory responses may lead to increased lung permeability. The current protocol is clear on how to proceed. If there is a sustained increase in FiO_2 without an increase in O_2 saturation, then the subject will be evaluated by the clinical team and other diagnostic measures will be employed: chest x-ray, ultrasound, CT scan to assist in understanding the sustained desaturation.

Progressive lung dysfunction may occur in the presence of pneumothorax, pneumonia, pulmonary embolism or other condition(s) directly related to the subject's traumatic injuries. We anticipate that if progressive lung dysfunction does occur, FiO_2 will be maximized to ensure oxygen saturations above the 92% level. In addition, subjects will be evaluated by the clinical team at the institution to determine any additional diagnostic or therapeutic measures, such as CT scan, PEEP, anticoagulant therapy, etc.

In cases where the FiO_2 cannot be titrated from 1.0, the subject will continue in the manual control but the data will not be used because an FiO_2 of 1.0 will not inform the study.

Delay of treatment of a condition that causes desaturation is unlikely to occur in this patient population. Subjects will be cared for in a 2:1 ratio with an ICU nurse and a respiratory therapist. Symptoms of sustained hypoxia will be noted immediately and strategies employed to treat the hypoxemia will be employed, even in the absence of a specific diagnosis. Pulmonary embolism, pneumonias or pneumothorax will be readily diagnosed with diagnostic radiological tests.

Ventilator risks:

There are known risks associated with all ventilatory strategies. These are well known and characterized in the 731 Operation Manual. The PCLC adapted Operation Manual also includes specific information on the operation and management of the device during PCLC operation. There are no unanticipated ventilator-centric risks associated with this protocol.

3.4 Potential Benefits

One potential benefit to participants is the constant equilibration of oxygen saturation to remain within the physiologic target range of 92 to 96%, preventing exposure to excessive inspired O_2 levels while at the same time preventing transient hypoxemia.

Another potential benefit will be the ability to prevent hyperoxemia, by keeping the SpO_2 within the target range.

4. STUDY OBJECTIVES

The specific objective of this IDE clinical study is to test a physiologic closed-loop algorithm which will continuously adjust the level of inspired oxygen concentration (FiO_2) of a mechanical ventilator using physiologic closed-loop control (PCLC) to maintain a target level of hemoglobin oxygen saturation (SpO_2) based on readings from a pulse oximeter in critically ill patients in the Surgical ICU. Results from the study will be applicable to patients in the hospital and in the prehospital environment as well as during transport. The 731 Series ventilator used in the study is identical to the FDA-cleared device (K071526, K091238, K103318, K111473) except that the software has been revised to support include FiO2 control algorithm. In addition, the military has approved the device for use in all military ground and air transport vehicles.

4.1 Primary Objective

The primary effectiveness objective is to demonstrate that use of PCLC is not inferior to the manual control in keeping hemoglobin oxygen saturation (SpO_2) within the target range of 92 to 96% while the primary safety objective is to demonstrate that the use of PCLC is not inferior to the manual control in maintaining the oxygen saturation (SpO_2) at or above 88% level.

4.1.1a Primary effectiveness variable:

To assess the relative duration of time with SpO_2 between 92 and 96% (inclusive) during the study period.

4.1.1b Secondary effectiveness variable:

To assess the relative duration of time with SpO_2 between 92 and 96% (inclusive) when FiO_2>21% and $SpO_2 \geq 92\%$ when $FiO_2 = 21\%$.

4.1.2a Primary effectiveness hypothesis

The use of PCLC to maintain hemoglobin oxygen saturation (SpO_2) within the target range of 92 to 96%, as measured by the relative duration, is not inferior to the manual control (MC).

4.1.2b Secondary effectiveness hypothesis

The use of PCLC to maintain hemoglobin oxygen saturation (SpO_2) within the target range of 92 to 96% when $FiO_2 > 21\%$ and $SpO_2 \geq 92\%$ when $FiO_2 = 21\%$, as measured by the relative duration, is not inferior to the manual control (MC).

4.1.3 Primary safety variable

To assess the relative duration of time with SpO_2 <88% during the study period.

4.1.4 Primary safety hypothesis

The use of PCLC to maintain hemoglobin oxygen saturation (SpO_2) level at or above 88%, as measured by the relative duration, is not inferior to the manual control (MC).

4.2 Secondary Objectives

Four additional safety related question will be addressed:

1. The rate of serious adverse events related to the PCLC is not different than those attributed to the MC group
2. The rate of serious adverse events not related to the PCLC is not different than those attributed to the MC group
3. The number of missed diagnosis attributed to the PCLC is not different than those attributed to the MC group
4. The rate of device related adverse events related to the PCLC is not different than those attributed to the MC group.

4.3 Study Design

- The trial will employ a two group parallel design in which subjects will be randomized to one of the two ventilatory strategies for a 12 hour period. Twelve hours was selected because it captures most scenarios where mechanical ventilation could be required in the preshospital and transport environments in both military and civilian use. The two ventilatory strategies are: 1) manual adjustment of the ventilator FiO_2 by the treatment team based on physician order or according to current protocol (manual control period) or 2) automatic adjustment by the system algorithm (closed-loop period). Manual adjustment will use the same SpO_2 target (94%) as the closed loop system. During closed-loop control, the FiO_2 can be over-ridden by the clinician at any time.

- This is a multicenter trial with four sites (The University of Cincinnati Level 1 Trauma Center, The Los Angeles County Medical Center Level 1 Trauma Center, The University of Texas Health Science Center at Houston Level 1 Trauma Center, and Regions Hospital Level 1 Trauma Center). All patients age 18 to 65 inclusive admitted to the Trauma/Acute Care service and requiring invasive mechanical ventilation will be screened for the study. This age range is intended to represent the group of warfighters and support personnel to be treated with this system. These patients will be unable to provide consent due to the severity of their injuries. Their legal representative will be approached as soon as possible. Once consent has been obtained the patient will be randomly assigned to one of the two study arms and enrolled in the study; subjects are not considered to be enrolled in the study until they have been successfully randomized to receive either CLC or manual control of the study ventilator.

- Baseline characteristics including demographic information, anatomic Injury Severity Score (ISS), physical exam findings, and physiologic (APACHE II) markers of disease severity, and admitting diagnoses will be assessed for all subjects. An arterial blood gas obtained prior to study enrollment will be recorded to define the degree of lung injury. Ventilator settings and vital signs immediately prior to the start of the clinical study will also be recorded.

Subjects will be studied for a total of 12 hours and will be monitored for an additional 24 hours

- During the entire study period, oxyhemoglobin saturation (SpO_2) will be continuously recorded. In addition, patient vital signs and ventilator settings (mode, respiratory rate, tidal volume, FiO_2, airway pressures, PEEP) will be monitored continuously and recorded. Any blood gases (including pH, $PaCO_2$, and PaO_2) performed for routine care will also be recorded. Following the first hour of each study period, a single blood gas will be drawn to verify the relationship of SpO_2 and SaO_2 and to assure adequate $PaCO_2$ and pH. The total amount of blood drawn will be ~1 teaspoon (5 ml). During each study period the number of manipulations of FiO_2 by clinicians and by the system algorithm will be recorded automatically. The Case Report Form will also capture the times of any clinically significant events (hypotension, defibrillation, adjustment of FiO2 by ≥10%) and these times will be merged to the measurement times. This data acquisition plan (collection of data from the monitor, ventilator, and CRF elements) will provide the ability to interpret the results in detail and monitor the safety of the trial.

As noted previously, the primary efficacy variable will be control of SpO_2 within the target range, 92 to 96%. The table below compares the protocol for both the manual and PCLC periods.

Variable	**Manual Control**	**Closed-Loop Control**
FiO_2	Set as directed by clinician	Set as directed by clinician
SpO_2 Target	92 to 96% following the Manual Protocol, Figure 3	92 to 96%, using the PCLC system
SpO2 Desaturation Upper Limit	88%	88%
If Desaturation Occurs	Follow manual control protocol (figure 3)	Permit closed-loop algorithm to manage unless otherwise directed by clinician.

When the subject is in the manual control period, FiO_2 will be adjusted manually following the protocol in Figure 3. If SpO_2 falls below 88%, the ventilator will trigger the Low SpO_2 alarm (medium priority) and the treatment team will respond and take corrective actions. This is the current standard of care. In order for this to take place, the alarm must trigger, a caregiver must respond, determine the cause, and take corrective action.

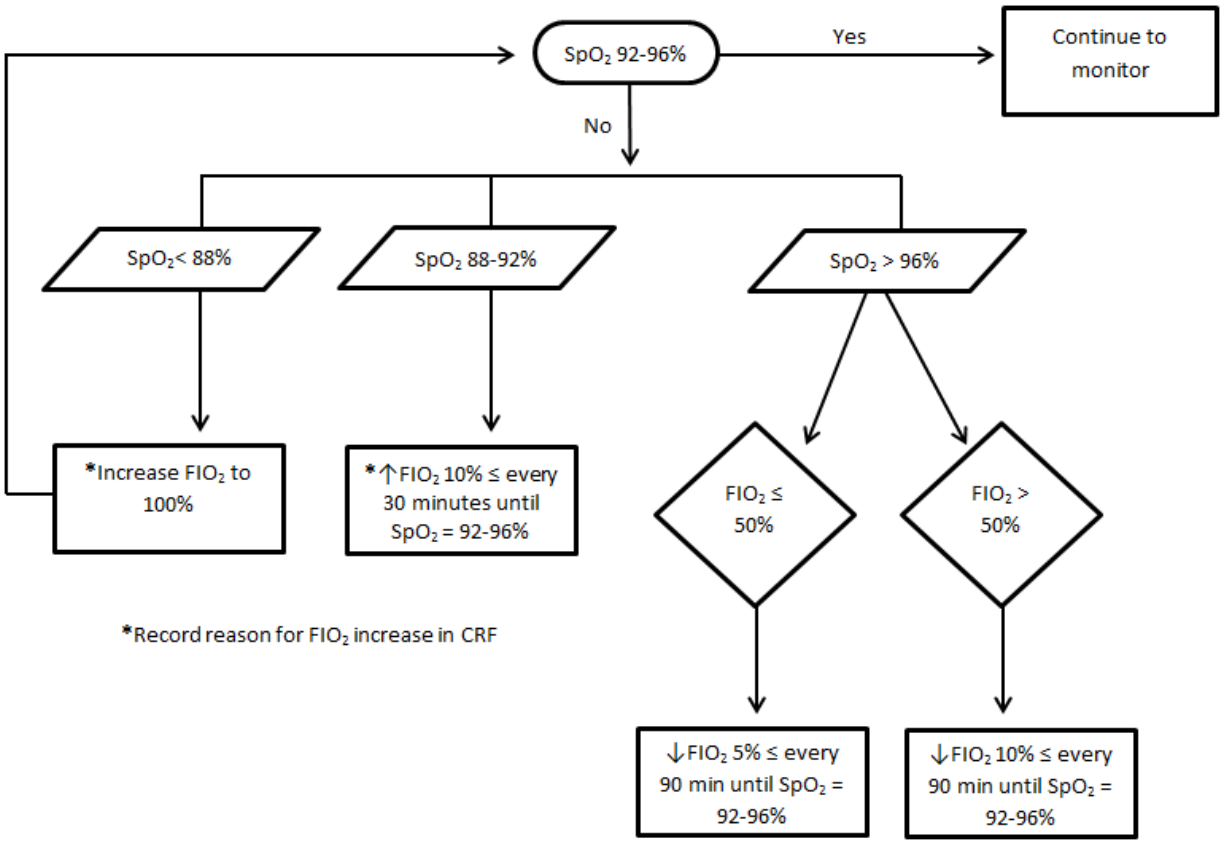


Figure 3

The closed-loop control system includes both audible and visual alarms to alert the clinician of an unreliable signal from the pulse oximeter, malposition of the pulse oximeter sensor, and subject SpO_2 less than 88%. Details of these alarms are documented in Appendix B which is taken from the Operation Manual. All alarms and low SpO_2 conditions will be recorded automatically on the laptop computer data logger.

If the subject requires a procedure in the ICU that the standard of care requires an increase in FiO_2 to 1.0 (e.g. bronchoscopy) the data collection will automatically continue but such data will

not be considered in the statistical analysis because such procedures are not part of the trial protocol. The Case Report Form will capture such events and note the times that such procedures began and were completed. Data inclusion in the statistical analysis will resume once FiO_2 control returns to the trial protocol. If the subject requires transfer to the operating room, radiology for treatment or some other non-ICU location, data collection will not be included in the statistical analysis until the subject returns to the ICU. These incidents outside of the ICU will also be captured on the Case Report Form. The goal of the study will be to have a minimum of 12 hours of data collection for each subject in either arm of the study

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1 Study population

All patients between the ages of 18 and 65 inclusive, admitted to the Trauma/Acute Care service and requiring invasive mechanical ventilation will be screened for the study. This age range is intended to represent the group of warfighters and support personnel to be treated with this system.

5.2 Sample size

The target sample size is 105 subjects per study arm for a total of 210 subjects. The detail of the sample size estimation is given in section 12.

5.3 Subject Inclusion Criteria

All subjects must meet all of the inclusion criteria and none of the exclusion criteria in order to be eligible to participate:

- The subject's legally authorized representative will provide signed and dated informed consent.
- Age 18 - 65, inclusive.
- Admission to a surgical or neurosurgical intensive care unit following traumatic injury or acute surgical illness
- Requirement for endotracheal intubation
- Requirement for mechanical ventilation
- Patient is currently receiving inspired oxygen concentration (FiO_2) ≥40%

5.4 Subject Exclusion Criteria

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

- Age under 18 or over 65
- Isolated or severe head injury (Glasgow Coma Scale = 6 or less) with expected survival less than 24 hours
- Brain death
- Anticipated survival less than 48 hours

- Pregnant female
- Patient in whom a pulse oximeter cannot detect a reliable signal due to hypotension, hypothermia, or other injury
- Known carbon monoxide poisoning
- Uncontrolled diabetic
- Patient who is unable to maintain SpO_2 level of 88% at an FiO_2 of 100% due to their medical condition.

  (NOTE: Being in the trial would impose no additional risk to a patient who presents with this condition however, data from a patient presenting with this pathophysiology would not provide insight into the performance of the controller as it would simply maintain that patient on an FiO_2 of 100%.)
- Patient with chronic hypercarbia.
- Patient where a physician believes that FiO_2 PCLC could be detrimental to the management of the patient.
- Prisoner
- SpO2 to SaO2 difference >4%
- Patient with core temperature <35° C

5.5 Strategies for Recruitment and Retention

There will be no compensation to subjects for study participation.

We anticipate subject participation not to exceed 24 hours of data collection (to produce 12 hours of evaluable data) for the entire study; however subjects will be monitored for adverse events for 24 hours following the end of the intervention. Subjects will be terminated from the study after the 24 hour period ends.

We have chosen the four Level 1 trauma units to maximize recruitment of a study population that meets all of the inclusion criteria. Each trauma unit admits approximately 85 trauma patients/year that would be eligible for this study and we plan to recruit equal numbers of subjects from each trauma unit. If this is not feasible, no more than 60% of the total subjects will come from a single study site.

5.6 Treatment Assignment Procedures

5.6.1 Randomization Procedures

Once informed consent has been obtained from the patient's family or legal representative, the patient will be enrolled in the study and randomly assigned to one of the two ventilatory strategies. Subjects will be randomized using a stratified, blocked randomization scheme with random block sizes of 4 and 6, generated by the study statistician. Study participants will be allocated with equal probability to each study group with stratification by center. The randomization procedure will generate a study number for each participant that links the corresponding group allocation in accordance with block size and strata. An independent statistician which is not part of the research team will validate and generate the final randomization assignment. As each subject is entered into the study, study personnel in Cincinnati will consult this randomization scheme to determine which study arms will the subject need to be assigned to.

5.6.2 Subject Withdrawal

Subject's authorized legal representative may voluntarily withdraw consent from the study or the investigator may terminate a subject's participation.

An investigator may terminate a study subject's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

Subject discontinuation due to an AE, or other medical condition, will be followed up by the clinical study site staff to insure appropriate care and to record any events that are related or unrelated to safety or effectiveness outcomes of this study and this will be reported to the DSMB.

5.6.3 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. See the list below. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the principle investigator, funding agency, the Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform each of the IRBs and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects resulting from the PCLC system or study design.
- Insufficient adherence to protocol requirements by the study team.
- Data that is not sufficiently complete and/or evaluable.

6 STUDY INTERVENTION

Study Product Description

The device used in the in study is a 731 Series ventilator whose software has been modified to include FiO_2 PCLC. In all other ways the device is identical to devices that are used routinely by civilian and military care providers. The 731 has an integrated pulse oximeter that provides the signal used by the PCLC algorithm to adjust the FiO_2 as required. In addition to the standard ventilator and pulse oximetry alarms, the modified code also has additional alarms that are related to PCLC, these are described in Appendix B. The data signal also includes all alarm and device condition information (power status, battery status, barometric pressure, ambient temperature, etc.).

6.1 Acquisition

Study product will be loaned to the study team by the sponsor and will include:

- Ventilator with modified software bearing appropriate investigation labeling
- Single-patient use breathing circuits
- Single-patient use pulse oximeter sensors
- AC/DC power supply
- Data acquisition computer with shielded USB interface cable
- Operating manual that covers both normal and PCLC operation and alarm features.

At the conclusion of the study or in the event the study is terminated prematurely, the ventilator and all durable accessories will be returned to the sponsor.

6.2 Formulation, Packaging, and Labeling

The ventilator will be labeled for investigational use only and will be under the control of the study team at each location. Consumables are not modified and are supplied in their standard packaging.

6.3 Product Storage and Stability

Product will be under the control of the study team at each location who will be responsible for configuring the system for use in the study. While the study will take place in an ICU setting the device is cleared for an extreme range of operating and storage environments and as such, no special storage requirements are necessary. Processing the device between patients will follow the procedures defined in the standard labeling which calls for single-use consumables to be discarded while the device is cleaned following the hospital's device cleaning procedures.

6.4 Accountability Procedures for the Study Product

Each study location will provided with 2 systems, as described above. The systems will be under the control of the local study team. Consumables will be provided as needed. *At the conclusion of the study or in the event the study is terminated prematurely, the ventilator and all durable accessories will be returned to the sponsor.*

7 STUDY SCHEDULE

7.1 Screening

7.1.1 Visit 1: Screening/Enrollment

- Obtain and document consent from family member or legal representative on screening consent form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility.

7.1.2 Visit 2: Time 0 + 12 hours

- Administer the intervention that will be either manual control of FiO_2 or automated closed-loop-control of FiO_2 depending on the randomization assignment. Following administration of the intervention
- Assess physiological status
- Record adverse events as observed by investigator.
- Record results of physical examinations.
- Record any clinician changes in ventilator settings.
- Record any blood gas results from routine care
- Assess vital signs

7.1.3 Visit 3: Time 24 hours after the intervention

- Assess physiological status
- Record adverse events as observed by investigator.
- Record results of physical examinations.
- Assess vital signs

8. STUDY PROCEDURES /EVALUATIONS

8.1 Study Procedures/Evaluations

1. Medical history from medical records.
2. Physical examination (list the vital signs [including height and weight] and organ systems to be assessed. Address details in the MOP.); if appropriate, discuss what constitutes a targeted physical examination and at what visits it may occur.

8.2 Clinical Laboratory Evaluations

1. Baseline blood gas analyses, as ordered by the clinical team.
2. Arterial blood gases
3. Continuous transcutaneous oxygen saturation

9. ASSESSMENT OF SAFETY

This study involves a previously cleared continuous ventilator with an investigational component – the physiologic closed-loop controller. Reporting of certain events is mandatory because of the study population or study design characteristics; the study is conducted at multiple sites, and will require centralized safety oversight.

9.1 Specification of Safety Parameters

9.1.1 Primary Safety variable:

To assess the relative duration of time with SpO_2 <88% during the study period.

9.1.2 Secondary safety variables:

- Evaluation of missed diagnoses
- Rate of serious device-related AEs
- Rate of serious AEs not related to the device
- Rate of device-related AEs

9.2 Unanticipated Problems

We consider unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets 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 subject 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 subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.3 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

9.4 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.5 Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

The PI will record all reportable events with start dates occurring any time after the patient is randomized until 24 hours after the subject is removed from the study ventilator. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

9.6 Characteristics of an Adverse Event

9.6.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Unlikely, Possibly, Related)
    i. The event is known to occur with the study intervention.
    ii. There is a temporal relationship between the intervention and event onset.
    iii. The event abates when the intervention is discontinued.
    iv. The event reappears upon a re-challenge with the intervention.
2. Not Related

i. There is no temporal relationship between the intervention and event onset.

ii. An alternate etiology has been established.

9.6.2 *Expectedness of SAEs*

The Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. All serious adverse events will be subsequently reported to the DSMB.

9.6.3 *Severity of Event*

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)

2. Moderate: minimal, local, or noninvasive intervention indicated; moderate impact on ADL

3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

9.6.4 Reporting Procedures

SAE's require expedited reporting when meeting the following criteria:

- The incident is serious
- Unexpected given the subject's condition and use of mechanical ventilation
- Suspected adverse reaction to closed-loop control of FiO_2. This would include a determination by the PI that the event is **not** related to consequences of the underlying disease or condition under study or events common in the study population.

These events are required to be reported to the FDA within 7 calendar days of the sponsor's initial receipt of the information if characterized as fatal or life-threatening. Non-fatal or non-life threatening events must be reported no later than 15 calendar days after the sponsor determines that the serious suspected adverse reaction (SSAR) or other information qualifies for reporting.

All SAEs are to be reported to the IRB and the DSMB as per policy.
The Data Safety Monitoring Board (DSMB) will be required to review all SAEs periodically regardless of causality.

10. STUDY OVERSIGHT

10.1 Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) composed of members with expertise in clinical medicine, mechanical ventilation, anesthesia, and biostatistics will provide oversight of safety events. The DSMB will meet after approximately 25%, 50%, and 75% of the study is enrolled, but not less than once per year. If safety concerns arise, more frequent meetings may be held. The DSMB will operate under the rules of the approved charter.

- The DSMB will contact Zoll to assure there is prompt identification of any adverse event(s) that could affect either human subject protection and/or clinical study data quality. This monitoring will include both on-site and off-site file review of the communal data depository which will have all of the IDE data, forms etc.

- Adverse events are defined in Appendix of the Protocol.

- Adverse events and safety data will also be reviewed by the study medical monitor who will have authority to terminate the study at any time due to safety concerns.

- ZOLL is responsible for stopping the trial if there is a risk to either human subject protection and/or clinical study data quality and reporting the decision to the FDA.

10.2 Training

The procedures for the physiologic closed-loop ventilation on the 731 Series ventilators are familiar to the University of Cincinnati Medical Center (UC). The staff has been trained and is experienced with the 731 Series ventilator as the device is currently used at UC for care and transport of patients. Training for the other clinical sites will be performed by staff from UC, based on their expertise, training and a Modified Operation Manual. Training will detail: study design, contraindications of use, using the closed-loop system, new alarms associated with the closed-loop functionality, interpreting the closed loop symbols on the user interface, documentation requirements (case report form) and adverse event reporting.

11. CLINICAL SITE MONITORING

Clinical trial monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, to verify that the reported clinical trial data are accurate, complete, and verifiable from source documents, and to verify that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with Good Clinical Practices (GCP), and with the applicable regulatory requirement(s). Both on-site and remote monitoring will be conducted.

12. STATISTICAL CONSIDERATIONS

12.1 Sample size

12.1.1 Primary Efficacy objective:

The primary efficacy endpoint is the relative duration of time where SpO_2 remains between 92 and 96% (inclusive). This will be obtained from continuously monitoring the subjects SpO_2 level throughout the study period such that at least 12 hours of monitoring data are available for each subject. The difference in the average amount of time will be the basis for the efficacy outcome comparison between the two ventilatory strategies.

To assess power for this objective the sample size calculation is based on preliminary data estimating the relative duration of time that SpO_2 remains between 92 and 96% (inclusive). To determine the noninferiority margin, the guidelines provided by FDA were followed (*http://www.fda.gov/downloads /drugs/guidancecomplianceregulatoryinformation /guidances/ucm202140.pdf*). From our preliminary data, the relative duration of time in which the SpO_2 remained between 92 and 96% in a four hour time interval for the MC group was 0.30 with 95% CI (0.23, 0.38). Following the guideline mentioned above we used half of the lower confidence bound to be the margin of non-inferiority (i.e. 0.12, which is equivalent to 7.2 minutes per hour) From our preliminary data, the SD for the MC and PCLC group was 0.33 and 0.23 respectively. Assuming a noninferiority margin of 0.12, a sample size of 91 subjects per group will achieve 80% power with a 2.5% one-sided significant level when the true difference between the group means is assumed to be zero. Allowing a 15% attrition rate for potential withdrawal of subjects the required sample size is 105 per group.

12.1.2 Primary Safety objective:

The primary safety endpoint is the relative duration of time with SpO_2 <88% over the study period. This will be observed by continuously monitoring each subject's SpO_2 level throughout the study period such that at least 12 hours of monitoring data are available for each subject. From our preliminary data the observed relative time where SpO_2 <88% was 0.004 and 0.002 for the MC and PCLC group respectively. The proposed sample size of 105 per group will allow us to conclude non-inferiority with a margin of 0.004 (which is equivalent to 15 seconds/hr) with 95% power with a 2.5% one-sided significant level.

Therefore for this study we are proposing to enroll a total of 210 subjects to test the noninferiority hypothesis for both our primary safety and effectiveness outcomes. For all sample size estimates, PASS version 12 (PASS, NCSS LLC., Utah, US) was used.

If noninferiority is demonstrated, the proposed sample size also has 80% power to test for the superiority of the LLC group versus MC group both in terms of the primary effectiveness and safety outcomes if the true difference between ventillatory strategies is at least 0.14 (which is equivalent to 8.2 minute per hour) for the primary efficacy endpoint and is at least 0.003 (which is equivalent to 10 second per hour) for the primary safety endpoint.

12.2 Statistical Analysis

For the primary outcomes, the intent-to-treat (ITT) population will be used for all efficacy and safety analyses. All subjects that were randomized and started the assigned ventilation strategy protocol will be included in the ITT. All summary tables for quantitative parameters will display mean, standard deviation, median, interquartile range, and range (minimum and maximum), as well as number of missing data (if relevant). All summary tables for qualitative parameters will display counts, percentages and number of missing data if relevant. Baseline characteristics will be described using the ITT population. Demographics, medical history and other baseline variables will be summarized as appropriate to the type of data. The primary effectiveness outcome will be defined as the proportion of time during the 12 hour monitoring period that the subject's SpO2 levels were within the target range relative to the actual total monitoring time (which is targeted to be 12 hours for all subjects). By using the proportion of time instead of the actual time, we are able to normalize the outcome based on the total amount of monitoring time available. We will assess normality of the response variables within each of the two groups by visual inspection of the histograms and box plots and by performing the test for normality of data using the Shapiro Wilk test. If the assumption of normality for the primary effectiveness outcome does not seem tenable, we will use the arcsine square root transformation which is recommended to normalize skewed percentage data. A one-sided lower 97.5% confidence interval will be calculated for the difference between the two monitoring strategy groups (PCLC minus MC) in terms of the effectiveness outcome (duration where SpO_2 remains between 92 and 96% relative to the total monitoring time) and the lower limit will be compared to the noninferiority margin of 0.12. Similar analyses will be conducted for the secondary effectiveness outcome with the only difference being the way the duration is calculated for the secondary effectiveness outcome. For this analysis, the target duration will be calculated as amount of time that SpO2 remains between 92 and 96% when $FiO_2 > 21\%$ and $SpO_2 \geq 92\%$ when $FiO_2 = 21\%$. The safety outcome (duration where SpO_2 remains above 88% relative to the total monitoring time) will be assessed using a one-sided lower 97.5% confidence interval and the lower limit will be compared to the non-inferiority margin of 0.004. If non-inferiority is established for an endpoint, we will proceed in conducting a superiority test and will compare the lower confidence limit to 0.

For the analysis of secondary safety outcome, data point estimates will be reported with 95% confidence intervals followed by a Fisher's Exact Test at the 5% level of confidence. Specifically the percentage of subjects reporting at least one adverse event (i.e serious, any device related, etc.) will be calculated for each group and compared using Fisher's Exact Test. The relative risk of each adverse event with the corresponding two-sided 95% confidence interval will be presented.

Missing data*:* The primary analysis is an intent to treat analysis. In order to minimize the possibility of missing data, the total duration of monitoring will be extended for each subject as needed in order to collect at least 12 hours of evaluable data. As a sensitivity analysis, the primary outcome measure also will be calculated as the relative time the subject was on target compared to the total amount of time they were on manual or closed-loop control. Therefore each subject should have the outcome measurement. The amount of missing data is expected

to be low based on past experience with subject retention. However there is a very low probability that some subjects may die before completing 12 hours of monitoring on the device. In this case, the relative duration will be derived by using the total duration of time the subject was on target relative to the monitoring time until they died. If a subject does not have 12 hours of monitoring data on the device due to a reason other than death, we will conduct sensitivity analysis by assuming different scenarios. In a worst case scenario, the primary outcome will be computed as the total time in the target range divided by 720 minutes. In a best case scenario, the primary outcome will be computed as the total time in the target range divided by the total amount of time the subject was observed (i.e. <720 minutes). In the event of missing data on the primary safety and efficacy outcomes (except where the subject died), the reason for the missing values will be explored, and the pattern of missing values (e.g. missing at random, missing completely at random) will be evaluated. In addition, analyses excluding those subjects without 12 hours of monitoring will also be conducted as sensitivity analyses.

13. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity. Subjects' medical records will be made available to study monitors and auditors.

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

ZOLL will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, and codified in 45 CFR Part 46.

14.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject 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 subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the legally authorized representative. Consent forms will be IRB-approved, and patient's family or legal representative is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the legal representative and answer any questions that may arise. The legal representative will sign the informed consent document prior to any study-related assessments or procedures. The family or legal representative may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to the family or legal representative for their records. The rights and welfare of the subjects will be protected by emphasizing to the family or legal representative that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

Individuals aged 18 to 65, of any gender or racial/ethnic group are eligible to participate in the study.

14.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover any study information relating to subjects.

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.

ZOLL may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

15. DATA HANDLING AND RECORD KEEPING

15.1 Data Management Responsibilities

Complete documentation of the data management tasks and processes will be maintained as part of the Data Management Plan (DMP). The DMP will provide information such as key personnel and outline processes for CRF and database development, data cleaning and data reconciliation.

15.2 Data Capture Methods

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the local investigator. All source documents and laboratory reports will be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete.

Subject data will be collected during the subject participation period and will be recorded onto case report forms (CRFs) as applicable. Data that are reported and available in an electronic format can be maintained in that manner and does not have to be reported onto a CRF, although it can be integrated into our database, described below.

This project will use Medidata Rave® as its Electronic Data Capture (EDC) software, which is a robust EDC platform for capturing, managing and reporting clinical research data. This system includes a robust query management system based on the Data Quality Plan, which will identify data quality checks to be programmed into the database design. Frequent monitoring of the database throughout the study will allow for corrective action to be taken quickly if problems are identified with the data collection process.

15.3 Types of Data

Patient data collected will be: vital signs (blood pressure, heart rate), all laboratory studies including hematology and chemistry blood panels, arterial blood gases, end-tidal CO_2 measurements, transcutaneous oxygen saturation, airway pressure, compliance, resistance. Ventilator data will include ventilator settings, ventilator output, FiO_2, rate, tidal volume, etc.

15.4 Study Records Retention

Study records will be maintained for at least three years. Study documents will be retained for a minimum of 2 years or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. 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.

15.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions will be developed and implemented promptly.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to ZOLL and the local IRB, according to their requirements.

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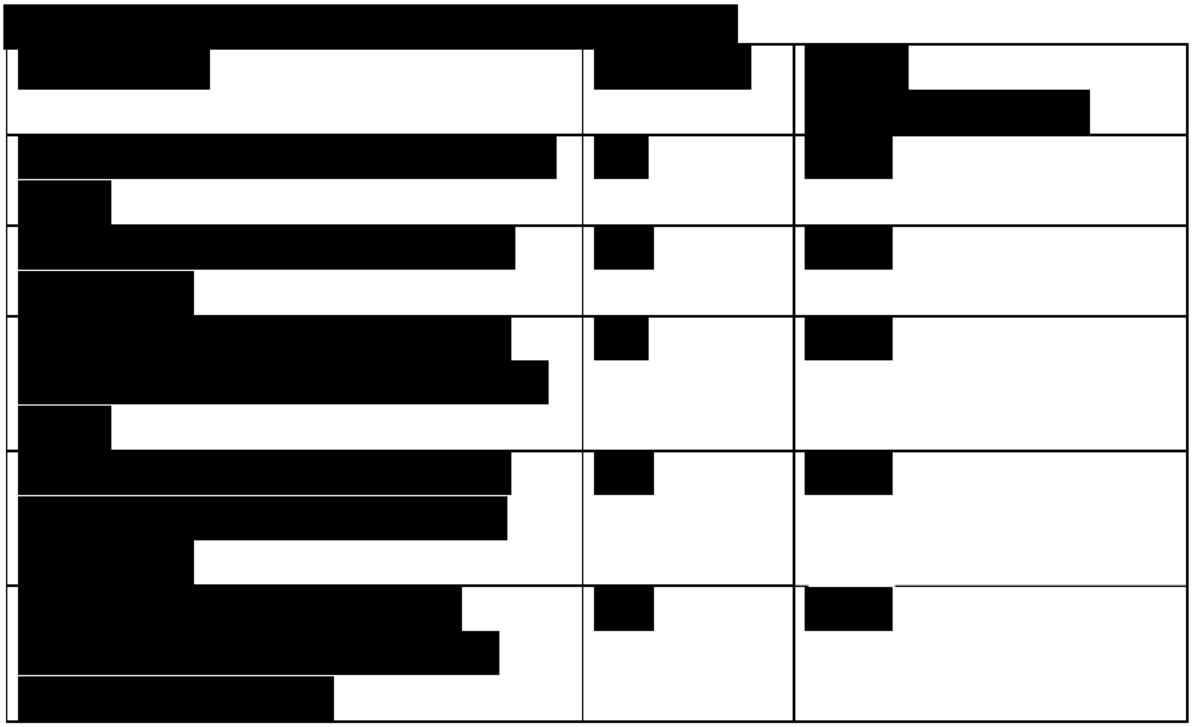

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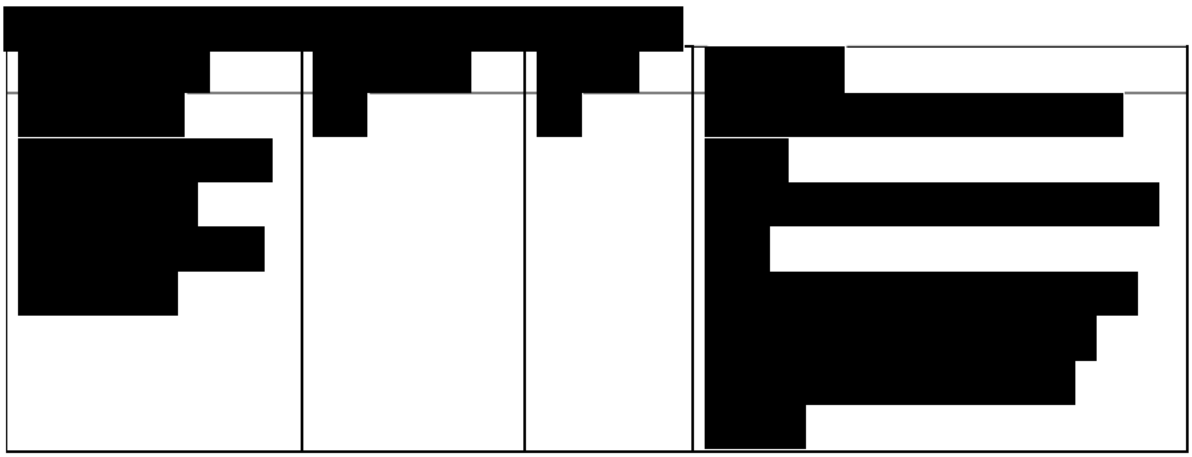

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APPENDIX C: REFERENCES, RATIONALE – REPORT OF PRIOR INVESTIGATION

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