AWARD NUMBER: W81XWH-20-2-0001

TITLE: Multicenter Implementation Trial of Targeted Normoxia Strategy to Define Oxygen Requirements for Combat Casualty Care

PRINCIPAL INVESTIGATOR: Adit Ginde, MD, MPH

CONTRACTING ORGANIZATION: Regents of the University of Colorado, Aurora, CO

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4. TITLE AND SUBTITLE

Multicenter Implementation Trial of Targeted Normoxia Strategy to Define Oxygen Requirements for Combat Casualty Care

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W81XWH-20-2-0001

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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Erin Anderson, RN

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5d. PROJECT NUMBER
001146918

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Regents of the University of
Colorado,
Ilana Speigel
13001 E 17Th Place
Aurora CO, 80045-2571

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)

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13. SUPPLEMENTARY NOTES N/A

14. ABSTRACT

Background: Oxygen therapy has undisputed importance in combat casualty care to treat/prevent morbidity associated with hypoxia. However, generous supplemental oxygen is routine, and often results in hyperoxia. Emerging evidence indicates that even modest hyperoxia can increases morbidity/mortality, however limited evidence exists specifically for trauma patients. In addition, oxygen is a limited resource that is challenging to obtain in austere settings eg, prolonged field care and enroute care, requiring
substantial resources, space, weight and logistics to procure. Therefore, it is critical to determine oxygen titration goals for combat injured to optimize care by reducing harm associated with hypoxia and hyperoxia and to conserve limited oxygen supply.

Preliminary Data: From our prior USSOCOM-funded work, we recently published a trauma-specific systematic literature review of oxygen targets along with an expert consensus of military and civilian experts in trauma surgery, emergency medicine, critical care, and military operational medicine. Our findings demonstrate remarkable potential to reduce oxygen requirements by implementing a consensus- based definition ofnormoxia, based on a goal oxygen saturation of90-96°10. \Ve also pilot-tested the targeted normoxia intervention to demonstrate feasibility and safety for the proposed multicenter implementation trial.

Objective/Hypothesis: Our objecllve is to determine the feasibility, safety, and effectiveness oftbc targeted normoxia approach to conserve oxygen and improve clinical outcomes in critically injured patients. We

hypothesize that more targeted use of oxygen therapy, to limit exposure to both hyperoxia and hypoxia, will safely reduce the needs for concentrated oxygen in the deployed, combat setting.

Specific Aims: \Ve will conduct a prospective multicenter clinical trial, achieving the following aims:

Aim 1. Measure the impact of targeted normoxia on oxygen requirements in critically injured patients. We will define the oxygen requirements for critically injured patients along with determining the proportion requiring high levels of supplemental oxygen (anticipated *to* be low). Specific to the resource-limited setting, we will estimate the potential reductions in oxygen consumption using the targeted normoxia approach.

Aim 2. Determine the safety of targeted normoxia. compared to conventional oxygenation. Specifically, we will determine the rate and duration of hypoxic and hyperoxic events for the targeted normoxia approach, compared to conventional oxygenation that relies on generous oxygen administration.

Aim 3. Determine the clinical effectiveness of the targeted normoxia approach. Specifically, we will compare hospital mortality, neurological status at discharge, hospital-free and ventilator-free days, and time to room air.

Project Design: We will conduct a multicenter, stepped wedge cluster randomized trial of the targeted normoxia approach in adult emergency department trauma patients, with a focus on those admitted to the intensive care unit. Consistent with our current pilot study of targeted normoxia (approved by local IRB and HRPO), \Ve \Viii conduct this trial under a waiver of consent since the implementation of this protocol is minimal risk (exception from informed consent [EFIC] is not required).

Proposed sites: Denver Health, Oregon Health and Sciences University, San Antonio Military .Medical Center, University of Alabama-Birmingham $_1$ University of Cincinnati, University of Pittsburgh, University of Texas Houston, Vanderbilt University
Impact: Our findings will provide immediately actionable data to define oxygenation practices in critically injured warfighters and civilians and aid in the development of clinical practice guidelines. Our lessons learned will optimize patient outcomes while conserving oxygen supplies, which will reduce weight, volume, and logistical burdens in deployed, combat settings. Furthermore, our findings will impact materiel solutions such as portable oxygen concentrators and closed loop oxygenation/ventilation systems.

Military Benefit: Our research proposal will fill a critical gap in knowledge of safe and effective oxygenation targets in critical combat casualties. These results will define best practices for oxygen titration that can supplant current practices of liberal/excessive oxygen administration and optimize care of combat injured.

15. SUBJECT TERMS
None listed

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified	27	**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

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1. **INTRODUCTION:** Oxygen therapy has undisputed importance in the care of critically ill medical and trauma patients to treat and prevent morbidity associated with hypoxia. However, generous supplemental oxygen is routine, and often results in hyperoxia. The objective is to determine the effectiveness of a multimodal educational intervention to reduce supplemental oxygen use in critically injured patients. We will also evaluate the safety and effectiveness of the more targeted use of oxygen therapy.

2. **KEYWORDS:** oxygenation, oxygen delivery, mechanical ventilation, normoxia, hyperoxia, hypoxia, critically ill, trauma, prolonged field care, limited resources, traumatic brain injury, hemorrhage

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

Goals/Milestones

Major Task 1: Preparatory Work
Local IRB Reliance – *01MAY2020- **100% complete***
Finalize Protocol – *01JUNE2020- **100% Complete***
Central IRB Approval – *01JUL2020- **100% Complete***
HRPO Approval – *01SEP2020- **100% complete***
Develop Data Collection Infrastructure – *01SEP2020- **100% complete***
Develop Standard Operating Procedures (SOPs) – *01SEP2020-**100% complete***
Create Site Materials – *01SEP2020- **100% complete***
Site Initiation Visits/Training – ***25% complete***
- Site 1: Oregon Health and Sciences University- *28SEP2020*
- Site 2: San Antonio Military Medical Center -*10DEC2020*

Major Task 2: Implementation
Randomized Implementation –*01OCT2020 – **25% complete***
Site Monitoring- *01OCT2020 – **25% complete***
Site Maintenance/Retraining- *01OCT2020 -**25% complete***

Major Task 3: Data Collection/Data Analysis
Data Collection- *01OCT2020 -**20% complete***
Data Management/Cleaning- *01OCT2020- **20% complete***
Data Analysis- *01NOV2020 – **No interim analysis will be completed for this trial***
Dissemination of Results- *01APR2021*
Report Findings- *01FEB2023*

- **What was accomplished under these goals?**

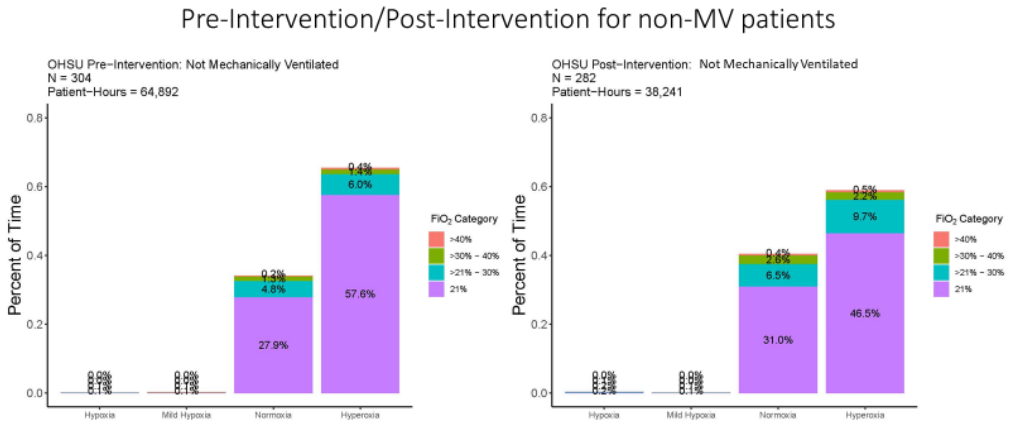
AIM 1:
- Received Local IRB Reliance Agreements
- Finalize Protocol Core Protocol
- Received local IRB approval
- Received HRPO Approval
- Developed and Finalized Data Collection Infrastructure
- Develop and Disseminated Standard Operating Procedures (SOPs) to Sites
- Developed and Disseminated Site Materials
- Successfully Completed Two Site Initiation Visits/Training
    - Site 1: Oregon Health and Sciences University-28SEP2020
    - Site 2: San Antonio Military Medical Center -10DEC2020

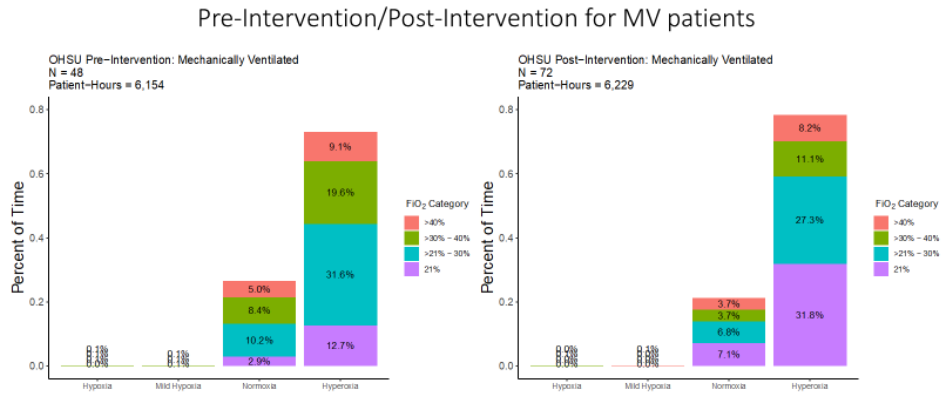
AIM 2:
- Began Randomized Implementation at the first two sites
    - Site 1: Oregon Health and Sciences University- 15OCT2021
    - Site 2: San Antonio Military Medical Center -15JAN2021

-Began Site Monitoring at the first two sites
-Began Site Maintenance/Retraining at the first two sites

AIM 3:
-Began Data Collection at the first two sites
Oregon Health and Sciences Enrollment:
- Total Enrollment: 1,053
- Pre-Intervention: 487
- Washout: 152
- Post- Intervention:414

Pre/Post Intervention Graphs:





San Antonio Military Medical Enrollment:

- We are unable to provide data/graphs for SAMMC at this time due to an upload issue, we are working diligently to resolve the issue and will provide data in our next quarterly report.
- Total Enrollment:560

-Began Data Management/Cleaning at the first two sites
-Began on study reporting analysis at the first two sites, to ensure compliance and review data for safety signals

- **How were the results disseminated to communities of interest?**

During our monthly investigator meetings, we present relevant data and review areas in need of improvement to participating sites and military participants. We will present the methods abstract at SOMSA 2021. We plan to present trial preliminary results at MHSRS 2021.

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

AIM 1:

- Complete site initiation visits for the next 3 enrolling sites (schedule TBD)
  - University of Cincinnati (Launch July 15, 2021)
  - University of Texas at Houston (Launch October 15 2021)
  - Vanderbilt University (Launch January 15, 2022)

AIM 2:

- Continue to implement the randomized implementation
- Continue site monitoring all sites that enter into the implementation phase of the trial Continue site maintenance and retraining at sites that have entered into the implementation phase of the trial

AIM3:

- Continue data collection for post implementation sites
- Prepare non-implementation sites for pre-intervention data collection
- Continue data management activities

- Continue data cleaning
- Continue analyzing on-study reporting compliance documents to ensure safety and compliance

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

- **What was the impact on the development of the principal discipline(s) of the project?**
  - Developed the core protocol to inform participating institutions of study design, multi-modal education and provided study materials to sites to ensure proper implementation a sites.
- **What was the impact on other disciplines?**
  - Educated physicians, nurses, respiratoryve regarding the importance of oxygen titration and the negative effects of hyperoxia.
- **What was the impact on technology transfer?**

  Nothing to report
- **What was the impact on society beyond science and technology?**

  Nothing to Report

5. **CHANGES/PROBLEMS:**

Nothing to Report

- **Changes in approach and reasons for change**

  Nothing to report
- **Actual or anticipated problems or delays and actions or plans to resolve them**

  Nothing to report
- **Changes that had a significant impact on expenditures**

  Nothing to report

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:**

  Nothing to report
- **Significant changes in use or care of vertebrate animals:**

  N/A
- **Significant changes in use of biohazards and/or select agents:**

  N/A

6. **PRODUCTS:**

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

- **Other Products**

  Nothing to report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?** Please see below for University of Colorado personnel nearest month worked. Please see financial report for collaborating institutions (Oregon Health and Sciences University, San Antonio Military Medical Center, Denver Health, University of Cincinnati, University of Texas-Houston, Vanderbilt University, University of Alabama-Birmingham and University of Pittsburgh) personnel nearest month worked.

Name:	Dr. Adit Ginde, MD, MPH
Project Role:	Principle Investigator
Researcher Identifier:	Not Available
Nearest person month worked:	0.93
Name:	Vikhyat Bebarta, MD
Project Role:	C-Investigator
Researcher Identifier:	Not Available
Nearest person month worked:	0.93
Name:	Erin Anderson, RN
Project Role:	Project Manager
Researcher Identifier:	Not Available
Nearest person month worked:	6.75
Name:	Jenn Peers, RN, BSN
Project Role:	Study Coordinator
Researcher Identifier:	Not Available
Nearest person month worked:	4.17
Name:	Shelby Shelton, MPH
Project Role:	Study Coordinator
Researcher Identifier:	Not Available
Nearest person month worked:	1.23
Name:	Jessica Cwik
Project Role:	Study Coordinator
Researcher Identifier:	Not Available
Nearest person month worked:	3.22
Name:	Amanda Martinez, MPH
Project Role:	Study Coordinator
Researcher Identifier:	Not Available
Nearest person month worked:	5.89
Name:	Aimee Steinwand
Project Role:	Study Coordinator
Researcher Identifier:	Not Available
Nearest person month worked:	4.20

Name:	Conner Jackson, MS
Project Role:	Masters Biostatistician
Researcher Identifier:	Not Available
Nearest person month worked:	1.75

Name:	John Rice, PhD
Project Role:	PhD Analyst
Researcher Identifier:	Not Available
Nearest person month worked:	1.20

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Change to PI other support:

See Below

Previous, Current, and Pending Support

GINDE, ADIT A., MD

CURRENT SUPPORT

Title: *Colorado PETAL Clinical Center*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI) (Moss / Ginde)
Role: PD/PI
Description/Aims: The goal of this application is to participate in the selection and conduct of clinical trials for the prevention and early treatment of acute lung injury across a network of 12 clinical centers. Our clinical center includes two academic and four community hospitals in the greater Denver area and a robust infrastructure for recruitment of critically ill emergency department and intensive care unit patients into clinical trials.
Award Number: 1U01HL123010
Funding Period: 06/17/14-04/30/23
Amount:
Time Commitment: 12.5%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: National Center for Advancing Translational Sciences (NCATS)
Funding Agency: Colorado Clinical and Translational Sciences Institute
Role: Co-Investigator
Description/Aims: The CTSA to the University of Colorado Denver supports the institutional academic home for research and training in clinical and translational sciences.
Award Number: UL1TR002535 (Sokol)
Funding Period: 05/18/18-04/30/23
Amount:
Time: 10%
Agency Contact: Pablo Cure, 301-827-2014,pablo.cure@nih.gov
Overlap: None

Title: *Prevention and Early Treatment of Acute Lung Injury (PETAL) Network: "Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS)*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Co-Investigator

Description/Aims: The goal of this phase III trial is to determine the impact of a restrictive fluids strategy (vasopressors first followed by rescue fluids) or a liberal fluid strategy (fluids first followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension.
Award Number: U01HL123009 (Thompson/Schoenfeld
Funding Period: 06/17/2014-04/30/21
Amount:
Time Commitment: 1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *Brain Oxygen Optimization in Severe Traumatic Brain Injury – Phase 3 (BOOST-3)*
Funding Agency: National Institute of Neurological Diseases and Stroke (NINDS)
Role: Co-Investigator
Description/Aims: The goal of this study to determine if there is evidence of clinical efficacy of a treatment protocol based on brain tissue oxygenation (PbtO2) monitoring compared to treatment based on intracranial pressure (ICP) monitoring alone.
Award Number: U01NS099046 (Barsan)
Funding Period: 07/01/18-06/30/24
Amount:
Time Commitment: 1%
Agency Contact: Maria Mendoza-Puccini, 301-496-9135, maria.mendoza.puccini@nih.gov
Overlap: None

Title: *EMS-TruShoC' – A Prospective Trial of Low-Dose, High-Frequency, On-Site Training to Improve Trauma Field Care in Austere Settings*
Funding Agency: Defense Health Agency (J9, Research and Development Directorate); US Department of the Air Force (59th Medical Wing)
Role: Co-Investigator
Description/Aims: The goal of this project is to implement EMS-TruShoC in an austere setting and assess the resultant educational and clinical outcomes. These prehospital trauma resuscitation concepts will inform future efforts to translate into USSOF and conventional military prehospital training and sustaining knowledge.
Award Number: FA8650-18-2-6934 (Mould-Millman/Schauer)
Funding Period: 07/30/18-07/29/21
Amount:
Time Commitment: 1.75%
Agency Contact: Clifford Johnson, 937-713-9922, Clifford.johnson.4@us.af.mil
Overlap: None

Title: *Precision Medicine Approach to Vitamin D3 Administration in Critical Illness*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: SubAward PI/Co-Investigator
Description/Aims: The goal of this study is using a precision medicine approach to investigate the clinical, genetic, and biochemical factors that determine response to vitamin D3 administration in critical illness.

Award Number: R01HL544166 (Leaf)
Funding Period: 07/01/19-06/30/23
Amount:
Time Commitment: 5%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *The Impact of Fluid Resuscitation on Glycocalyx Degradation in Septic Shock*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Co-Investigator (PI: Shapiro/Schmidt)
Description/Aims: The goal of this project is to determine the mechanism of intravenous fluid resuscitation in glycocalyx degradation and adverse clinical outcomes in septic shock.
Award Number: R01HL149422 (Shapiro/Schmidt)
Funding Period: 09/01/19-05/31/23
Amount:
Time Commitment: 1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title*: Establishing the Epidemiology and Outcomes of Combat-Relevant Prolonged Trauma Care: A Prospective Multicenter Prehospital Pilot Study in South Africa*
Funding Agency*:* Department of Defense (USAMCMR)
Role: Co-Investigator
Description/Aims: The goal of this project is to assess the effect of prolonged durations of prehospital care, and key prehospital interventions, on morbidity and mortality of patients with combat-like injuries.
Award Number: BA190054 (Mould-Millman)
Funding Period: 09/30/19-09/29/21
Amount:
Time Commitment: 5%
Agency Contact: Jennifer Shankle, 301-619-2193, Jennifer.e.shankle.civ@mail.mil
Overlap: None

Title: *Multicenter Implementation Trial of Targeted Normoxia Strategy to Define Oxygen Requirements for Major Burn Patients: An Approach to Reduce Warfighter Morbidity, Deployed Logistical Burden of*
Oxygen, and Readiness Costs
Funding Agency: Department of Defense/ Medical Technology Enterprise Consortium (MTEC)
Role: Principal Investigator
Description/Aims: The goal of this study is to determine the feasibility, safety, and effectiveness of the targeted normoxia approach to conserve oxygen and improve clinical outcomes in major burn patients.
Award Number: MTEC-19-08-MuLTI-0043
Funding Period: 01/30/20-01/29/23
Amount:

Time Commitment: 10%
Agency Contact: Jenifer Ojeda, 301-619-0193, Jenifer.f.ojeda.civ@mail.mil
Overlap: None

Title: *Multicenter Implementation Trial of Targeted Normoxia Strategy to Define Oxygen Requirements for Combat Casualty Care*
Funding Agency: Department of Defense (Joint Warfighter Medical Research Program)
Role: Principal Investigator
Description/Aims: The goal of this study is to determine the feasibility, safety, and effectiveness of the targeted normoxia approach to conserve oxygen and improve clinical outcomes in critically injured patients
Award Number: JW190515 (Ginde)
Funding Period: 03/01/20-02/28/23
Amount:
Time Commitment: 10%
Agency Contact: Sandy Snyder, 301-619-7047, sandy.j.snyder.civ@mail.mil
Overlap: None

Title: *Innovative Methods to Evaluate the Role of Influenza Vaccines in Attenuating Severe Disease in Adults*
Funding Agency: Centers for Disease Control and Prevention (CDC)
Role: SubAward PI/Co-Investigator
Description/Aims: The goal of this study is to understand the role of influenza infection and other viral infections including COVID-19 in critical illness, define and sub-phenotype severe influenza disease, and quantify the effectiveness of influenza vaccines for mitigating influenza-associated morbidity and mortality.
Award Number: 75D30120R67837 (Self)
Funding Period: 03/27/20-06/30/21
Amount: (est, depending on enrollment)
Time Commitment: 1%
Agency Contact: Vallerie Redd, 770-488-2845
Overlap: None

Title: *Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease (ORCHID)*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Co-Investigator/Site-PI
Description/Aims: This project will be a randomized controlled trial to compare the safety and efficacy of hydroxychloroquine versus placebo in hospitalized patients with laboratory-confirmed COVID-19
Award Number: 5U01HL123009-06S1 (Thompson)
Funding Period: 04/15/20-04/14/21
Amount:
Time Commitment: 1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *CORAL: PETAL COVID-19 Observational Study*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Site-PI
Description/Aims: Observational study of hospitalized patients with COVID-19 using both retrospective and prospective methods.
Award Number: 5U01HL123009-06S2 (Thompson)
Funding Period: 04/24/20-04/23/21
Amount:
Time Commitment: 1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *Clinical Trial of COVID-19 Convalescent Plasma in Outpatients (C3PO)*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Site PI
Description/Aims: The goal of this study to determine the efficacy and safety of a single dose of convalescent plasma (CP) for preventing the progression from mild to severe COVID-19 illness.
Award Number: 1OT2HL156812 (Korley)
Funding Period: 06/01/20-05/31/21
Amount: SubAward (est, depending on enrollment)
Time Commitment: 1%
Agency Contact: Maria Mendoza-Puccini, 301-496-9135, maria.mendoza.puccini@nih.gov
Overlap: None

Title: *Internationally Coordinating Center for ACTIV-3 Trial Initiative*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Co-Investigator/Site PI
Description/Aims: The goal of this project is to design and oversee the trial, drafting, and revising standard operating procedure documents and FAQs, interactions with DSMB, NHLBI, International Coordinating Center (ICC), running and attending meetings, and serving as an on-call PETAL Investigator for the ACTIV-3 COVID-19 protocol.
Award Number: 1OT2HL156812 (Thomas)
Funding Period: 07/15/20-07/14/21
Amount: (est, depending on enrollment)

Time Commitment: 10%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *An end-user assessment of the novel iView video laryngoscope*
Funding Agency: USAF/AFMC
Role: Site co-investigator
Description/Aims: The goal of this study to is to compare the use of the novel iView laryngoscope to traditional video laryngoscopy during acute airway management.
Award Number: FA8650-20-2-6227 (Schauer)
Funding Period: 10/01/20-09/30/21

Amount:
Time Commitment: 2%
Agency Contact: Vanessa Vazquez, 937-938-3192, Vanessa.vazquez.5@us.af.mil
Overlap: None

Title: *Passive Immunity for Our Nation (PassItOn)*
Funding Agency: National Center for Advancing Translational Sciences (NCATS)
Role: Site PI
Description/Aims: The goal of this phase III trial is to compare the efficacy and safety of convalescent plasma versus placebo among adults hospitalized with COVID-19.
Award Number: 3UL1TR002243-04S3 (Bernard)
Funding Period: 08/18/20-08/31/21
Amount: (est, depending on enrollment)
Time Commitment: 1%
Agency Contact: Rashmi Gopal-Srivastava, gopalr@mail.nih.gov
Overlap: None

Title: *Epidemiology and Outcomes of Combat-Relevant Prolonged Trauma Care: A Prospective Multicenter Prehospital Study in South Africa*
Funding Agency: Department of Defense/U.S. Army
Role: Co-PI
Description/Aims: The goal of this project is to conduct a multicenter epidemiologic study that assesses the effect of prolonged durations of prehospital care, and key prehospital interventions, on morbidity and mortality of civilian patients with combat-like injuries.
Award Number: BA190049
Funding Period: 09/30/2020 – 09/29/2024
Amount:
Time Commitment: 3%
Agency Contact: Jennifer Shankle, 301-619-2193, Jennifer.e.shankle.civ@mail.mil
Overlap: None

Title: *Adult Inpatient/Outpatient VE Case-Control Study*
Funding Agency: Centers for Disease Control and Prevention (CDC)
Role: SubAward PI/Co-Investigator
Description/Aims: The goal of this study is to evaluate vaccine effectiveness of SARS-CoV-2 vaccination against symptomatic, medically attended SARS-CoV-2 infection by vaccine product.
Award Number: 75D30121F00002 (Self)
Funding Period: 02/05/21-02/14/22
Amount:
Time Commitment: 1%

Title: *Implementation and Effectiveness of Monoclonal Antibodies to Treat High-Risk Outpatients with COVID-19*
Funding Agency: National Center for Advancing Translational Sciences (NCATS)
Role: Co-Investigator

Description/Aims: The goal of this project is to develop, implement, and evaluate strategies to optimize equitable nMAb access in Colorado and determine the effectiveness and safety of nMAb treatment in high-risk COVID-19 outpatients.
Award Number: UL1 TR002535-03S3 (Sokol/Ginde)
Funding Period: 3/15/2021-4/30/2022
Amount:
Time: 15%
Agency Contact: Pablo Cure, 301-827-2014,pablo.cure@nih.gov
Overlap: None

Title: *Trial of Early Antiviral Therapies during Non-hospitalized Outpatient Window (TREAT NOW) for COVID-19 to Reduce the Burden of Illness for U.S. Service Members*
Funding Agency: FY20 BA 6.4 CARES Act Research and Development (RDT&E)
Role: Civilian PI
Description/Aims: The goal of this phase III trial is to test the efficacy and safety of the antiviral agent lopinavir/ritonavir to prevent disease progression and improve recovery in outpatients with COVID-19.
Award Number: AC20COV08
Funding Period: 4/1/21-3/31/22
Amount:
Time Commitment: 10%
Agency Contact: Mr. Ed Chagoy (59MDW), 210-292-2761, edward.a.chagoy.civ@mail.mil

Title: *Human IFN Beta-1a In Severe CoronavirUS (HIBISCUS)*
Funding Agency: FY20 BA 6.4 CARES Act Research and Development (RDT&E)
Role: Civilian PI
Description/Aims: The goal of this phase III trial is to test the efficacy and safety of intravenous interferon beta-1a in the treatment of patients with severe hypoxemic respiratory failure/ARDS due to COVID-19
Award Number: AC20COV09
Funding Period: 4/1/21-9/30/22
Amount:
Time Commitment: 10%
Agency Contact: Mr. Ed Chagoy (59MDW), 210-292-2761, edward.a.chagoy.civ@mail.mil

PREVIOUS SUPPORT

Title: *Reevaluation of Systemic Early neuromuscular blockade (ROSE)*
Funding Agency: NHLBI/Massachusetts General Hospital Prevention and Early Treatment of Acute Lung Injury Network
Role: Co-Site PI/Co-Investigator

Description/Aims: The goal of this phase III trial is to determine the efficacy and safety of neuromuscular blockade in reducing mortality of emergency department and intensive care unit patients with moderate-severe acute respiratory distress syndrome.
Funding Period: 11/01/2015-06/30/2018
Amount:
Time Commitment: 1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET)*
Funding Agency: NHLBI/Massachusetts General Hospital Prevention and Early Treatment of Acute Lung Injury Network
Role: Principal Investigator
Description/Aims: The goal of this phase III trial is to determine if early administration of vitamin D reduces 90-day mortality in critically ill, vitamin D deficient patients at high-risk for developing acute respiratory distress syndrome (ARDS). I lead the conduct of a 3,000 patient, 48-institution randomized controlled trial.
Funding Period: 05/01/2016-01/31/2019
Amount:
Time Commitment: 10%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *Targeting Steroid Resistance During Acute Exacerbations of COPD with Respiratory Failure – The AECOPD Resistance Study*
Funding Agency: NIH/Colorado Clinical and Translational Sciences Institute (CCTSI) Team Science Award (PI: Vandivier)
Role: Co-Investigator
Description/Aims: The goals of this study are to determine the mechanisms and clinical implications of steroid resistance in emergency department patients during acute exacerbation of chronic obstructive pulmonary disease with respiratory failure who require mechanical ventilation and ICU admission.
Funding Period: 07/01/2016-06/30/2018
Amount:
Time Commitment: 1%
Agency Contact: Tim Lockie, 720-848-6660, tim.lockie@cuanschutz.edu
Overlap: None

Title: *Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat-Injured Special Operations Forces*
Funding Agency: Department of Defense/U.S. Special Operations Command
Role: PD/PI
Description/Aims: The goal of this application is to determine the feasibility, safety, and potential effectiveness of targeted normoxia as a strategy to conserve oxygen and improve clinical outcomes in critically ill trauma patients.
Award Number: W81XWH-17-C-0241

Funding Period: 09/29/17-01/28/20
Amount:
Time Commitment: 10%
Agency Contact: Douglas Simpson, douglas.simpson@socom.mil
Overlap: None

Title: *Vitamin D to Improve Outcomes by Leveraging Early Treatment: Long-term Brain Outcomes in Vitamin D Deficient Patients (VIOLET BUD)*
Funding Agency: Vanderbilt - National Heart, Lung, and Blood Institute (NHLBI)
Role: SubAward PI/Co-Investigator
Description/Aims: The goal of this project is to determine the effect of vitamin D repletion on long-term cognitive outcomes in critically ill patients.
Award Number: R56HL141567 (Han)
Funding Period: 09/05/18-08/31/19
Amount:
Time Commitment: 10%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov
Overlap: None

Title: *Vitamin C, Thiamine, and Steroids in Sepsis (VICTAS)*
Funding Agency: Johns Hopkins University -The Marcus Foundation, Inc
Role: SubAward PI
Description/Aims: The goal of this study is to test the efficacy of vitamin C, thiamine, and steroids in reducing in-hospital mortality in critically ill patients with sepsis.
Award Number: #2393 (Rothman)
Funding Period: 10/01/18-12/31/19
Amount:
Time Commitment: 2%
Agency Contact: Amanda Bistran-Hall, 410-361-7999, abistra1@jhmi.edu
Overlap: None

Title: *Influenza Vaccine Effectiveness for Preventing Laboratory-Confirmed Severe Influenza-Associated Illness in US Adults*
Funding Agency: Centers for Disease Control and Prevention (CDC)
Role: SubAward PI/Co-Investigator
Description/Aims: The goal of this study is to understand the role of influenza infection in critical illness and the effectiveness of influenza vaccines for mitigating influenza-associated morbidity and mortality.
Award Number: 75D30119C05670 (Self)
Funding Period: 07/10/19-07/09/20
Amount:
Time Commitment: 1%
Agency Contact: Vallerie Redd, 770-488-2845
Overlap: None

PENDING

Title: *Randomized Trial of Fresh Frozen Plasma Versus Albumin in Acute Burn Resuscitation*

Funding Agency: Department of Defense/Military Burn Research Program
Role: Co-Investigator
Description/Aims: The goal of this study is to compare the safety and efficacy of fresh frozen plasma vs albumin for acute resuscitation of burn shock.
Award Number: MB200032 (Wiktor)
Funding Period: 6/1/21-5/31/24
Amount:
Time Commitment: 5%
Agency Contact: Eva Lai, eva.lai.ctr@mail.milrlap:
Overlap: None

OVERLAP

None

- **What other organizations were involved as partners?**
- Oregon Health and Sciences University
- San Antonio Military Medical Center
- Denver Health Medical Center
- University of Cincinnati
- University of Texas- Houston
- Vanderbilt University
- University of Alabama-Birmingham
- University of Pittsburgh

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:**

  Nothing to Report

- **QUAD CHARTS:**

  Attached

9. **APPENDICES:**

2.Methods Abstract: Submitted and approved for presentation at SOMSA 2021

3.Preliminary Results Abstract: Submitted to MHSRS 2021

Multicenter Implementation Trial of Targeted Normoxia Strategy to Inform Oxygen Requirements for Combat Casualty Care

PI: Adit Ginde, MD, MPH
Organization: University of Colorado Denver
Co-PI: MAJ Steven Schauer, DO
Organization: Army Institute of Surgical Research

Award Amount: 3,796,345

Objectives

Our **overall objective** is to determine oxygen titration goals for combat injured to optimize care by reducing harm associated with hypoxia and hyperoxia and to conserve limited oxygen supply

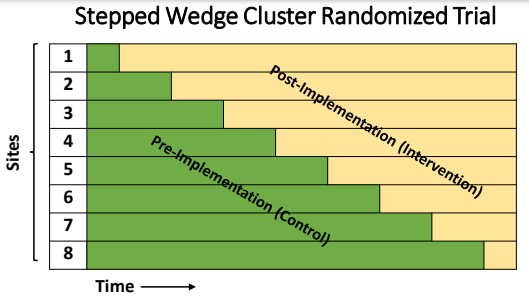
Aim 1. Measure the impact of targeted normoxia implementation on oxygen requirements in critically injured patients

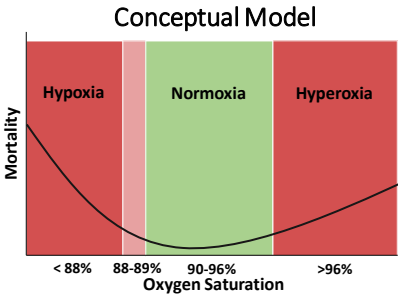
Aim 2. Determine the safety of targeted normoxia

Aim 3. Determine the clinical effectiveness of targeted normoxia

Approach

Multicenter cluster randomized, stepped wedge implementation trial of the targeted normoxia approach (SpO2 90-96%). Efficiency will be greatly enhanced by a waiver of informed consent since protocol implementation is minimal risk (EFIC not required).





Timeline and Cost

Activities	Year 1	Year 2	Year 3
Preparatory Work			
Implementation			
Data Collection			
Analysis/Dissemination			
Estimated Budget ($K)	$1289	$1389	$1125

Updated: March 31, 2021

Goals/Milestones

Major Task 1: Preparatory Work
- ☒ Local IRB Reliance
- ☒ Finalize Protocol
- ☒ Central IRB Approval
- ☒ HRPO Approval
- ☒ Develop Data Collection Infrastructure
- ☒ Develop Standard Operating Procedures (SOPs)
- ☒ Create Site Materials
- ☐ Site Initiation Visits/Training – ***25% complete***

Major Task 2: Implementation
- ☐ Randomized Implementation -***25% complete***
- ☐ Site Monitoring -***25% complete***
- ☐ Site Maintenance/Retraining- ***10% complete***

Major Task 3: Data Collection/Data Analysis
- ☐ Data Collection -***20% complete***
- ☐ Data Analysis -***20% complete (on-study data)***
- ☐ Dissemination of Results
- ☐ Report Findings

Strategy to Avoid Excessive Oxygen (SAVE-O2) for Critically Ill Trauma Patients: A Multicenter Clinical Trial to Define Oxygen Requirements for Combat Casualty Care

David J. Douin, MD[1]; Erin L. Anderson, RN[1]; MAJ Steven G. Schauer, DO, MS[3]; John Rice, PhD[2]; Layne Dylla, MD, PhD[1]; Conner Jackson, MS[2]; Alex Cheng, PhD[5]; Col Vikhyat S. Bebarta, MD[1,4,6]; Adit A. Ginde, MD, MPH[1,6]

[1] University of Colorado School of Medicine, Aurora, CO
[2] Colorado School of Public Health, Aurora, CO
[3] US Army Institute of Surgical Research, JBSA Fort Sam Houston, TX
[4] US Air Force 59th Medical Wing, Office of the Chief Scientist, JBSA Lackland, TX
[5] Vanderbilt University Medical Center, Nashville, TN
[6] Center for COMBAT Research, University of Colorado School of Medicine, Aurora, CO

Background: Recent evidence supports targeting normoxia (SpO2 90-96% or PaO2 60-100mmHg) to avoid hyperoxia. Our objective is to determine the feasibility, safety, and effectiveness of targeted normoxia to conserve oxygen and improve clinical outcomes in critically injured patients.

Methods: This prospective multicenter clinical trial will enroll critically ill trauma patients at eight level 1 trauma centers in the United States (NCT04534959). We will follow patients from emergency department through hospital discharge or to day 90 - whichever comes first. Each hospital will contribute pre-implementation (control) and post-implementation (intervention) data. The start of the intervention period will be defined by randomized timing in a stepped wedge cluster randomized controlled trial design. All sites will begin in the control phase with usual care. When sites reach their randomly assigned time to transition, there will be a one-month training period, which does not contribute to data collection. Following the one-month training period, the site will remain in the intervention phase for the duration of the trial. The primary outcome is supplemental oxygen free days, defined as number of days alive and not on supplemental oxygen.

Results: The Colorado Multiple Institutional Review Board, the Single IRB for this trial, approved with a determination of minimal risk. This was subsequently approved by the Human Research Protections Office with the same determination. Vanderbilt University is serving as the data coordinating center. As of November 30, 2020, one site has transitioned into the intervention phase. The next site transition will occur on January 15, 2021. Preliminary results will be available for the 2021 SOMA conference.

Discussion/Conclusions: We hypothesize targeted normoxia will safely reduce the need for concentrated oxygen. These data will inform military stakeholders on oxygen requirements for critically injured warfighters, while reducing logistical burden in prolonged combat casualty care.

Disclosures: Funded by Joint Warfighter Medical Research Program (JWMRP) W81XWH-20-2-0001. This abstract expresses the authors' opinions and does not reflect the policy or opinions of the Department of the Army, Department of the Air Force, Department of Defense, or US Government.

Abstract Word Count: 293

Strategy to Avoid Excessive Oxygen (SAVE-O2) for Critically Ill Trauma Patients: A Multicenter Cluster Randomized, Stepped Wedge Trial for Targeted Normoxia

Layne Dylla, MD, PhD[1]; David J. Douin, MD[1]; Erin L. Anderson, RN[1]; MAJ Steven G. Schauer, DO, MS[2,3]; John D. Rice, PhD[4]; Conner Jackson, MS[4]; Alex Cheng, PhD[5]; Martin A. Schreiber, MD[6]; Col Vikhyat S. Bebarta, MD[1,3,7]; Adit A. Ginde, MD, MPH[1]

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[6] Oregon Health and Sciences University, Portland, OR
[7] Center for COMBAT Research, University of Colorado School of Medicine, Aurora, CO

Background: Prevention of hypoxia is critical to avoid secondary injury in critically ill trauma patients and often results in widespread supplemental oxygen use. Many patients are exposed to supraphysiological levels of oxygen, “hyperoxia”, which is also associated with increased mortality. The ability to safely conserve supplemental oxygen has many implications in terms of logistics, weight, and power requirements in combat casualty care and prolonged field care settings. Our objective is to determine the feasibility, safety, and effectiveness of targeting normoxia (pulse oximetry (SpO_2) of 90-96%) to conserve oxygen and improve clinical outcomes in critically ill patients.

Methods: This is a multicenter cluster randomized, stepped wedge implementation trial to determine the effectiveness of a multimodal intervention to target normoxia in critically ill trauma patients (NCT04534959). Eight Level 1 US trauma centers are randomized to cross over from a control pre-implementation phase (“control” - usual care) to the post-implementation (“intervention”) phase at three-month intervals in randomized order. During the one-month run-in phase for the intervention, we use a multimodal intervention tailored to each sight that includes multiple educational activities, electronic health record best practice alerts, recurring feedback regarding patient time in various oxygenation categories with and without supplemental oxygen, and/or protocols to down-titrate supplemental oxygen in hyperoxic patients (SpO_2>96% and on supplemental oxygen). Within a site, adults (aged 18 years or older), who meet criteria for inclusion into a state or national trauma registry and are admitted to a surgical or trauma intensive care unit (ICU) within 24 hours of arrival to a participating hospital are included in analysis. Prisoners and women with a known pregnancy are excluded. The primary outcome is supplemental-oxygen-free days, defined as the number of days a patient is alive and not on supplemental oxygen from time of presentation to day 28, with death assigned a value of -1. Additional secondary outcomes included ventilator-free days, hospital-free days, in-hospital mortality, and time to mortality. As of March 2021, one site has contributed preliminary data from both the pre- and post-implementation phase for review.

Results: Preliminary data from the first site to undergo cross-over to the post-implementation phase is complete; updated data will be provided at the time of presentation. The pre-implementation phase consisted of 311 patients, contributing 71,046 patient-hours of data. Pre-implementation patients had an average age of 55 years and were 28% female, 8% Hispanic, 4% non-Hispanic Black, 73% non-Hispanic White, and 14% other. The post-implementation phase consisted of 301 patients, contributing 44,470 patient-hours of data to date. Patients in the post-implementation population had an average age of 58 years and were 30% female, 6% Hispanic, 2% non-Hispanic Black, 70% non-Hispanic White, and 14% other.

Overall, there was a slight increase in the proportion of patient-time spent normoxic (SpO_2 90-96%) (32.5% pre-implementation and 37.8% post-implementation). Among patients who were hyperoxic (SpO_2>96%), there was an increase in the proportion of patient-time spent on supplemental oxygen (12.4% pre-implementation, 17.3% post-implementation). There was a similar proportion of patient-time spent hypoxic (SpO_2<88%) (0.2% pre-implementation, 0.3% post-implementation).

In non-mechanically ventilated patients, there was an increase in the proportion of patient-time spent normoxic (34.2% pre-implementation vs 40.5% post-implementation). However, among patients who were hyperoxic, there was an increase in the proportion of patient-time on supplemental oxygen (7.8% pre-implementation, 12.4% post-implementation). Again, there was a slight increase in the proportion of patient-time spent hypoxic (0.2% pre-implementation, 0.5% post-implementation).

In mechanically ventilated patients, there was a decrease in the proportion of patient-time spent normoxic (26.5% pre-implementation, 21.3% post-implementation), but also a reduction in supplemental oxygen use in this sub-group (23.6% pre-implementation, 14.2% post-implementation). Among those who were hyperoxic, there was also a reduction in supplemental oxygen use (60.3% pre-implementation, 46.6% post-implementation). This was also true of those patients found to be hyperoxic on high levels of FiO_2 (>40%) (9.1% pre-implementation, 8.2% post-implementation) and on moderate levels of FiO_2 (>30-40%) (19.6% pre-implementation, 11.1% post-implementation). Finally, there was a reduction in the proportion of patient-time spent hypoxic (0.3% pre-implementation, 0.1% post-implementation). Given that these are preliminary results, no assessment of statistical significance was made. Rather, trends are used to inform further multimodal interventions.

Conclusions: Preliminary data from the first site randomized to cross-over to the post-implementation phase of SAVE-O2 suggests that a multimodal intervention to target normoxia in critically ill trauma patients can increase the proportion of patient-time spent in normoxia. In non-mechanically ventilated patients, the total patient-time spent hyperoxic and on supplemental oxygen is minimal and close to our target of <10% total patient-time spent hyperoxic and on supplemental oxygen. The greatest improvement in oxygenation practices appears to be in mechanically ventilated patients where we reduced the amount the proportion of patient-time spent hyperoxic and on supplemental oxygen from 60.3% patient-time to 46.6% patient-time post-implementation. While doing

so, we did not observe a clinically significant difference in the proportion of patient-time spent in hypoxia overall. More attention is needed for mechanically ventilated patients who are hyperoxic to reduce supplemental oxygen use. We hypothesize that the final results will demonstrate that this intervention will reduce supplemental oxygen use, improve time spent in normoxia, and improve patient outcomes (with a primary endpoint: supplemental oxygen free days). This has many important implications for reduced supplemental oxygen use in the combat setting, including potentially reducing the amount of supplement oxygen required in remote and prolonged field care settings.

Disclosure: Funded by Joint Warfighter Medical Research Program (JWMRP) W81XWH-20-2-0001. This abstract expresses the authors' opinions and does not reflect the policy or opinions of the Department of the Army, Department of the Air Force, Department of Defense, or US Government.

Learning Objectives:
1. Describe the multimodal approach used by the SAVE-O2 trial to improve compliance with targeted normoxia
2. Analyze the preliminary data for the SAVE-02 trauma trial.
3. Discuss the potential implications of targeted normoxia in civilian and military critically ill trauma