

**AWARD NUMBER:** W81XWH-21-1-0677

**TITLE:** Study to Improve Deployment-Related Asthma by Using L-Citrulline Supplementation (SEALS)

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**CONTRACTING ORGANIZATION:** University of Colorado Denver, Aurora, CO

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**13. SUPPLEMENTARY NOTES****14. ABSTRACT**

The overall goal of this proposal is to determine if L-citrulline can be used to improve asthma control in subjects with deployment-related asthma. We have previously shown that adult patients with poorly controlled asthma have an abnormal regulation of an amino acid called L-arginine and airway nitric oxide (FeNO). In healthy people, nitric oxide is present in amounts that help keep the airways open. However, in some patients with asthma, nitric oxide and L-arginine are often low. Our preliminary data in obese asthmatics show that L-citrulline, which is an amino acid that can be metabolized into L-arginine, improved lung function and asthma control, while increasing the levels of FeNO. Based on this, we hypothesize that an L-citrulline-based drug strategy will normalize nitric oxide metabolism, suppress oxidative inflammatory responses and improve airway function in previously deployed patients with asthma. Our proposal presents a clinical trial approach to treat deployment related asthma patients using L-citrulline as an add-on therapy to improve asthma control. Our results will potentially show that L-citrulline is a safe, tolerable medication that can make a significant impact on the respiratory health of a large segment of our active and veteran population at a reasonable cost.

**15. SUBJECT TERMS** None listed.

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**1. INTRODUCTION:**

Service men and women returning from deployment are significantly more likely to develop asthma and severe respiratory symptoms from airway obstruction. Why this happens is not well known, but exposure to diesel, burn pits, combat dusts, and sandstorms are thought to play a role. Ultimately, patients with deployment related asthma develop a complex airway disease that does not respond well to standard asthma medications. Therefore, it is imperative that we study safe and affordable treatments that could improve quality of life and symptoms. The overall goal of this study is to determine if L-citrulline can be used to improve asthma control in subjects with deployment-related asthma.

**2. KEYWORDS:**

Respiratory health, deployment related asthma, veterans, l-citrulline

**3. ACCOMPLISHMENTS:**

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

<b><u>Major Goals for First 12 Months of the Planning Phase Based on our SOW</u></b>		
<b>Subtask 1: Prepare Regulatory Documents and Research Protocol for Study</b>		
<b>Goals</b>	<b>Timeline (Months)</b>	<b>% Completed</b>
Coordinate with sites for material transfer agreements (MTAs) or subcontracts submission	1-3	100%
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	100%
Coordinate with Sites for flow chart for all study steps, web data collection and database requirements	1-6	100%
Finalize assessment measurements	1-3	100%
Finalize consent form, study documents & human subjects protocol	1-3	100%
<i>Milestone Achieved: Finalization of Study Documents for Regulatory Approval by Month 3</i>		100%

**Subtask 2: Submission of documents for Regulatory Review & Approval**

<b>Goals</b>	<b>Timeline (Months)</b>	<b>% Completed</b>
Coordinate with Sites for IRB protocol submission and approval	3-6	100%
Coordinate with Sites for VA Medical Center IRB submission and approval	3-6	100%
Coordinate with Sites for review and approval from USAMRDC Office of Research Protections (ORP), Human Research Protection Office (HRPO)	3-6	100%
Recruit Data Safety Monitor	6-9	100%
<i>Milestone Achieved: All Regulatory Requirements Approval by Month 12</i>	12	100%

**Subtask 3: Study Drug Acquisition**

<b>Goals</b>	<b>Timeline (Months)</b>	<b>% Completed</b>
Coordinate with School of Pharmacy and Skyridge Pharmacy to put contracts in place for L-citrulline procurement	1-6	100%
Obtain study drug	9-42	75%
Obtain IND/IDE (FDA) approval for this trial	9-12	50%
<i>Milestone Achieved: Obtaining Study Drugs Throughout Study</i>		

**Subtask 4: Hire & Train Study Staff for Clinical Trial**

<b>Goals</b>	<b>Timeline (Months)</b>	<b>% Completed</b>
Coordinate with Sites for job descriptions design	1-3	100%
Advertise and interview for project related staff	1-3	100%
Coordinate for space allocation for new staff	1-3	100%
Complete all required study trainings	1-12	100%
Coordinate with Sites for All Staff Protocol Training	10-12	50%
<i>Milestone Achieved: All Staff Hired and Trained by Month 12</i>		75%
<i>Milestone Achieved: Study Begins by Month 13</i>		

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

### **1. Major Activities**

- The major activities we worked on during the Planning Phase were to complete the protocol, finalize lab collection processes, and complete study materials for the required regulatory submissions for the study. This required substantial coordination between the University of Colorado Denver, National Jewish Health, and the VA to gather all the regulatory documents during this past year.
- All sites have either completed or have nearly completed specific internal institutional processes for human subjects research.
- During this first year, we hired and trained all study team members at the University of Colorado and National Jewish Health in order to be ready for the activation of the Clinical Trial Phase of the study.

### **2. Specific Objectives**

- Our specific objectives during this Planning Phase were to complete the protocol and study materials for submission to the regulatory entities, to get all regulatory approvals in place, and to have our teams be complete and fully trained before starting the Clinical Trial phase.
- Another major goal we wanted to achieve during this time was coordination with Sky Ridge Pharmacy to put contracts in place for L-citrulline procurement, which should be ready by the start of the trial phase.

### **3. Significant Results or Key Outcomes**

- In the Planning Phase of the study, we were able to submit our documents to the regulatory entities (VA IRB, the Colorado Multiple Institutional Review Board (COMIRB), ClinicalTrials.gov as well as HRPO approval before we start our Clinical Trial Phase.
- We registered the SEALS Study with the NJH Human Research Protection Program (HRPP) to facilitate coordination among relevant departments at NJH (laboratory, clinical research unit) and to obtain required review of the study protocol, consent forms, and recruitment and other documents by the NJH HRPP administrator. NJH officially ceded IRB review to COMIRB.
- The most significant result was receiving our purple clearance letter from the VA and we recently received COMIRB approval, as well as HRPO approval. The purple clearance letter was a 4 month process involving VA IRBnet application, submission of required documents and addressing comments received on submission.
- We completed the WOC process for necessary staff members at the VA.

#### **4. Other Achievements**

- The newly hired NJH study coordinator received formal training and achieved competence in all of the following areas: NIOSH-certified spirometry; CITI training (biomedical research, Good Clinical Practice, Health Information Privacy and Security); record-keeping and retention; IRB regulatory and FDA regulated documents; IATA specimen shipping/handling; protocol deviation and adverse event reporting; and all of the requirements for the SEALS clinical trial (including informed consenting, investigational drug dispensing, Rapid COVID antigen testing, EKG, phlebotomy, lab specimen storage, FeNO, bronchodilator administration; methacholine challenge, 6-minute walk test, IOS training).
- At both the NJH and RMRVA sites, we continued to clinically evaluate military personnel with post-deployment respiratory symptoms, identified those with deployment-related asthma, and obtained their consent to participate in clinical research, further laying the groundwork for SEALS subject recruitment beginning in January 2023.

#### **Stated Goals Not Met**

Currently, we are right on target to complete all of our goals listed above. Sky Ridge Pharmacy has procured all supplies for the study drug and placebo for the course of our Clinical Trial Phase. We noted the obtaining of study drug only to be partially complete (75%) because we will be receiving the drugs throughout the course of the Clinical Trial Phase. The FDA amendment has been submitted for this study and we are awaiting their approval. Our All Staff Protocol Training goal is set at 50% as we are planning on holding this in-person training sometime in November 2022. All these pending goals will be complete prior to the end of our Planning Phase (12/31/2022).

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

All staff were trained on the protocol and study procedures during this Planning Phase. Trainings included CITI trainings (human subjects), site specific trainings, Good Clinical Practice (GCP), protocol training, FDA regulations, human subjects protection, and lab trainings. New coordinators were certified in research related procedures and devices (see previous section). In addition to extensive training through Clinical Research Services at National Jewish Health (NJH), the NJH study coordinator came over to train with the University of Colorado staff during the summer to help assure comparability of findings based on shared clinical research practices. In addition to regular monthly update calls between the University of Colorado and NJH study teams, regular meetings were held with lab scientists at the University of Colorado, National Jewish Health, and Hospital for Sick Children to discuss and train on upcoming lab sample collection and troubleshoot any issues related to processes and procedures for the labs.

The site investigators (Holguin, Sharma, Rose, Krefft) and some study staff attended the 2022 International Meeting of the American Thoracic Society where they participated and learned more about asthma-related clinical trial topics. They presented an abstract titled “Asthma Endotypes in Post-9/11 Deployment-Related Asthma” (Appendix A), which further laid the groundwork for SEALS study subject recruitment and endotyping. While they did not present data accrued during this SEALS trial, they did participate in scholarly discussion sessions, case reports (see Appendix B abstract on “Submarine Veteran with New Onset Asthma”) and research presentations on respiratory health and deployment-related asthma.

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

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.*

Nothing to Report

**4. IMPACT:**

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

Nothing to Report

**What was the impact on other disciplines?**

Nothing to Report

**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

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

SEALS research coordinators from the University had to obtain Without Compensation (WOC) status through the VA, a process that takes several months, in order for the VA to be a recruitment/performance site for SEALS.

**Changes that had a significant impact on expenditures**

As soon as we received word that the study had been approved by DoD for funding, a position was posted at NJH to hire a research coordinator. Because of COVID pandemic related hiring challenges, the position was not filled until February 2022. This resulted in a modest delay in expenditures on this subcontract award, which will be addressed during the planning period extension granted through December 2022.

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

Nothing to report as the study has not been activated yet.

**Significant changes in use or care of human subjects**

Nothing to Report

**Significant changes in use or care of vertebrate animals**

Nothing to Report

**Significant changes in use of biohazards and/or select agents**

Nothing 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**

Nothing to Report

- **Other Products**

Nothing to Report

## **7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

**What individuals have worked on the project?**

*Name: Fernando Holguin, MD, MPH  
No Change*

*Name: Sunita Sharma, MD, MPH  
No Change*

*Name: Daniel Winnica, PhD  
No Change*

*Name: Jennifer Bitzan  
No Change*

*Name: Margaret Hope Cruse  
No Change*

*Name: Abigail Hills  
No Change*

*Name: Cuining Liu  
No Change*

*Name: Noah Lowen, MS*

*Project Role:*

*Researcher Identifier (e.g. ORCID ID): N/A*

*Nearest person month worked: 1*

*Contribution to Project: Noah is lead study coordinator at National Jewish Health. He will help recruit and consent participants, and complete research study visits. In addition to his efforts with study investigators at NJH, Noah will work closely with Ms. Bitzan at the University of Colorado to ensure study progress and participate in all study related trainings.*

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

Nothing to Report

**What other organizations were involved as partners?**

**Organization Name:** National Jewish Health

**Location of Organization:** 1400 Jackson Street, Denver, CO 80206

**Partner's Contribution to the Project:**

- *In-kind support*
- *Facilities*
- *Collaboration*

**Organization Name:** Rocky Mountain Regional VA Medical Center (VAMC)

**Location of Organization:** 1700 North Wheeling St, Aurora, CO 80045

**Partner's Contribution to the Project:**

- *Facilities*
- *Collaboration*
- *Personnel exchanges*

**Organization Name:** The Hospital for Sick Children

**Location of Organization:** 555 University Ave, Toronto, Canada

**Partner's Contribution to the Project:**

- *Collaboration*

**Organization Name:** Skaggs School of Pharmacy (University of Colorado)

**Location of Organization:** MS C238, 12850 E. Montview Blvd, Rm V20-3127, Aurora, CO 80045

**Partner's Contribution to the Project:**

- *Other: Provides formulary support of the L-citrulline and matching placebo; stability analysis*

**Organization Name:** Sky Ridge Pharmacy

**Location of Organization:** 10495 S. Progress Way, Unit 100, Parker, CO 80134

**Partner's Contribution to the Project:**

- *Other: Prepares, provides L-citrulline and matching placebo*

## 8. SPECIAL REPORTING REQUIREMENTS

**COLLABORATIVE AWARDS:**

**QUAD CHARTS:**

## 9. APPENDICES:

### Appendix A

**Title:** Asthma Endotypes in Post-9/11 Deployment-Related Asthma

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**Authors:** SD Krefftt<sup>1-3</sup>, L Zell-Baran<sup>2,4</sup>, K Pang<sup>2</sup>, C Onofrei<sup>2</sup>, R Kraus<sup>2</sup>, S Sharma<sup>3</sup>, F Holguin<sup>3</sup>, CS Rose<sup>2-4</sup>

<sup>1</sup>Veterans Administration Eastern Colorado Health Care System, Aurora, CO, United States

<sup>2</sup>National Jewish Health, Denver, CO, United States

<sup>3</sup>University of Colorado School of Medicine/Anschutz Medical Campus, Aurora, CO, United States

<sup>4</sup>Colorado School of Public Health, Aurora, CO, United States

#### **Rationale:**

Military deployment to southwest Asia and Afghanistan has been linked to new-onset asthma. Studies have focused on asthma epidemiology in deployed personnel, but little is known about asthma characteristics (e.g., T helper2 [Th2] and non-Th2 endotypes) that may affect disease severity and treatment response. Many with post-9/11 deployment-related asthma (DRA) report suboptimal asthma control despite use of standard asthma medications. We examined differences in demographic, exposure, and clinical characteristics in military personnel with Th2 compared to non-Th2 DRA. We hypothesized that non-Th2 asthmatics would be older, more obese, and have more tobacco exposure than Th2 asthmatics.

#### **Methods**

We conducted a retrospective observational study of patients in a subspecialty pulmonary clinic between 2011 and 2021 with DRA (defined as new-onset asthma by ATS/ERS lung function criteria during or after post-9/11 deployment). Th2 DRA was defined based on one or more of the following: IgE>100 IU/mL, serum eosinophils $\geq$ 300, FeNO $\geq$ 30 ppb, or positive skin tests for atopy. We used SAS 9.4 to examine differences in demographic, exposure, and clinical characteristics between those with Th2 and non-Th2 DRA. We compared continuous variables via T-test (Satterthwaite result) and categorical variables via Chi-square or Fisher's exact test.

#### **Results**

Of 226 total participants, 77 had DRA, with 69 having endotype data available. Most were male (87%), with average age 39.5 years. There were 43 (62%) with Th2 and 26 (38%) with non-Th2 endotypes (Table 1). There were no significant differences between groups in smoking status, age, or family history of asthma. Those with Th2 DRA had shorter deployment duration and frequency and lower exposure index scores than the non-Th2 group, though differences were not statistically significant. Reported burn pit exposure was similar between groups. Those with Th2 DRA were significantly more likely to have had combat occupations (62% vs 21%, p=0.02). Chronic rhinitis and/or sinusitis was significantly more common in the Th2 group (26% vs 4%, p=0.02). We found

no significant differences between Th2 and non-Th2 DRA groups in relevant co-morbidities, rest or exercise pulmonary function, or severity of airways hyperresponsiveness on methacholine challenge.

## Conclusions

Both Th2 and non-Th2 asthma endotypes occur in those with DRA. Combat occupations and rhinitis/sinusitis were significantly more common in those with Th2 DRA, but age, smoking, and obesity were similar between groups. Future efforts will focus on understanding DRA risk factors and mechanisms, and on exploring responses to asthma treatment based on DRA endotype to optimize asthma control.

Table 1. Demographics, Deployment Exposures, and Clinical Characteristics

	Th2 n=43	Non-Th2 n=26	Aggregate	P
<b>Demographics</b>				
Age, mean ± SD	38.3 ± 9.6	41.4 ± 11.4	39.5 ± 10.3	0.25
Male sex, n (%)	40 (93%)	20 (77%)	60 (87%)	0.07 <sup>#</sup>
<i>Smoking status, n (%)</i>				
• Never smoker	27 (63%)	18 (69%)	45 (65%)	0.59
• Current/ever smoker	16 (37%)	8 (31%)	24 (35%)	0.59
• Smoking pack-years, mean ± SD (n=23)	13.0 ± 19.2	7.7 ± 10.5	11.1 ± 16.6	0.40 <sup>#</sup>
<i>Other</i>				
Family History of Asthma, n (%) (n=53)	4/29 (13.8%)	5/24 (20.8%)	9/53 (17%)	0.72 <sup>#</sup>
<b>Deployment Characteristics</b>				
<i>Deployment Location, n (%)</i>				
• Iraq	29 (67%)	20 (77%)	49 (71%)	0.40
• Afghanistan	23 (53%)	14 (54%)	37 (54%)	0.98
Deployment duration (months), mean ± SD	18.5 ± 16.6	21.9 ± 18.8	19.8 ± 17.4	0.45
Exposure intensity index of all exposures, <sup>‡</sup> mean ± SD (n=67)	1140 ± 1324	1488 ± 1497	1275 ± 1393	0.09 <sup>^</sup>
Burn pit exposure (n=67)	37/41 (90%)	23/26 (88%)	60/67 (90%)	1.0 <sup>#</sup>
<b>Combat occupational code (n=40)</b>	16/26 (62%)	3/14 (21%)	19/40 (48%)	<b>0.02<sup>#</sup></b>
<b>Comorbid conditions</b>				
<b>Chronic rhinitis or sinus disease, n (%)</b>	11 (26%)	1 (4%)	12 (17%)	<b>0.02<sup>#</sup></b>
Laryngeal dysfunction (ILO/LPR), n (%)	6 (14%)	6 (23%)	12 (17%)	0.35 <sup>#</sup>
GERD, n (%)	27 (63%)	19 (73%)	46 (67%)	0.38
Sleep disordered breathing (defined as OSA, complex sleep apnea, nocturnal hypoxia), n (%)	23 (53%)	15 (58%)	38 (55%)	0.73
Obesity (based on BMI of 30+ and clinic summary), n (%)	20 (47%)	15 (58%)	35 (51%)	0.16
<b>Pulmonary physiology</b>				
FEV1 baseline (pre, % predicted), mean ± SD	84.1 ± 14.5	88.8 ± 17.8	85.9 ± 15.9	0.26
FEV1/FVC <LLN, n (%)	9 (20.9%)	2 (7.7%)	11 (15.9%)	0.19 <sup>#</sup>
FEV1/FVC <70%, n (%)	10 (23.3%)	3 (11.5%)	13 (18.8%)	0.34 <sup>#</sup>
RV > 120% predicted, n (%) Stocks reference	18 (41.9%)	11 (42.3%)	29 (42.0%)	0.97
Methacholine PC[-20] FEV1, mean ± SD (n=46)	4.0 ± 5.2	3.4 ± 3.0	3.8 ± 4.4	0.58
VO2 max % predicted, mean ± SD (n=61)	83.6 ± 19.7	92.5 ± 20.2	87.0 ± 20.2	0.10

<sup>^</sup>This variable was log-transformed before comparison to fit test assumptions.

<sup>#</sup>Fisher exact test used due to small cell sizes.

<sup>‡</sup>Exposure index was calculated using the following formula:

$$(\text{Months Deployed} * \text{Frequency of Exposure to Burn Pits in days/month}) + (\text{Months Deployed} * \text{Frequency of Exposure to Sandstorms in days/month}) + (\text{Months}$$

Deployed\*Frequency of Exposure to **Diesel Exhaust** in days/month) + (Months  
Deployed\*Frequency of Exposure to **IED Blast** in days/month) + (Months  
Deployed\*Frequency of Exposure to **Controlled Detonations** in days/month) + (Months  
Deployed\*Frequency of Exposure to **Mortar Fire** in days/month)

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Defense. Additional funding support was provided through the Sergeant Sullivan Fund at the National Jewish Health.

## Appendix B

### Submarine Veteran with New Onset Asthma Case Report, ATS 2022 (POSTER PRESENTATION)

R Kraus, R Meehan, CS Rose

National Jewish Health, Denver, CO, University of Colorado Anschutz Medical Campus, Aurora, CO, Colorado School of Public Health, Aurora, CO

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**Introduction:** Military personnel deployed on submarines work in enclosed environments for extended periods. Nuclear submarines employ unique methods to generate oxygen and remove carbon dioxide and other air contaminants during prolonged submersion. We describe a patient with new-onset asthma after multiple extended submarine deployments.

**Case Description:** A 33-year-old never smoker with no personal/family respiratory disease history noted new-onset hacking cough and postnasal drainage while deployed on a 45-day nuclear submarine mission. He reported a strong 'amine odor' throughout this and subsequent submarine deployments. His symptoms persisted with return stateside.

Three weeks later, he deployed on a 90-day submarine mission. His symptoms worsened, including dyspnea, dry skin, and severe cough triggering reflux. Sitting directly under submarine air vents worsened his cough. With return, he was treated for presumed pneumonia, with minimal improvement.

Two months later, he deployed for a third (90-day) submarine mission, with immediate worsening of cough and reflux. During this mission, a two-hour electrical fire disabled the automatic oxygen generator, requiring use of oxygen-generating chlorate 'candles,' creating a low oxygen environment for most of the deployment. On return, he was treated for presumed allergies.

Two months later, he deployed on a fourth submarine mission (120 days), again triggering cough, dyspnea, dry skin, and new-onset wheezing. The oxygen generator again malfunctioned, requiring

oxygen-generating ‘candles’ with a prolonged low oxygen environment and persistent strong amine odor.

Subsequent pulmonary consultation led to diagnoses of new-onset asthma (based on positive methacholine challenge with normal chest imaging) and sleep apnea. His symptoms improved with treatment, but he was disqualified due to asthma from subsequent deployment.

**Discussion:** The temporal onset of this submariner’s respiratory symptoms during his first submarine mission, with progressive worsening on each subsequent mission, raised concern for amine exposure causing new-onset asthma. Monoethanolamine is used in submarines to scrub excess airborne carbon dioxide. Several studies link new-onset asthma with occupational exposure to amines, a class of chemicals that can have both irritant and immune-sensitizing properties. Additional potential airborne hazards aboard nuclear submarines include aldehydes, acrolein, ozone, nitrogen oxides, refrigerants and volatile organic compounds. Nuclear submariners live and work continuously in low (~19%) oxygen and high carbon dioxide environments. They may experience smoke exposure from confined space fires, low physical activity causing metabolic syndrome, circadian misalignment, and chronic stress/shift work. This case underscores the need for additional studies of submarine air quality and potential respiratory disease risks to submariners.

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