AWARD NUMBER: W81XWH-18-C-0156

TITLE: Smart Oxygenation System (SOS) Provides Early Warning of Lung Injury

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RECIPIENT: The University of Texas Medical Branch, Galveston , TX

REPORT DATE: September 2021

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2021	Annual	31Aug2020-30Aug2021

4. TITLE AND SUBTITLE

Smart Oxygenation System (SOS) Provides Early Warning of Lung Injury

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-18-C-0156

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Michael Kinsky, M.D.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The University of Texas Medical Branch at Galveston

Galveston, TX 77555

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Background: Most pulmonary injuries are insidious and declare themselves over a period of hours or even days. Most recently, tactical military changes have resulted in increased time between casualty injury and definitive care e.g., prolonged field care, increased transport times and initial damage control surgery and resuscitation. The following types of injuries could increase due to longer time between injury and evacuation
1- smoke and chemical inhalation injury exposure
2- blast injuries resulting in concomitant pulmonary contusions [50% incidence of ARDS]
3- penetrating injuries to lung parenchyma
4- post resuscitation and acute lung injury
5-TBI induced lung dysfunction [neurogenic pulmonary edema]
6-atelectasis due to pain, over sedation and splinting after injury or initial surgery

15. SUBJECT TERMS
NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	23	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

Background: Most pulmonary injuries are insidious and declare themselves over a period of hours or even days. Most recently, tactical military changes have resulted in increased time between casualty injury and definitive care e.g., prolonged field care, increased transport times and initial damage control surgery and resuscitation. Prompt recognition and treatment of pulmonary dysfunction will be need to be addressed. Towards this end, we have shown that closed loop control [CLC]-oxygen [FiO2] can better maintain target oxygen saturation [efficiency] while reducing oxygen utilization (improved efficiency with limited resources). Our group also demonstrated that CLC systems possess unique diagnostic utility. Specifically, activity of the CLC-FiO2 algorithm identifies pulmonary (dys)function, especially using the SpO2/CLC-FiO2 ratio. We have incorporated this index into a decision support smart oxygenation system (SOS), which alerts pulmonary distress hours earlier than standard monitoring. Further, our experimental data using this decision support SOS shows that it initiates life-saving interventions [LSI] e.g., rescue ventilation, earlier, which improves overall lung function e.g., reduces severity of acute respiratory distress syndrome [ARDS]. While this provides an excellent diagnostic frame in intubated patients, it has limits. We therefore identified a CLC system called FreeO2 [OxyNov] that works in spontaneously ventilated patients. Further, we identified a non-invasive monitor that measures tidal volume and minute ventilation called Exspiron [Respiratory Motion Inc.]

Objective and hypothesis: We hypothesize that seamless integration of CLC-FreeO_2 oxygen delivery system with Exspiron into our decision support SOS for at-risk casualties, will more rapidly assess and treat pulmonary injury. This approach will not only provide targeted therapeutic oxygen, but also, serve as a "watch dog" to rapidly and effectively assess and treat lung injuries in combat casualties. We will develop and perform proof of concept testing for the SOS prototype integrating FreeO2 system and Exspiron. We have three **Specific Aims:**

Aim 1: Develop robust SOS prototype for use in spontaneous ventilation

Aim 2: Measure oxygenation and ventilatory indices during progressive hypoxemia in volunteers (n=10) without (visit 1) and with (visit 2) an extra-thoracic restriction device to simulate ARDS

Aim 3: Pilot clinical testing and SOS algorithm tuning and software update

Study Design: We will first assemble hardware and software to link FreeO2 and Exspiron system into SOS. The hardware assembly, driver development, connectivity and system architecture and simulation testing will be performed before human testing. We will then test the predictability of the SOS in volunteers undergoing hypoxia or hypoxia plus extrathoracic restriction. On each study visit one and two, each volunteer will receive different levels of oxygen; either – room air (RA), O_2 via nasal cannula (NC: 2 L/min) or FreeO_2 after hypoxia. The difference for study visit two is that volunteers will undergo hypoxia plus extra-thoracic restriction. Outcomes will test timing when the $S/_{CLC}F$ ratio <250. Non-invasive ventilation indices from Exspiron will be also integrated into the SOS. Next, studies will be performed in selected patients undergoing extubation from the OR to post anesthesia recovery unit (PACU) [UTMB] and ICU [University of Cincinnati (UC)]. We envision PACU patients ASA I/II patients (n=40) and ASA III/IV patients (n=40) [n=80 total] will normalize (no LSI), a surrogate of reassuring pulmonary function. This will determine the impact of autonomous delivery of oxygen on timing of interventions (PACU efficiency. Other data will be integrated and analyzed similarly e.g., low minute ventilation by Exspiron, etc. Data generated from these studies will be incorporated into the decision support SOS prototype and used to develop future trials. Critical to this effort, additional software updating is needed to make the SOS more robust. This includes risk analysis as well as incorporating the SOS to provide predictive indices.

Relevance: Acute lung injury contributes to significant morbidity and mortality in military settings.

2. KEYWORDS:

Acute lung injury, closed loop oxygenation for therapy and diagnosis, smart oxygenation system (SOS), human testing, oxygen “watch dog”

3. ACCOMPLISHMENTS:
What were the major goals of the project?

Objective 1: Develop a robust SOS for spontaneous ventilation	**Timeline (Months) estimate**	**QTR Period**	**Date/ Month actual**
Major Task 1: SOS hardware assembly			Complete yr1
Major Task 2: Driver development, connectivity & architecture for SOS.			Complete yr1
Major Task 3: Simulation testing and study support			Complete yr1
Objective 2: Implementing oxygenation and ventilatory indices after hypoxia ± CWR	**Timeline (Months)**	**QTR period**	**Date/month actual**
Major Task 1: Obtain Regulatory Approvals			
Subtask 1: Submit human use protocol for local IRB review	pre-award	-	0
Subtask 2: Submit human use protocol HRPO review	pre-award	-	0
Milestone: final Local IRB approval	3	1	2
Milestone(s): final HRPO approval	3	1	2
Major Task 2: Study enrollment - Hypoxia alone with and without chest wall restriction (CWR)			
Subtask 1: Enroll subjects; collect oxygenation and ventilation data before /after hypoxia ± CWR	13-30	9-11	10 subjects enrolled – COVID19 issues Completed
Objective 3: Pilot clinical testing and SOS algorithm tuning and software update	**Timeline (Months)**	**QTR period**	**Date/month actual**
Major Task 1: Obtain Regulatory Approvals			
Subtask 1: Submit human use protocol for local IRB review	35	11	09/21
Subtask 2: Submit human use protocol HRPO review			
Milestone: final Local IRB approval at UTMB/UC			
Milestone(s): final HRPO approval			
Major Task 2: Study enrollment		Site 1 UTMB	Site 2 UC
Subtask 1: Subjects 0 – 40			
Subtask 2: Subjects 41 – 80			
Major Task 3: Prototype revision			
Subtask 1: Improve Robustness [Arcos - sub]	35	11	08/21
Subtask 2: Add predictive Modeling [Arcos - sub]			

What was accomplished under these goals?

Our accomplishments are structured based on fulfilling the primary objectives. Since we have just completed year one of the project, the bulk of the reporting will focus on Objective 1.

Objective 1: months 0-12. The PI and team will work with Arcos Inc., to develop connectivity and interoperability of two primary systems (OxyNov's FreeO2 system and Respiratory Motion's Exspiron system). Engineers from Arcos will provide hardware and software (table computer system with Java based communication drivers) that incorporates oxygenation/ventilation indices from these two systems to develop a graphical user Decision Support interface called Smart Oxygenation System (SOS). Towards this end, a user manual, risk analysis, driver connectivity and start-up instructions, simulation testing and implementation will be key milestones for year 1.

Objective 2: months 13-24. The SOS will be utilized in healthy volunteers. Specifically, oxygenation and ventilatory indices will be captured during progressive hypoxemia in volunteers (n=10) without (visit 1) and with (visit 2) an extra-thoracic restriction device to simulate ARDS. Tasks and key milestones in this objective will test the predictability and timing of the SOS to identify pulmonary distress in volunteers undergoing hypoxia or hypoxia plus extrathoracic restriction (when the SpO2/CLC-FiO2 ratio <250). A manuscript will be prepared and submitted.

Objective 3 [option]: months 25-36. Pilot clinical testing and SOS algorithm tuning will be performed in selected patients undergoing extubation from the OR to post anesthesia recovery unit (PACU) [UTMB] and ICU [University of Cincinnati (UC)]. Tasks in this objective will determine the impact of autonomous delivery of oxygen on timing of interventions (PACU efficiency vs ICU rescue ventilation). Other data will be integrated and analyzed similarly e.g., low minute ventilation by Exspiron, etc. Data generated from these studies will be incorporated into a manuscript(s) and the decision support SOS prototype for developing future trials.

Objective 1:

- **Complete [figure 1 shows SOS device complete]**

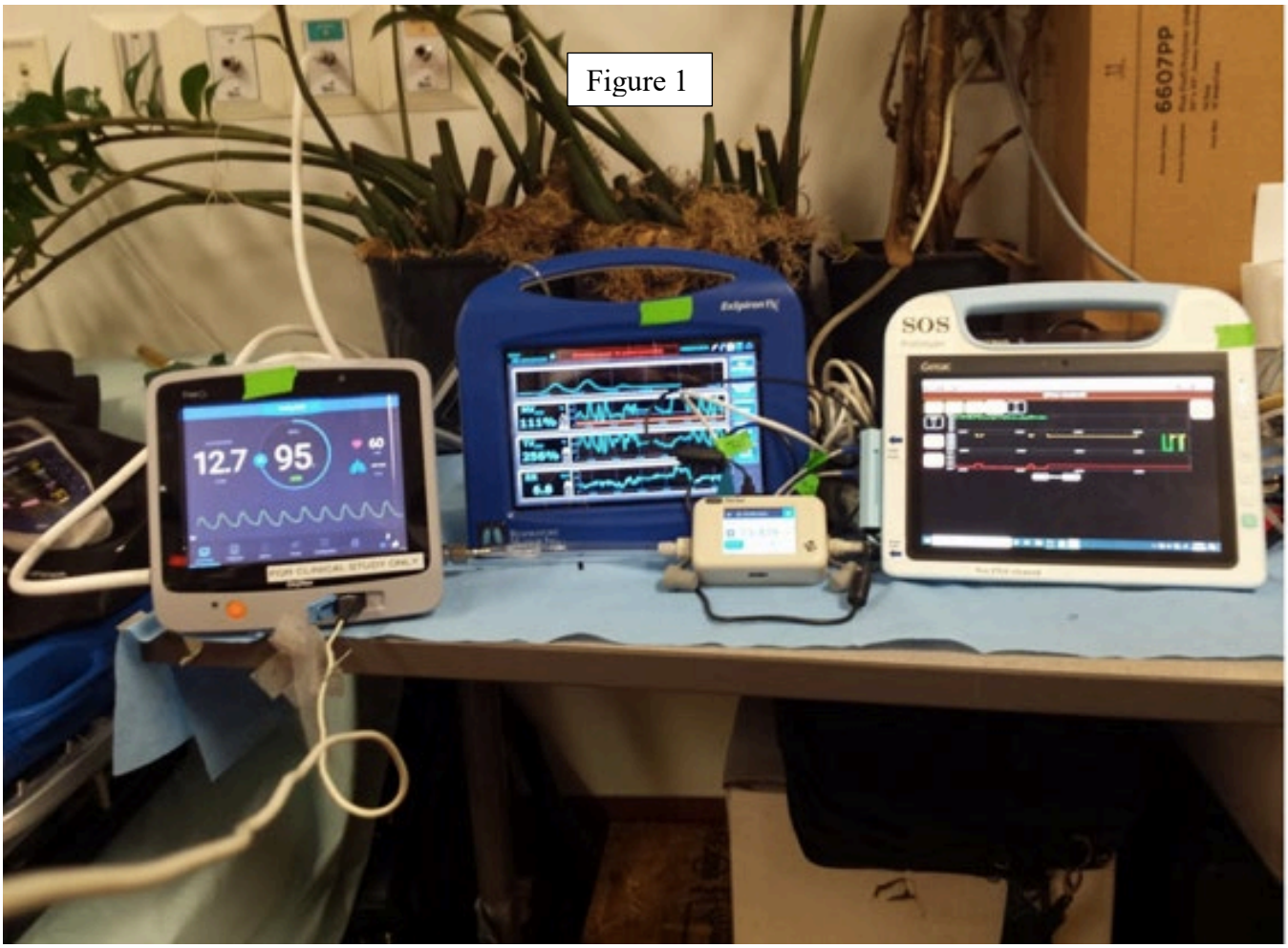
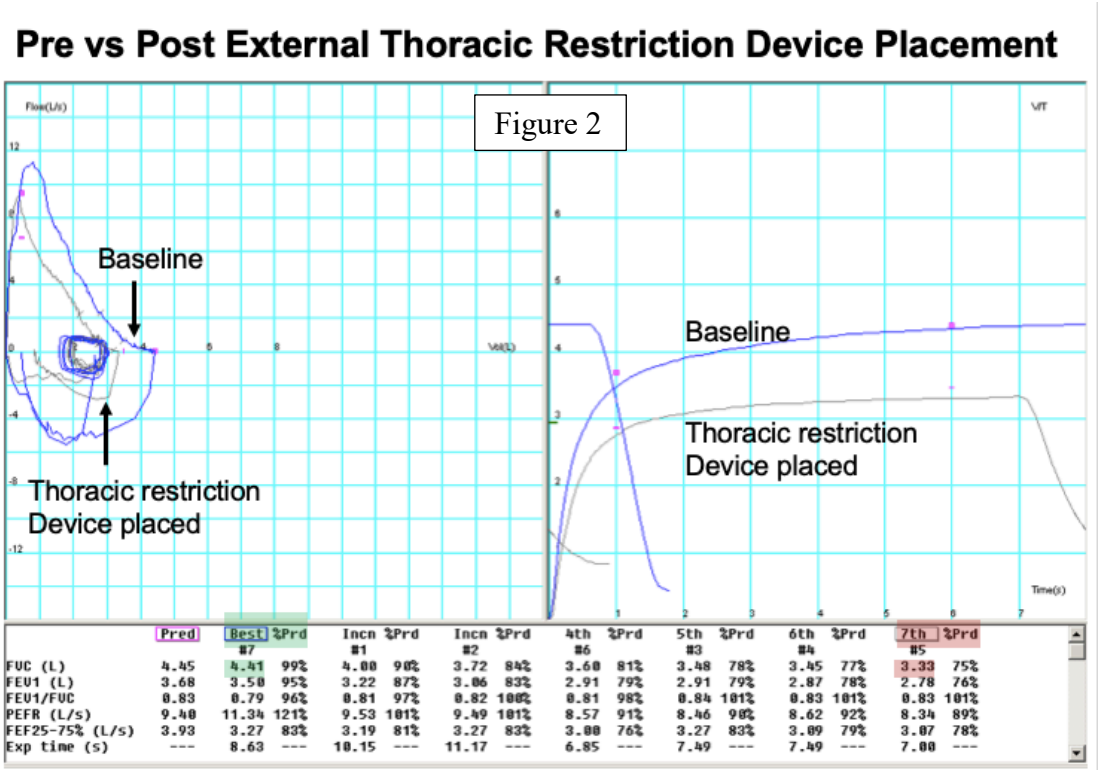


Figure 1. Shows the connection hardware for the SOS, which includes Exspiron and the FreeO2 system in closed loop oxygen control mode along with a pulse oximeter. Integrated from the FreeO2 oxygen output, a flow sensor is connected to the SOS, which allows for second to second display of O2 via nasal cannula [L/min], SpO2 and the CLC SpO2/FiO2 ratio [based on L/min conversion]. The SOS allows for ventilatory parameters primarily from Exspiron and oxygenation parameters from the FreeO2 pulse oximeter + flow sensor. Detailed warning alerts and alarms are displayed via built in software.

Objective 2: [Year 2]

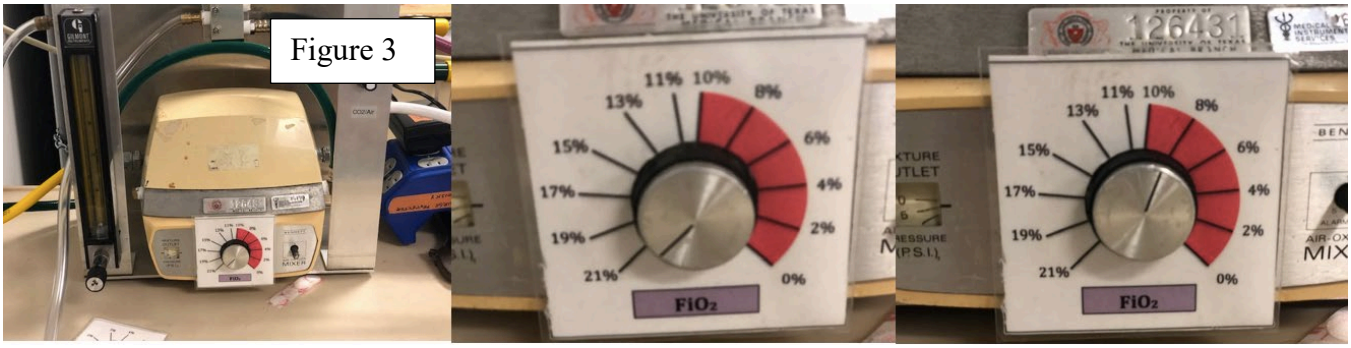
- All IRB and HRPO documentation to test the SOS prototype for YR 2 studies were completed in QTR 1.
- **Pre-testing for thoracic restriction and simulation testing:**
    - The PI/team developed a thoracic restriction device that can reduce vital capacity by 1 L. This was performed by measuring pre-and post-forced vital capacity (FVC) before and after placing bound elastic banding.
    - Repeat testing on different subject – shown below – demonstrates consistency



	Pred	Best	%Prd	Incn #1	%Prd	Incn #2	%Prd	4th #6	%Prd	5th #3	%Prd	6th #4	%Prd	7th #5	%Prd
FVC (L)	4.45	4.41	99%	4.00	90%	3.72	84%	3.60	81%	3.48	78%	3.45	77%	3.33	75%
FEV1 (L)	3.68	3.50	95%	3.22	87%	3.06	83%	2.91	79%	2.91	79%	2.87	78%	2.78	76%
FEV1/FVC	0.83	0.79	96%	0.81	97%	0.82	100%	0.81	98%	0.84	101%	0.83	101%	0.83	101%
PEFR (L/s)	9.40	11.34	121%	9.53	101%	9.49	101%	8.57	91%	8.46	90%	8.62	92%	8.34	89%
FEF25-75% (L/s)	3.93	3.27	83%	3.19	81%	3.27	83%	3.00	76%	3.27	83%	3.09	79%	3.07	78%
Exp time (s)	---	8.63	---	10.15	---	11.17	---	6.85	---	7.49	---	7.49	---	7.00	---

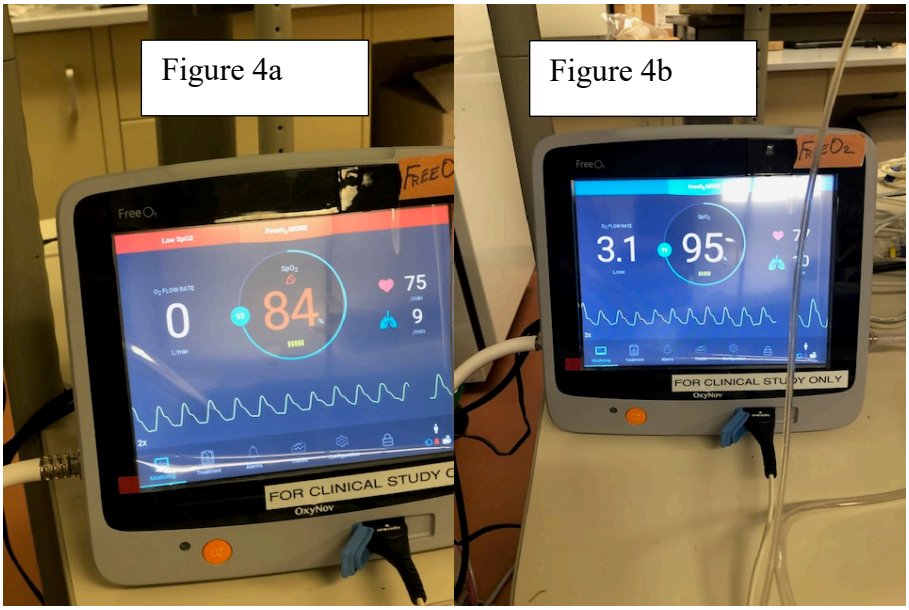
Figure 2. Pulmonary function data show a marked reduction in forced vital capacity pre intervention [(baseline) 4.41 L] to 3.33L post implementation of external thoracic restriction. The subject noted some discomfort in breathing, specifically on exhalation. Minimal change in respiratory dynamics and tidal volume at rest [data not shown but minute ventilation via Exspiron unchanged].

Hypoxia studies. Using a mix of air and nitrogen, we specifically titrated the FiO2. Essentially, air and nitrogen sources are regulated with flow meters. Two "tubes" are connected in a Y shaped pattern and then connected to a sealed facemask (used for patients undergoing general anesthesia). This provides a complete seal between the subject and mask allowing for inhalation and exhalation of respiratory gases via standard of care Datex monitor [an additional check monitor for FiO2]. The sealed facemask also permitted a nasal cannula insert to test the CLC of O2, room air [no flow] and fixed flow O2.



The total flow output, which connects to the subject via a modified Jackson-Reese system can be adjusted to ensure adequate minute ventilation with no rebreathing of external gas input.

Induction of hypoxia and hardware system check for CLC FiO2 and O2.
Prior to performing our main study, we performed a dry run [part inspection & hardware /monitor checks] and a "wet run" in which we induced hypoxia for short duration of time. Hypoxia was induced by setting the FiO2 to 8% by mixing nitrogen in air at a flow rate of 10 L/min [above minute ventilation] (see figure 4a). A nasal cannula was inserted between the mask and subject, however, the oxygen source was not connected and therefore the flow was zero. A fairly rapid reduction in FiO2 occurred [approximately 1 min] and oxygen saturation (SpO2) decreased to 84%. Then, we initiated the CLC of O2 via nasal cannula, which increased O2 (figure 4b). While the FiO2 (theoretically environment or patient with lung disease) the CLC titrated O2 to 94% [set point just for this prelim study].



During quarter 8-10, we recruited and completed the series of hypoxia experiments in ten volunteers. Each volunteer was screened, enrolled and studied on two separate occasions or study Arms (with or without extrathoracic restriction).

Method summary: We enrolled ten volunteers, however, the first volunteer underwent an abbreviated protocol. This volunteer "served as a wet trial run" and therefore the subject's data set was not included. Therefore, nine volunteers (n=9) underwent a series of three, 40- min, hypoxia challenges (based on type of supplemental oxygen) with and without thoracic restriction (randomized and separated by one week). Specifically, each volunteer was randomized, separated by at least one week, with or without an extra-thoracic restriction device (corset placed around lower thoracic cavity) to simulate (when FiO2 low) acute respiratory distress syndrome (ARDS). For each hypoxia study, volunteers had three different "treatment" arms: 1) room air (RA: no oxygen flow via nasal cannula), fixed oxygen (fixedO2; 2L O2 via nasal cannula) and closed loop control (CLC: algorithm in which oxygen delivered via nasal cannula based on pulse-oximetry). Baseline data included forced vital capacity (FVC) and expiratory volume over one second (FEV1) and respiratory impedance/reactance with and without extra-thoracic restriction. On day of study, a pulse-oximeter, non-invasive blood pressure cuff, and Exspiron (a patch placed on chest that measures minute ventilation, respiratory rate and tidal volume). Then a fitted face-mask connected to a high flow circuit (30 L/min) that blended air and nitrogen to induce graded hypoxia from FiO2 of 0.21 to 0.08 and back to 0.21. A nasal cannula, below the face-mask, was connected to a flow meter via FreeO2 system (this allowed titration of oxygen at zero (RA), 2 L fixed O2 (Fixed) or in closed loop control (CLC), which automatically delivered O2 to achieve a SpO2 of 94%). All devices were connected to the

SOS prototype – which digitally sampled variables each second and displayed the following; end-tidal carbon dioxide, SpO2, oxygen flow {FiO2 calculated as: each 1L increases FiO2 by 0.04}, SpO2/FiO2 ratio, tidal volume (TV), respiratory rate (RR) and minute ventilation (MV)).
Volunteers were monitored throughout the protocol by an anesthesiologist. Hypoxia was stopped if SpO2 <60% for, > 3min or the subject became symptomatic (intolerant). SOS data was analyzed and comparisons were made between groups [restriction vs non restriction] and over time.
Results: Data are reported in mean ± SEM, unless otherwise indicated. Results: Prior to hypoxia, application of restriction device significantly decreased FVC (non-restriction: 5.54±0.53L vs restriction: 4.65±0.33 L; p<0.001). X5 also became more negative with restriction (non-restriction: -0.67 cmH2O/L/sec vs restriction: -1.47 cmH2O/L/sec; p< 0.004).

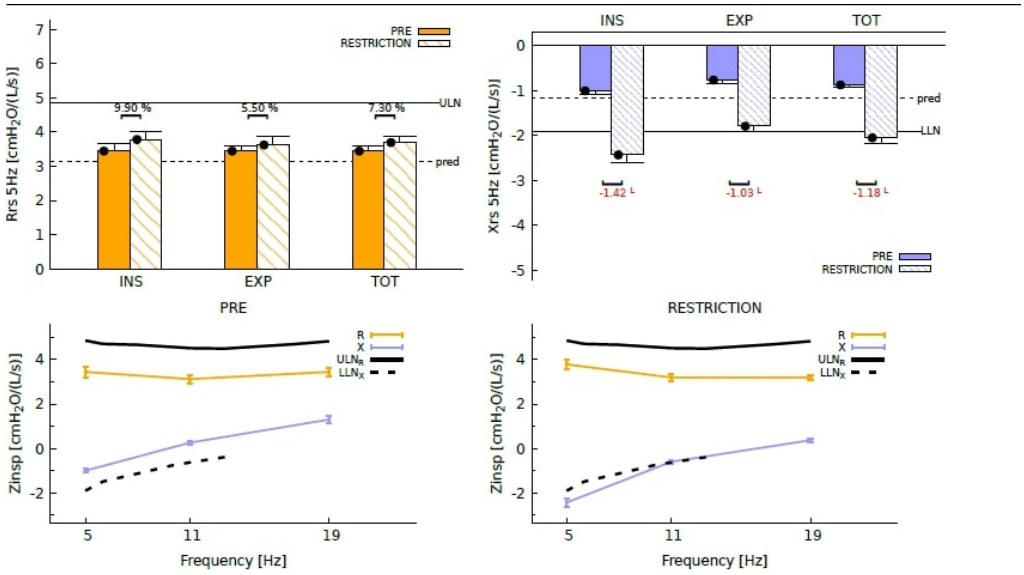
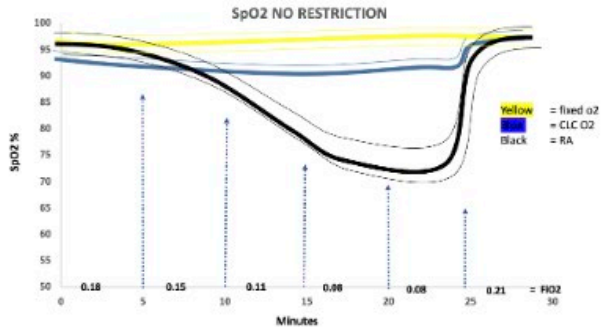


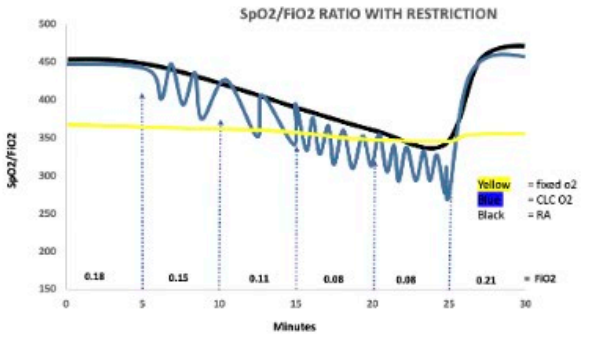
Figure 5. Pulmonary function show a marked reduction in forced vital capacity pre intervention [(baseline) 4.41 L

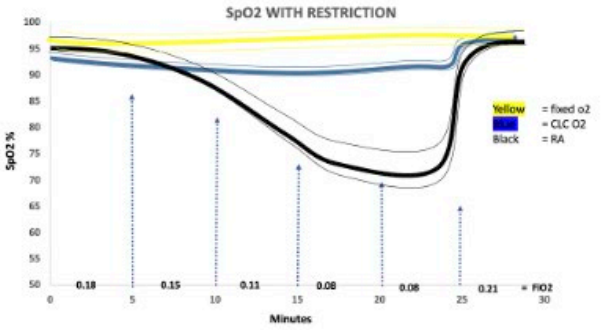
In general, volunteers undergoing hypoxia with and without extra-thoracic restriction, for all three oxygen "treatment" arms, had similar results. However, 3/9 volunteers in the RA (zero O2 given) treatment arm with extra-thoracic restriction could not continue the hypoxia study (intolerance). The greatest physiologic changes occurred in after hypoxia in RA group, which was anticipated. Surprisingly, Exspiron ventilatory parameters (TV, RR and MV) did not significantly differ from baseline (FiO2 =0.21) vs hypoxia (FiO2 =0.08) for any treatment arm or condition (extra-thoracic restriction). Respiratory rate measured by capnograph, increased in RA treatment arm after hypoxia (14±2 to 17±2). A decrease in end-tidal CO2 by 15-20% (baseline: 36±3 vs hypoxia: 31±3) ± extrathoracic restriction. **Figure 6.** The SpO2 nadir during hypoxia (FiO2=0.08) was 78±2% and 74±3%, respectively for non-restriction and extra-thoracic restriction, respectively. The fixedO2 group resulted in a very narrow range of SpO2, irrespective of extra-thoracic restriction and level of hypoxia. Specifically, in all subjects, the SpO2 was maintained >95% (97±3%) throughout the study. The calculated SpO2/FiO2 ratio was maintained at 349 – 368, regardless of restriction or level of hypoxia. The CLC treatment arm was not statistically different for lowest SpO2, SpO2/FiO2 ratio and oxygen utilization with regards to extrathoracic restriction. On the other hand, the CLC system more efficiently maintained SpO2 values while reducing oxygen utilization (CLC group = 0.8±0.3 L/min vs fixed

= 2.0 ± 0 L/min stage, (p=.002)). For example, the SpO2 mean nadir was 92±3% and 92±2% for non-restricted and restricted, respectively.

Most interestingly, the SpO2/FiO2 ratio not only decreased with graded hypoxia but associated with periodic 'oscillations' as oxygen utilization was needed to maintain SpO2 at 94%. The oscillations had distinct characteristic amplitudes and frequencies (based on a S/F ratio > 25 change) that were not observed for RA or fixed O2. Restriction was associated with increased frequency and reduced amplitude.







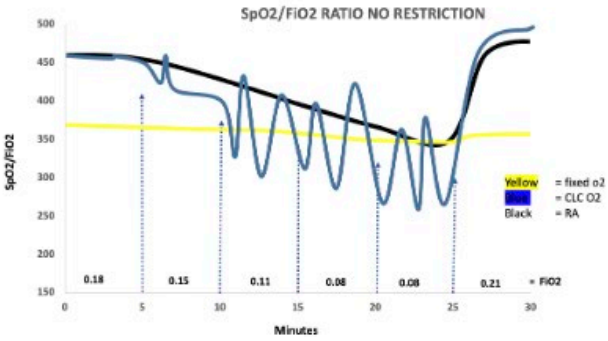


Figure 6A **Figure 6B**

Figure 6A. Data representation of [n=9] the SpO2 in volunteers [mean bold line ± SEM thin line] undergoing a hypoxia challenge (FiO2 adjusted from 0.21 to 0.08). Each volunteer underwent three oxygen protocols with either 2L/min (Fixed O2) [yellow], closed loop control (CLC) O2 to achieve 94% oxygen saturation [blue] or room air (RA)/no O2 [black]. In addition, hypoxia ± O2 was studied in subjects, separated by at least one week, without (top) or with (bottom) an extrathoracic restriction vest. Regardless of restriction, SpO2 remained at or above baseline in the fixed O2 group, between 90-100% in the CLC group and dose dependently decreased in the no O2 (RA) group [SpO2 nadir @ 75%]. **Figure 6B.** shows the SpO2/FiO2 [S/F] ratio. Method and groups described. The S/F ratio decreased in fixed O2 group to @ 350. The S/F ratio in the no O2 (RA) dosed dependently decreased (nadir @ 350). On the other hand, after hypoxia, the S/F ratio in CLC group demonstrated a unique signature of peaks and troughs. Lower FiO2 were associated with the S/F ratio <300. Extrathoracic restriction was associated with higher number of events (frequency) albeit lower amplitude. No restriction resulted in higher amplitude but less events **(see table 1)**.

CLOSED LOOP S/F RATIO WITH NO RESTRICTION (SF CL NO R) AND WITH RESTRICTION (SF CL R): OSCILLATION AND AMPLITUDES TABLE (ALL SUBJECTS)

FiO2 level		0.08			0.11			0.15			0.18	
		Peak Amplitude	TOTAL number Oscillations		Peak Amplitude	TOTAL number Oscillations		Peak Amplitude	TOTAL number Oscillations		Peak Amplitude	TOTAL number Oscillations
SF ratio CLC – no restriction	mean	114	18	mean	94	9	mean	57	10	mean	51	4
	SD	57	10	SD	41	5	SD	23	5	SD	24	2
SF ratio CLC – with restriction	mean	68	21	mean	80	11	mean	63	11	mean	40	6
	SD	58	12	SD	50	6	SD	32	6	SD	11	3

Table 1 – Shows frequency and amplitude "oscillation" patterns during closed loop control of oxygen during hypoxia. Per hypothesis, the S/F ratio decreased despite maintaining SpO2 in the CLC, however, the data further showed a unique signature in the extent and duration of how CLC algorithm maintains a target SpO2. Specifically, extrathoracic restriction in face of hypoxia (0.08) treated with CLC resulted in a higher number of events (frequency). However, the amplitude (difference between S/F over a several breaths) was reduced. While no restriction was associated with the opposite (less frequent events but with much larger differences in S/F ratio over several breaths). This is likely related to reduced excursion or tidal volume when the extrathoracic vest was placed.

Objective 3:

Major Task 1& 2

Our new statement of work will follow patients leaving the operating room (OR) and the post anesthesia care unit (PACU) with oxygen. The clinical data will help fine tune the Smart Oxygenation System's (SOS) features. This study will allow for us to determine usability (direct clinician engagement with the SOS) as well as feasibility for future work. Each study participant (patient) will be connected to SOS (FreeO2 system and Exspiron). The SOS will only record data or "black box" mode in subjects from the OR/PACU – clinical decisions will not be made based on the SOS.

An IRB protocol (#21-0253) has been submitted by the PI, Dr. Kinsky – awaiting final approval. This will be a multi-institution study (UTMB and University of Cincinnati [UC]). UTMB will be the IRB of record. The PI at UTMB will be Michael Kinsky, MD. Mr. Branson, MS RRT is a professor emertis. Due to Mr. Branson's limited time, Krishna Athota, MD, director of the surgical intensive care unit, has agreed to be the PI of record from UC. Dr. Athota will be in charge of recruiting and executing the studies outlined. Mr. Branson, will still remain a consultant on the grant. Dr. Athota, is familiar with the protocol and SOS. UC is finalizing their secondary site contract and will submit to their IRB after UTMB approval.

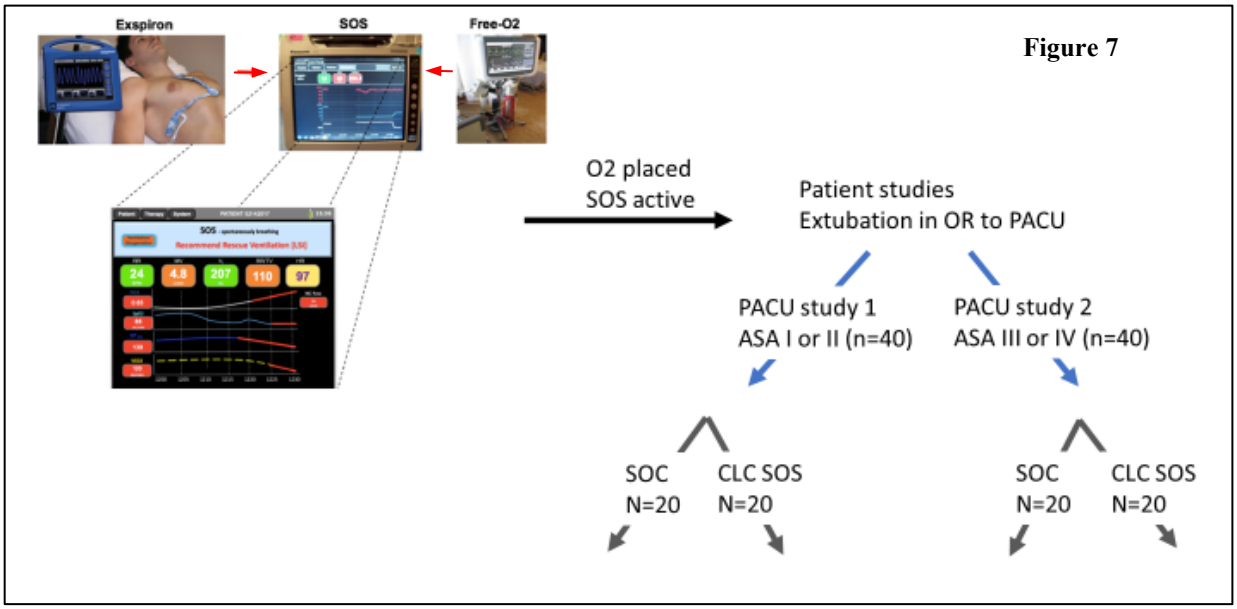


Figure 7. Top left shows the main components that connect to the SOS, which include a FreeO2 system and Exspiron. The SOS and components will be placed on each subject after extubation in the OR. Data and events will be recorded in the PACU until discharge.

Overview of the study

Studies will be performed in selected patients [based on type of surgery and American Society of Anesthesiology classification i.e., patient health status] undergoing surgery / extubation and recovery in the PACU. Subjects will remain in PACU until ready for discharge (based on specified discharge criteria at UTMB and UC. An equal number of subjects will be studied at UTMB and UC.

The first group (PACU study 1) will be generally healthy undergoing a surgery that has limited fluid shifts or cardiopulmonary balance. Whereas the second group (PACU study 2) will study patients that

have a history of organ dysfunction and undergoing major surgery e.g., > 500 mL blood loss and/or significant cardiopulmonary interactions.

SOC arm [n=20 X 2 (Group 1 and Group 2)]. Initial oxygen flow via nasal cannula in SOC arm will be set at 6 L/min. Thereafter, oxygen will be titrated up or down manually, which bypasses the $FreeO_2$ CLC algorithm. Data, including SpO_2, oxygen flow, heart rate and respiratory rate, however, is captured for onto the SOS. Standard of care criteria for adjusting oxygen flow will be the following: If there is evidence of clinical distress, e.g., tachypnea or bradypnea and SpO_2 <90% but >85%, oxygen flow is increased by 2 L/min [8 L/min], if after 5 min, SpO_2 fails to improve, oxygen flow is increased to 10 L/min, if after 5 min, SpO_2 fails to improve, oxygen flow is increased to 15 L/min. If after 5 min of 15 L/min O2 via nasal cannula (see advancement of oxygen):

CLC SOS arm [n=20 X 2 (PACU 1 and PACU 2 studies)]. Initial oxygen flow will be set to 6 L/min and thereafter oxygen flow is automatically titrated to achieve a SpO_2 of 93%. An expert clinician (Michael Kinsky, MD or Muzna Khan, RRT @ UTMB/ Krishna Athota, MD or Chris Blakeman, RRT @UC) will be present at bedside while the O_2 is delivered by $FreeO_2$ system. The expert clinician roles will primarily ensure safe delivery of oxygen – make sure delivered O2 is appropriate. These clinicians will be present side-by-side with PACU staff. If oxygen levels increase above 15 L/min > 5min – protocol for advancement of oxygen (below) will be initiated. This event (time) will be recorded as this indicates changing the oxygen delivery connection from nasal cannula to non-rebreather valve mask – see **Advancement of oxygen**. Additionally, the CLC SOS will be discontinued. Other rescue parameters, as described, will be followed.

Advancement of oxygen: the nasal cannula is replaced with a non-rebreather valve mask ("non-re-breather" allows the FiO_2 to approach 0.8-1.0). The oxygen flow rate, time of non-rebreather valve mask placement and total time will be recorded. If oxygenation fails to improve or continues to deteriorate, the following LSI's will be recorded and implemented:
1. LSI –Non-invasive positive pressure ventilation (NIPPV)
2. LSI –Re-intubation and mechanical ventilation
There could be more sudden instances in which graded FiO_2 increments are bypassed and that require immediate LSI. These will be noted and recorded.

Decrease in oxygen and collection parameters- We anticipate that increased oxygen needs will be rare or transient in this population. Most likely, oxygen flow will be decreased or even removed within 30-60 minutes of PACU stay; especially in PACU 1 studies. For SOC, oxygen flow rate is assessed every 10 min and primarily based on SpO_2. Thus, if SpO_2 > 93%, FiO_2 is reduced to 3 L/min and if after 10 min SpO_2 > 93%, then oxygen flow is reduced to 1.5 L/min or even to room air or more rapidly, if clinical warranted. For the CLC SOS, oxygen is automatically titrated to achieve a SpO_2 = 93%. The CLC O2 uses a specific mathematical algorithm based on current SpO_2, rate of change of SpO_2 and time / difference from current SpO_2 vs SpO_2 of 93% to wean oxygen. The study will stop, upon discharge from the PACU [or team indicates PACU sign out]. Final times will be noted, and the equipment will be removed. The following parameters, which are continuously recorded by the SOS include: [from $FreeO_2$] SpO_2, FiO_2est, SpO_2/FiO_2 ratio, RR, HR and [from Exspiron] TV, RR and MV. We will also note and record study over-rides. As discussed, the SOS will be recording in the background. Data will be analyzed after each subject completes the testing. 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	92 to 96%, using the PCLC system
SpO2 Desaturation Upper Limit	88%	88%
If Desaturation Occurs	Follow manual control (figure)	Permit closed-loop algorithm to manage unless otherwise directed by clinician.

Primary Data: SpO2, FiO2, L/min O2 is automatically captured. Data is streamed and recorded each second. These variables will be converted into a 24 hr format for data comparison. For control (manual control) group, SpO2, FiO2 and L/min are data logged and recorded into EPIC at various interval.

We envision that most PACU patients' pulmonary function (ASA I/II patients (n=40) and ASA III/IV patients (n=40) [n=80 total]) will return to basal levels and not require additional life-saving intervention (LSI), especially in PACU study 1. Normalization is a surrogate of reassuring pulmonary function. On the other hand, we anticipate a longer stay and oxygenation needs for PACU study 2 patients. We also anticipate that a small subset of patients in PACU group 2 will require advancing oxygen needs and/or LSIs. Ventilatory indices from the Exspiron will also be captured, integrated and analyzed for the SOS e.g., altered minute ventilation by Exspiron, etc. This two-pronged approach of determining oxygen needs and ventilatory parameters will provide tuning [and used for predictive modeling] for the SOS. Data generated from these initial studies will be used to develop future trials.

Major Task 3

Software update

Critical to this effort, software updating is needed to make the SOS more robust. This includes risk analysis as well as incorporating the SOS to provide predictive indices. The PI has met with Arcos's team to discuss these new milestone applications to the existing SOS. Most recently, Arcos's has been contract has been approved. These new updates will improve the SOS readiness level specifically with regards to further risk analysis. Initial software changes are underway – with an auto system start up. Additionally, Arcos is constructing another SOS for UC, which is near complete. This will allow UC to do studies outlined in objective 3.

The new technical objectives will be scheduled for Task 3:

1. SOS Prototype Improvements
    1. Automate SOS start-up and set-up
    2. User interface improvements:
    3. Refine data logger and update manager as needed
    4. Update decision support recommendations as needed
    5. Regulatory Plan and Draft Documents for 510(k) or IDE

1. Address TSI flowmeter in clinical use
2. User's Manual, Risk Management, etc.

2. Assemble an SOS prototype
    1. Procure hardware (Nonin + Expiron + SOS tablet + TSI flowmeter) and assemble
    2. Software safety and reliability testing, provide a test report
3. Support UTMB's bench testing and clinical study use
4. Analyze UTMB provided respiratory data and develop a predictive algorithm with machine learning

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

- NCE is required and paper work underway
- Obtain final IRB approval PACU study at UTMB
- Obtain HRPO approval and UC
- Post approval studies will commence and be completed in a 4 month period
- Software will be iterative – potentially a separate prototype working in parallel

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The proposed will test a clinical prototype that is suitable for military and civilian clinical testing, in patients and volunteers in different patho-physiologic states. Our initial vision would be to incorporate other non-invasive ventilation indices e.g., Exspiron [non-invasive minute ventilation (MV)] into the SOS, which would increase diagnostic capabilities. Our long-term vision is to incorporate $S/_{CLC}F$ ratio, cardiopulmonary indices (MV and perfusion – production of carbon dioxide, or VCO2) into a SOS monitoring algorithm such as automated decision-support those evolve for use in military and civilian trauma patients. We anticipate that the SOS algorithms will use threshold values or targets e.g., to define specific interventions such as need for rescue ventilation or other airway interventions. An advantage of this SOS is that it is non-invasive, seamless (coupled to supportive systems), easy to interpret by any skill level (as SpO2 and oxygen are known entities) and usable at any echelon. While we have outlined how this proposal fits into current capability gaps, it closely aligns with combat casualty care research program, research and development of technologies to diagnose and reduce acute secondary organ damage and health technology. Towards this end, our healthy volunteer studies successfully demonstrated two key issues 1 – watch dog display of S/F ratio in CLC and 2 – key signatures of varying amplitude and frequency in CLC mode. Patient studies are underway to tune the SOS.

What was the impact on other disciplines?

The technology and studies outlined in this proposal are highly relevant to hospital and ICU medicine, perioperative care and especially home health, pre-hospital and triage care.

What was the impact on technology transfer?

Not at this time

What was the impact on society beyond science and technology?

The impact here is potential change in behavior and decision making.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

COVID-19 has led to significant problems with conducting our clinical studies. We initially began recruiting subjects in January/February 2020 and had a few subjects slated to be screened. Due to supply chain ordering, we anticipated conducting studies in March. Then, COVID19 "hit". Like many programs, all clinical research was suspended that was not related to COVID19. In May/June 2020, we began re-engagement for the ability to do non-COVID19 research. However, Texas [Houston-Galveston area] underwent a significant wave of hospitalizations. In addition, February / March 2021 a winter storm impacted SE Texas resulting a shut down and loss of time. Finally, as often occurs, personnel changes resulting in loss of expertise. However, we now have trained new personnel. A no cost extension is needed to complete Option 3. We have submitted the IRB and are working closely with software engineers to ensure that the SOS is more robust and easier to use.

Actual or anticipated problems or delays and actions or plans to resolve them

As described above, the biggest challenge has been COVID19 and Winter storms that put us behind 8 -14 months. Like many institutions, UTMB was hit hard physically and financially. The PI hired and trained new research staff.

Changes that had a significant impact on expenditures

As above – COVID 19 and loss of personnel

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

None to report

Significant changes in use or care of vertebrate animals.

Not applicable

Significant changes in use of biohazards and/or select agents

None to report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to report

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers, and presentations.

Nothing to report

- **Website(s) or other Internet site(s)**

Nothing to report

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

We have a patent for the SOS

- **Other Products**

Software and other analysis have been submitted in previous quarterly reports

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: *Michael Kinsky, MD*
Project Role: *PI*
Researcher Identifier (e.g. ORCID ID): 0000-0002-2103-546X
Nearest person month worked: *1 mo/QTR*
Contribution to Project: *The PI has directed the efforts for acquiring requisite components, working with Dr. Kramer and Mr. Branson and Ms. Khan to develop the technical requirements for all of Arcos work this quarter*

Name: *George Kramer, PhD*
Project Role: *CO-I*
Researcher Identifier (e.g. ORCID ID): 0000-0003-0894-6768
Nearest person month worked: *<1 mo/QTR*
Contribution to Project: *The Co-I has dedicated his efforts for coordinating the technical requirements for all of Arcos work this quarter*

Name: *Rich Branson, MS RRT*
Project Role: *CO-I*
Researcher Identifier (e.g. ORCID ID): 0000-0002-0912-3360
Nearest person month worked: *<1 mo/QTR*
Contribution to Project: *The Co-I has dedicated his efforts for coordinating the technical requirements for all of Arcos work this quarter*

Name: *Muzna Khan, MS RRT*
Project Role: *CO-I*
Researcher Identifier (e.g. ORCID ID): 0000-0002-8096-981X
Nearest person month worked: *<1 mo/QTR*
Contribution to Project: *The Co-I has dedicated her efforts for coordinating the technical requirements for all of Arcos work this quarter.*

Name: *Catherine Sampston*
Project Role: *Post Doc*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *<1 mo/QTR*
Contribution to Project: The post doc has worked with the PI to assist in technical work, ordering parts, maintaining documentation and working with Arcos for initial instrument testing.

Name: *Roger Seeton, RN*
Project Role: *Research Nurse*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *1 mo/QTR*
Contribution to Project: The research nurse has worked with the PI to help with all documentation for IRB/HRPP and human subject material. As well as recruitment material. He has also helped with Arcos to ensure human safety.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? No.

What other organizations were involved as partners?

University of Cincinnati Arcos Inc.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

SMART OXYGENATION SYSTEM (SOS) PROVIDES EARLY WARNING OF LUNG INJURY
0011121518-0001/ USAMRAA
W81XWH18C0156

PI: Michael Kinsky, MD Org: University of Texas Medical Branch at Galveston Award Amount: $1,136K [option included]

Study/Product Aim(s)

Hypothesis: At-risk casualties, suffering from lung injury, can more rapidly be assessed and treated using a smart oxygenation system (SOS) that connects to a stand-alone closed loop control (CLC) oxygen system and a non-invasive ventilation monitor

Specific Aims

Aim 1: Develop robust SOS prototype for use in spontaneous ventilation

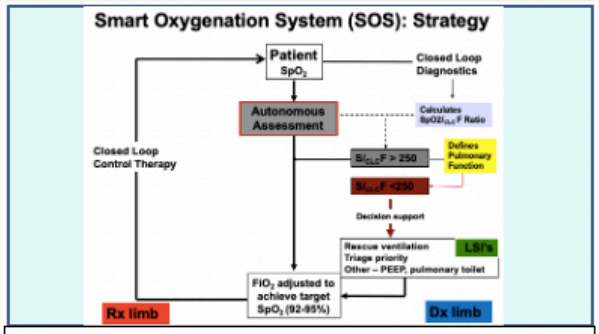
Aim 2: Measure oxygenation and ventilatory indices during progressive hypoxemia in volunteers (n=10) without (visit 1) and with (visit 2) an extra-thoracic restriction device to simulate ARDS – months 13-24

Aim 3: Pilot clinical testing and SOS algorithm tuning– months 25-36 [OPTION]

Approach

We will develop a user manual, connectivity to OxyNov's (closed loop control oxygen for spontaneous (sp.) ventilation) and Respiratory Motion's (non-invasive minute ventilation and tidal volume and respiratory rate) communication protocol to extract data packets e.g., SpO_2,, estimated FiO_2 and $S/_{CLC}F$ ratio, minute ventilation and respiratory rate, which will then be graphically displayed in real time. SOS Prototype will be tested in human volunteers first [hypoxia ± chest wall restriction (CWR)] and then patients [option] to determine pulmonary dysfunction.

Smart Oxygenation System (SOS): Strategy



Accomplishments: Exspiron driver complete. Sub-contract w/ Arcos finalized. FreeO2 system received [communication protocol pending]. Aim 2 continued review approved

Timeline and Cost

Activities CY	18	19	20	21
Develop robust SOS for sp. ventilation				
Implementing oxygenation and ventilatory indices after hypoxia ± CWR				
Pilot clinical testing [option]				
Estimated Budget ($K)	**$360K**	**$360K**	**($417K)**	

Updated: (September 30, 2021)

Goals/Milestones (Example)

CY18 Goal – SOS hardware assembly, driver development and support
- ☑✓SOS hardware requirements and user need
- ☑✓- Driver development, connectivity and architecture for SOS
- ☑✓ Simulation testing and study support [Risks/ prototype demo]

CY19/20 Goals – Obtain regulatory approval, study enrollment
- ☑✓ Regulatory approval
- ☑✓ Complete prototype and all testing

CY21 Goal – Option [Pilot testing and prototype work]
- ☐Regulatory approval – Submitted IRB
- ☐Data collection in PACU patients [SOS vs standard of care (SOC)]
- ☐Robust prototype and predictive modeling

Comments/Challenges/Issues/Concerns
- COVID-19 essentially shut down studies qtr 6-8 + qtr 10 February Storm

Budget Expenditure to Date

Projected Expenditure: 1.136K

Actual Expenditure: 719K + pre-encumbered