AWARD NUMBER: W81XWH-18-1-0083

TITLE: Addressing Neuromuscular Deficits for Improved Outcomes in Ankle Rehabilitation

PRINCIPAL INVESTIGATOR: Phillip Gribble

CONTRACTING ORGANIZATION: University of Kentucky, Lexington, KY

REPORT DATE: April 2022

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
April 2022	Annual	15MAR2021- 14MAR2022

4. TITLE AND SUBTITLE

Addressing Neuromuscular Deficits for Improved Outcomes in Ankle Rehabilitation

5a. CONTRACT NUMBER
W81XWH-18-1-0083

5b. GRANT NUMBER
DM170430

5c. PROGRAM ELEMENT NUMBER
Blank

6. AUTHOR(S)
Gribble, Phillip; Soute, Shawn; Wikstrom, Erik; Heebner Nick; Hoch, Matt; Johnson, Nathan; Powell, David

E-Mail: phillip.gribble@uky.edu

5d. PROJECT NUMBER
Blank

5e. TASK NUMBER
Blank

5f. WORK UNIT NUMBER
Blank

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Kentucky
900 South Limestone
Lexington, KY 40506

8. PERFORMING ORGANIZATION REPORT NUMBER
Blank

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)
Blank

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

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
Blank

14. ABSTRACT
The primary purpose of this study will seek to identify lateral ankle sprain (LAS) patients that do not respond to physical rehabilitation under a traditional medical model and who subsequently develop chronic ankle instability (CAI). The proposed study will evaluate established clinical outcomes along with innovative measures of brain and spinal cord function and ankle joint stability during a one-year follow-up after injury. Our hypothesis is that patients who develop CAI within one-year after injury will demonstrate poorer clinical outcomes, larger alterations in innovative measures of brain and spinal cord function, and early ankle joint cartilage turnover compared to the LAS patients that develop into Copers. The secondary purpose of this study will be to transition the results to methods that can be applied in multiple rehabilitation settings across civilian and military treatment facilities. We will determine which clinical measures are most related to the advanced brain and spinal cord measures.

15. SUBJECT TERMS
Lateral ankle sprain; sensorimotor; musculoskeletal treatment; physical readiness

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified	Unclassified	22	USAMRDC

Table of Contents

1. INTRODUCTION

Lateral ankle sprains (LAS) are the most commonly reported injury in military and civilian populations. Up to 70% of those who sustain a LAS will develop chronic ankle instability (CAI), with re-injury and persistent functional disability. In the military, those who suffer from CAI typically have less service time prior to discharge as a function of the physical limitations imposed by the ankle injury. Many with LAS history will develop ankle joint degeneration, marked by changes in its cartilage and has been shown even in young adults. This suggests the need to determine why some individuals follow the cascade of events of sustaining a LAS, to developing CAI, to developing osteoarthritis. A strong contribution to CAI appears to be related to lingering changes in the structure of the brain, which impacts efficient cortical regulation of overall body control. Standard of care (SOC) for LAS typically consists of symptom management or activity modification and a recovery protocol to improve motion and strength of the ankle but does not typically address central nervous system (CNS) deficiencies. However, the high rate of CAI suggests the SOC may not be sufficient. The purpose of this study is to compare the success of an innovative sensorimotor ankle rehabilitation training (SMART) protocol to mitigate the CNS deficiencies that likely lead to CAI and ankle joint degeneration. Ultimately, this study will utilize an integrative medicine approach (brain/spinal cord influence on neuromusculoskeletal injury rehabilitation) to address a common issue (why some people respond to treatment and are able to return to normal activities, while others do not) associated with LAS. This will improve the ability to disrupt the cascading transition from LAS to potential joint degeneration. This innovative and integrative approach to rehabilitation will significantly impact the short and long-term health and well-being of those affected by LAS.

2. KEYWORDS

Lateral ankle sprain; sensorimotor; musculoskeletal treatment; physical readiness

3. ACCOMPLISHMENTS

Major Goals and Accomplishments

SOW Goals	Timeline	Achieved
Major Task 1: Administrative Objectives	Months	Y/N
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	Y
Finalize consent form & human subjects protocol	1-3	Y
Coordinate with Sites for IRB protocol submission	1-3	Y
Coordinate with Sites for University of Kentucky IRB review	1-6	Y
Coordinate with Sites for University of North Carolina IRB review	1-6	Y
Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)	1-6	Y
Milestone Achieved: Local IRB approval at UK, UNC and BAMC	3	Y
Milestone Achieved: HRPO approval for all protocols and local IRB approval through University of Kentucky.	18	Y
Coordinate with Sites for job descriptions design	1-4	Y
Advertise and interview for project related staff	1-5	Y
Coordinate for space allocation for new staff	1-6	Y
Coordinate with Sites for Independent Evaluators hiring and trainings	5-11	Y
Coordinate with Sites for training Independent Evaluators until 100% concordance	8-11	Y
Milestone Achieved: Research staff trained	8-11	Y
Quarterly Reports to USAMRMC	Quarterly	Y
Annual Reports to USAMRMC	Annually	Y
Major Task 2: Technical Objectives		
Finalize assessment measurements	1-4	Y
Coordinate with Sites for flow chart for all study steps, web data collection and database requirements	4-6	Y
Milestone Achieved: 1st participant consented, screened and enrolled at each site	7-8	Y
Subject recruitment. Participants complete follow-up assessments upon completion of physical therapy for acute LAS	7-32	Y
Complete follow-up assessments 6 months after completion of physical therapy	13-38	N
Complete follow-up assessments 12 months after completion of physical therapy	19-44	N
Milestone Achieved: All participants enrolled and follow-up assessments completed	44	N
Data Analysis: Clinical, CNS, and MRI outcomes	7-48	N
Data interpretation and dissemination	36-48	N
Milestone Achieved: Report findings from completed assessments	36-48	N
Coordinate with Sites for annual IRB report for continuing review	Annually	Y
Submit amendments, adverse events and protocol deviations as needed	As Needed	Y

Summary

Human Subject Protections

Summary from Year 1: Approval of human subject protections was initiated on MAY 18 between the IRB offices of UK, UNC and WBAMC. Reliance agreements were discussed to recognize UK as the primary site for the study for all IRB offices. Initial approval of the study was obtained by the UK IRB on 10 MAY 18. Initial HRPO documents were submitted 4 JUN 18. Notification of receipt and initiation of review was received from Brittane Foy at MRMC on 11 JUN 18. Initial HRPO Administrative Review was received 2 AUG 18. Responses and supporting documents were returned to Brittane Foy 10 AUG 18. Second HRPO Administrative Review was received 5 NOV 18. Much of the 2nd Administrative Review required coordination and revisions to documents relative to WBAMC. From NOV 18 to JAN 19, Dr. Gribble coordinated with Larissa Schmersal, WBAMC Human Protections Administrator, to address requested revisions, as well as begin preparing CLAR materials to be submitted from WBAMC after HRPO review. By the end of Year 1 period (15 MAR 19), HRPO approval was not yet received.

Summary from Year 2: During Year 2, after a 4th HRPO Administrative Review was completed in MAY 19, initial HRPO approval was received 5 JUL 19. During JUL and AUG 19, Dr. Gribble prepared and submitted substantive changes to the protocol, including a site-PI change at WBAMC (CPT Golden) and modifications to the shared consent form. The Amendment Approval was received 6 SEP 19. Enrollment commenced in OCT 19. In JAN 20 during the UK IRB annual review, an oversight was discovered in the previously approved consent form related to HIPAA language that was not allowable by UK. Dr. Gribble worked with UK IRB, Dr. Schmersal and HRPO personnel during JAN 20 to modify the consent form to remove the HIPAA language and an Amendment Request was submitted 1 FEB 20, and approval of this amendment was received 11 MAR 20. Previously enrolled participants at all sites were re-consented with the new consent form. The HRPO Continuation Review was submitted in conjunction with the Amendment approval described above and was approved 11 MAR 20.

Summary from Year 3: During Year 3, modifications to improve recruitment and maintain study operations during COVID-19 restrictions were successfully submitted and approved. This allowed resumption of research that could be conducted in person while following COVD-19 mitigation guidelines, or to use a telehealth option temporarily. Personnel changes at WBAMC, including the departure of the site PI and the Clinical Research Coordinator, created further delays. Appropriate substantive changes submitted by Dr. Gribble were approved by UK IRB and HRPO to indicate this change in site PI corresponding with the addition of MAJ Stoute in this role at WBAMC starting in DEC 20. The HRPO Continuation Review was received and approved.

During Year 4, several modifications were submitted and approved. To expand recruiting efforts, we discussed a modification of the inclusion criteria with our Science Officer, which allowed to have participants with a previous ankle sprain, but no signs and symptoms of chronic ankle instability. A summary white paper of this proposal is in the Appendix. This proposal was approved by the UK IRB and

HRPO in MAY 21.

A new Clinical Research Coordinator at WBAMC, Ms. Sarah Tolley, joined the project in JUN 21. A modification to the IRB to reflect this was approved 13 JUL 21.

A modification to the IRB to reflect an update to the consent form to reflect that the intervention did not have a finite time period for completion was approved 17 AUG 21.

A modification to the IRB to reflect an update to the consent form to reflect MAJ Stoute's promotion from CPT with the updated rank was approved 14 OCT 21.

Dr. Gribble ensured that all subject personnel maintained appropriate CITI training and submitted the continuation review that was approved by the UK IRB 25 OCT 21.

Personnel

Ms. Sarah Tolley started the position as Clinical Research Coordinator at the WBAMC site on 14 JUN 21. This position had been vacant since SEP 20.

Ms. Katie Bain left her position as a graduate research assistant at UK in JUL 21. She completed her requirements for her PhD degree and accepted an employment opportunity elsewhere.

Mr. Tanner Eldridge was retained as a Research Associate with the project in AUG 21. Mr. Eldridge is a credentialed Athletic Trainer practicing in Lexington, KY. He assumed the intervention duties and assistance with participant scheduling that were previously conducted by Ms. Bain, working per diem for the project.

Equipment Acquisition

No equipment acquisitions took place in Year 4 of the project.

SOP Procedures and Site Visit

Site visits by Dr. Gribble to WBAMC and UNC were discussed with site personnel, but suspension of travel plans persisted due to COVID-19 related travel restrictions throughout the reporting period. Dr. Gribble anticipates resuming these during the next reporting period.

Opportunities for Training and Professional Development

Nothing to Report

Dissemination of Results to Communities of Interest
Nothing to Report

Plan for Next Reporting Period
As of this report, 19 participants have been enrolled across the three sites (UK: 6, UNC: 7; WBAMC: 6).
Due to an 18-month delay in initial HRPO approval followed by a two-year interruption from COVID-19 restrictions that began in MAR 20, enrollment and completion of interventions timelines had to be modified. While will continued to aggressively recruit during this reporting year, our sites have been experiencing considerable reductions in expected referrals since the global pandemic began. In DEC 21, we petitioned for and were granted a No Cost Extension year (NCE) to continue study operations beyond the study ending date (15 MAR 22).
Many aspects of musculoskeletal-related research enterprises have experienced significant interruptions and declines during this time period. We are encouraged that during this reporting period, enrollment did begin to increase, with 9 new enrolled participants, and study activities continued, such as some 6-month and 12-month follow-up sessions were completed at UK and UNC. We anticipate that additional follow-up sessions of previously enrolled participants will proceed successfully during this next reporting period. We anticipate that our enrollment numbers will increase in the NCE period, but our total enrollment may likely fall short of our intended enrollment goals. Our study team still believes that our data will provide valuable and impactful information that will contribute to the intended deliverables. Additionally, we anticipate discussing the possibility of a second no-cost extension period to accommodate the necessary 12-month follow-up testing for new participants enrolled during the upcoming NCE period.

4. IMPACT

Impact on Principal Disciplines of the Project

Nothing to Report

Impact on Other Disciplines

Nothing to Report

Impact on Technology Transfer

Nothing to Report

Impact on Society Beyond Science and Technology

Nothing to Report

5. CHANGES/PROBLEMS

Changes in Approach and Rationale
Nothing to Report

Actual or Anticipated Problems or Delays
We had an 18-month delay in the start of our enrollment while waiting for initial HRPO approval and amendments to our study protocols. A detailed summary of the timeline seeking HRPO approval is provided in our previous annual reports.

During Year 4, limitations in additional enrollment due to the COVID-19 outbreak that began to affect the United States in FEB 20 persisted. In-person research allowances were maintained at all three sites, but referrals to our study continued to be low, which we attribute to the societal restrictions in place. We explored and prepared methods to maintain enrollment growth, including expanding the inclusion criteria to allow for a previous ankle injury history without evidence of the development of chronic ankle instability (see Appendix). Access to some critical recruiting portals, such as in-person recruiting by our study personnel in the ED, continued to be restricted due to COVID-19 protocols.

The Clinical Research Coordinator at WBAMC site was vacated in SEP 20. Ms. Sarah Tolley began this position in JUN 21. This absence and delay in filling the position introduced significant delays in recruiting at this site.

Despite our efforts and alternative strategies, the COVID-19 pandemic has created significant, unanticipated delays in study operations in the lifespan of the study, including over the last 12 months. These delays justified out request for a No Cost Extension period to continue study activities. We are hopeful that in the coming year, these barriers will lessen and our trajectory of accomplishing study objectives will resume.

Changes in Expenditures

Dr. Gribble decreased effort to more closely match effort with project responsibilities.

- Reduced Nick Heebner from 10% to 5%, effective July 1, 2021.
- Reduced Matt Hock from 5% to 2%, effective July 1, 2021.

With the vacancy of Ms. Katie Bain as a doctoral student research assistant, expenditures for this position were eliminated as of 1 JUL 21. These duties were assumed by the new Research Associate, Mr. Tanner Eldridge, who is compensated on a per diem schedule.

These all lead to creating some surplus in the operating budget which Dr. Gribble as PI is using in the no-cost extension period that has been granted.

Changes in Use or Care of Human Subjects
Nothing to Report

6. PRODUCTS, INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Publications, Conference Papers, and Presentations
Nothing to Report

Websites or Other Internet Sites
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

Individuals Working on Project

Name:	**Phillip Gribble**
Project Role:	Principal Investigator
Nearest person month worked:	2
Contribution to Project:	Provide scientific oversight to the project and direct activities at UK, UNC and WBAMC. Assumes responsibility for the scientific integrity of the project; works closely with the site-PIs to ensure validity of the data and observations from the investigators. Ensure compliance with specific terms and conditions of the award as stated in the award notification. Supervise and co-mentor graduate student researchers.
Funding Support:	N/A
Name:	**Nick Heebner**
Project Role:	Co-Investigator
Nearest person month worked:	1
Contribution to Project:	Assist with data collection, interpretation and analysis
Funding Support:	N/A

Name:	**Matt Hoch**
Project Role:	Co-Investigator
Nearest person month worked:	0
Contribution to Project:	Assist with data interpretation and analysis
Funding Support:	N/A
Name:	**Nathan Johnson**
Project Role:	Co-Investigator
Nearest person month worked:	1
Contribution to Project:	Assist with data collection, interpretation and analysis
Funding Support:	N/A
Name:	**David Powell**
Project Role:	Co-Investigator
Nearest person month worked:	0
Contribution to Project:	Assist with data interpretation.
Funding Support:	N/A
Name:	**Kyle Kosik**
Project Role:	Co-Investigator
Nearest person month worked:	9
Contribution to Project:	Coordinate data collection sessions at UK. Assist with recruitment. Assist with data collection, interpretation and analysis
Funding Support:	N/A
Name:	**Katherine Bain**
Project Role:	Graduate Research Assistant
Nearest person month worked:	2.0
Contribution to Project:	Coordinate intervention sessions at UK. Assist with recruitment. Assist with data collection, interpretation and analysis

Funding Support:	1-month support on UK account
Name:	**Erik Wikstrom**
Project Role:	Co-Investigator
Nearest person month worked:	1.75
Contribution to Project:	Site PI at UNC. Provides oversight to all activities at UNC. Maintains communication with PI. Contributes to data interpretation and analysis from all sites.
Funding Support:	N/A
Name:	**Sarah Tolley**
Project Role:	Co-Investigator
Nearest person month worked:	6
Contribution to Project:	Clinical Research Coordinator. Coordinate intervention sessions at WBAMC. Assist with recruitment at WBAMC. Assist with data collection, interpretation and analysis at WBAMC. Maintains communication with site-PI at WBAMC and study PI at UK.
Funding Support:	N/A

Change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period

Matt Hoch, PhD

NEW Title: Musculoskeletal Health Considerations to Improve Resiliency and Lethality in Female Marines
Role: Principal Investigator
Time Commitments: 28%, 3.4 person months
Supporting Agency: United States Department of Defense, Office of Naval Research
Performance Period: 08/30/2021 – 08/29/2024
Level of Funding:
Sub-Awards: Naval Health Research Center, University of North Carolina Charlotte
Goals: The purpose of this study is to compare musculoskeletal injury and healthcare utilization patterns between male and female Marines. This study will also examine sex-specific contributing factors to musculoskeletal injury and threats to resiliency following musculoskeletal injury.
Aim 1: Examine differences in musculoskeletal injury risk between female and male service members across different occupations and phases of the deployment cycle. **Aim 2:** Compare healthcare utilization as a result of musculoskeletal injury

in female and male service members in combat and non-combat occupations. **Aim 3:** Identify sex-specific factors for musculoskeletal injury in active-duty service members. **Aim 4:** Determine the effect of musculoskeletal injury on resiliency in female and male service members. **Aim 5:** Explore field-based physiologic and biomechanical data captured using remote monitoring technology to assess musculoskeletal injury risk and recovery.
Point of Contact: Joshua Swift (Program Officer), Office of Naval Research, 875 North Randolph Street, Arlington, VA 22203-1995. (703) 696-0367

Title: Optimizing Musculoskeletal Health Outcomes through High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT)
Role: Co-Investigator
Time Commitments: No measurable effort
Supporting Agency: Office of Naval Research
Performance Period: 10/01/2021–09/30/2022
Level of Funding:
Goals: The scientific objective is to acquire high-resolution peripheral quantitative computed tomography (HRpQCT) to enable our team to make significant leaps forward in several identified areas where musculoskeletal injuries limit the readiness of military personnel's ability to return to duty.
Specific Aims: 1) Prospectively assess the effect of trabecular and subchondral bone microarchitecture on the development of post-traumatic osteoarthritis (PTOA); 2) Evaluate measures of trabecular and cortical bone tissue integrity following recovery of a tibia fracture; 3) Investigate the relationship of alterations of bone tissue integrity in patients that have sustained mild traumatic brain injury; 4) Improve the education of clinicians and clinician scientists engaged in the treatment, recovery and prevention of common skeletal tissue injuries and conditions.
Point of Contact: Joshua Swift, Joshua.m.swift@navy.mil, (703)696-0367

Nick Heebner, PhD

NEW Title: Musculoskeletal Health Considerations to Improve Resiliency and Lethality in Female Marines
Role: Co-Investigator
Time Commitments: 28%, 3.4 person months
Supporting Agency: United States Department of Defense, Office of Naval Research
Performance Period: 08/30/2021 – 08/29/2024
Level of Funding:
Sub-Awards: Naval Health Research Center, University of North Carolina Charlotte
Goals: The purpose of this study is to compare musculoskeletal injury and healthcare utilization patterns between male and female Marines. This study will also examine sex-specific contributing factors to musculoskeletal injury and threats to resiliency following musculoskeletal injury.
Aim 1: Examine differences in musculoskeletal injury risk between female and male service members across different occupations and phases of the deployment cycle. **Aim 2:** Compare healthcare utilization as a result of musculoskeletal injury in female and male service members in combat and non-combat occupations. **Aim 3:** Identify sex-specific factors for musculoskeletal injury in active-duty service members. **Aim 4:** Determine the effect of musculoskeletal injury on resiliency in

female and male service members. **Aim 5:** Explore field-based physiologic and biomechanical data captured using remote monitoring technology to assess musculoskeletal injury risk and recovery.
Point of Contact: Joshua Swift (Program Officer), Office of Naval Research, 875 North Randolph Street, Arlington, VA 22203-1995. (703) 696-0367

NEW Title: Optimizing Musculoskeletal Health Outcomes through High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT)
Role: Principal Investigator
Time Commitments: No measurable effort
Supporting Agency: Office of Naval Research
Performance Period: 10/01/2021–09/30/2022
Level of Funding:
Goals: The scientific objective is to acquire high-resolution peripheral quantitative computed tomography (HRpQCT) to enable our team to make significant leaps forward in several identified areas where musculoskeletal injuries limit the readiness of military personnel's ability to return to duty.
Specific Aims: 1) Prospectively assess the effect of trabecular and subchondral bone microarchitecture on the development of post-traumatic osteoarthritis (PTOA); 2) Evaluate measures of trabecular and cortical bone tissue integrity following recovery of a tibia fracture; 3) Investigate the relationship of alterations of bone tissue integrity in patients that have sustained mild traumatic brain injury; 4) Improve the education of clinicians and clinician scientists engaged in the treatment, recovery and prevention of common skeletal tissue injuries and conditions.
Point of Contact: Joshua Swift, Joshua.m.swift@navy.mil, (703)696-0367

Phillip Gribble, PhD

NEW Title: Optimizing Musculoskeletal Health Outcomes through High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT)
Role: Co-investigator
Time Commitments: No measurable effort
Supporting Agency: Office of Naval Research
Performance Period: 10/01/2021–09/30/2022
Level of Funding:
Goals: The scientific objective is to acquire high-resolution peripheral quantitative computed tomography (HRpQCT) to enable our team to make significant leaps forward in several identified areas where musculoskeletal injuries limit the readiness of military personnel's ability to return to duty.
Specific Aims: 1) Prospectively assess the effect of trabecular and subchondral bone microarchitecture on the development of post-traumatic osteoarthritis (PTOA); 2) Evaluate measures of trabecular and cortical bone tissue integrity following recovery of a tibia fracture; 3) Investigate the relationship of alterations of bone tissue integrity in patients that have sustained mild traumatic brain injury; 4) Improve the education of clinicians and clinician scientists engaged in the treatment, recovery and prevention of common skeletal tissue injuries and conditions.
Point of Contact: Joshua Swift, Joshua.m.swift@navy.mil, (703) 696-0367

Kyle Kosik, PhD

NEW Title: Optimizing Musculoskeletal Health Outcomes through High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT)
Role: Co-investigator
Time Commitments: No measurable effort
Supporting Agency: Office of Naval Research
Performance Period: 10/01/2021–09/30/2022
Level of Funding:
Goals: The scientific objective is to acquire high-resolution peripheral quantitative computed tomography (HRpQCT) to enable our team to make significant leaps forward in several identified areas where musculoskeletal injuries limit the readiness of military personnel's ability to return to duty.
Specific Aims: 1) Prospectively assess the effect of trabecular and subchondral bone microarchitecture on the development of post-traumatic osteoarthritis (PTOA); 2) Evaluate measures of trabecular and cortical bone tissue integrity following recovery of a tibia fracture; 3) Investigate the relationship of alterations of bone tissue integrity in patients that have sustained mild traumatic brain injury; 4) Improve the education of clinicians and clinician scientists engaged in the treatment, recovery and prevention of common skeletal tissue injuries and conditions.
Point of Contact: Joshua Swift, Joshua.m.swift@navy.mil, (703)696-0367

David Powell, PhD

NEW Title: Reduced BBB Water Exchange as a Preclinical Biomarker of Small Vessel Disease
Role: Co-investigator
Time Commitments: XX
Supporting Agency: NINDS
Performance Period: 2/1/2022 – 1/31/2025
Level of Funding:
Goals: This project will identify relations between a promising new biomarker of preclinical small vessel disease (SVD), cognition and brain connectivity patterns over time.
Point of Contact: Bruce Phillip Mertz, NINDS, bruce.mertz@nih.gov, 301-402-4954

Other Involved Partner Organizations

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

Collaborative Awards

Nothing to Report

Quad Chart

Addressing neuromuscular deficits for improved outcomes in ankle sprain rehabilitation

Program: Joint Program Committee 8/Clinical & Rehabilitative Medicine Research Program

Funding Opportunity Number: W81XWH-17-DMRDP-CRMRP-NMSIRRA

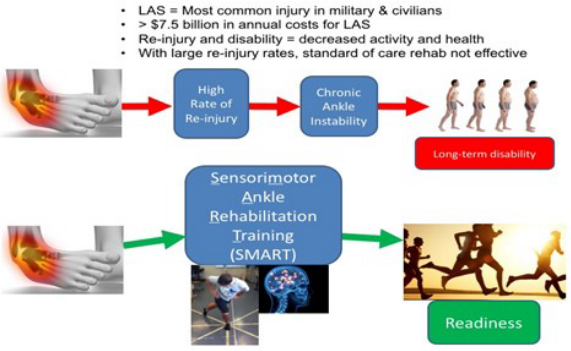
PI: Gribble, Phillip A **Org:** University of Kentucky **Award Amount:** $2.5 million

Study/Product Aim(s)

- **Aim #1:** Determine if a novel sensorimotor ankle rehabilitation training (SMART) protocol improves clinical outcomes (patient-reported function and quality of life, lateral ankle sprain (LAS) re-injury rates, postural control, ankle ROM) and ankle joint integrity (articular cartilage turnover) in LAS patients.
- **Aim #2:** Determine if SMART improves innovative measures of central nervous system (CNS) function (corticospinal excitability and brain white matter integrity) in LAS patients.
- **Aim #3**: Delineate the association between explanatory mechanistic measures (corticospinal excitability and brain white matter integrity) and the hypothesized improvements in clinical and ankle joint integrity in LAS patients receiving SMART.

Approach

We will compare SMART protocol against a standard of care protocol to demonstrate successful 1-year outcomes and lower rates of re-injury and disability. We expect improvement in clinical outcomes, CNS function and joint health, improving health in LAS patients, bringing translational application to military personnel.



Timeline and Cost

Activities CY	18	19	20	21
Regulatory/human subjects				
Participant enrollment, intervention implementation, post-testing				
1- year follow up testing				
Analysis of clinical, sensorimotor and MRI outcomes				
Estimated Budget ($K)	$745	$565	$580	$610

Goals/Milestones

CY19 Goal – 25% enrollment

- ❑ Post-testing complete on 25% of sample
- ❑ Analysis of outcomes begins

CY20 Goals – 100% enrollment

- ❑ Post-testing complete on 100% of sample
- ❑ 1 year follow up complete on 50% of sample
- ❑ Analysis of outcomes continues

CY21 Goal – Completion of follow-up and outcomes analysis

- ❑ 1 year follow up complete on 100% of sample
- ❑ Analysis of outcomes at all time points of 100% of sample

CY22 Goal

- ❑ Dissemination of data

APPENDICES

A. Summary of proposed modification to the inclusion criteria

B. Letter of approval of Continuation Review – University of Kentucky IRB

C. Email communication – HRPO approval of Continuation Review

To increase enrollment in our clinical trial (W81XWH-17-DMRDP-CRMRP-NMSIRRA), we wish to expand the inclusion criteria. The primary aim of the study is to prevent the development of chronic ankle instability (CAI) in individuals actively recovering from an acute ankle sprain that occurred within 72 hours prior to enrollment. Our original intent was to only enroll individuals that were actively recovering from a first-time ankle sprain as an attempt to explore the genesis of CAI. Our continual efforts in recruitment have shown a large number of respondents with an acute ankle sprain that self-report a history of a previous ankle sprain (>50). However, we have only enrolled 10 participants who have a first-time acute ankle. Based on discussions within our research team and consultation with our study's program officer, we will plan to amend our protocol to include participants who have sustained an acute ankle sprain and have a previous history of an ankle sprain, as long as they do not exhibit established symptoms of CAI. Specifically, at the time of screening a potential participant, we will use the initial criteria along with additional measures to confirm a participant does not have CAI before enrollment. These additional measures reflect the published criteria established by the International Ankle Consortium,[1] which include members of our study team, for defining CAI. The table below details the proposed expanded criteria. By widening the inclusion criteria of eligible participants, we will still meet our primary study objective of minimizing the development of CAI within 1 year of sustaining an acute ankle sprain. We are confident that this expanded inclusion criteria will improve our capacity to complete the scope of work within the allotted timeframe. To further explore our data, we will plan to include additional statistical analysis of our outcome variables within subsets of participants that either sustained their first ankle sprain or have sustained a previous ankle sprain but have not developed CAI at the time of enrollment.

Original Criteria	Additional Criteria
• 18-44 years • Sustained an acute ankle sprain within 72 hours of study enrollment • No previous history of an acute ankle sprain (***this criterion will be eliminated in favor of the criteria in the column to the right**) • No previous history of lower extremity surgeries or fractures • Lower extremity or head trauma in the last 3 months	• No previous ankle sprain in the last year • No symptoms of chronic ankle instability on either limb. The following criteria will be allowed to each limb at the time of enrollment[1]: ♦ ≤2 previous ankle sprains ♦ No reported giving way in the ankle within the last 6 months ♦ Ankle Instability Instrument: <5 ♦ Identification of Functional Ankle Instability: ≤11 ♦ Cumberland Ankle Instability Tool: ≥24

1. Gribble PA, Delahunt E, Bleakley C, et al. Selection criteria for patients with chronic ankle instability in controlled research: a position statement of the International Ankle Consortium. *The Journal of Orthopaedic and Sports Physical Therapy.* 2013;43(8):585-591.

University of Kentucky | Office of Research Integrity
IRB, RDRC

XP Continuation Review

Approval Ends:	IRB Number:
10/25/2022	44172

TO: Phillip Gribble, PhD, ATC
Health Sciences - Rehabilitati
PI phone #: 859- 218-0885

PI email: phillip.gribble@uky.edu

FROM: Chairperson/Vice Chairperson
Medical Institutional Review Board (IRB)

SUBJECT: Approval for Continuation

DATE: 10/26/2021

On 10/26/2021, the Medical Institutional Review Board approved your protocol entitled:

Addressing Neuromuscular Deficits for Improved Outcomes in Ankle Rehabilitation

Approval is effective from 10/26/2021 until 10/25/2022 and extends to any consent/assent form, cover letter, and/or phone script. If applicable, the IRB approved consent/assent document(s) to be used when enrolling subjects can be found in the "All Attachments" menu item of your E-IRB application. [Note, subjects can only be enrolled using consent/assent forms which have a valid "IRB Approval" stamp unless special waiver has been obtained from the IRB.] Prior to the end of this period, you will be sent a Continuation Review (CR)/Administrative Annual Review (AAR) request which must be completed and submitted to the Office of Research Integrity so that the protocol can be reviewed and approved for the next period.

In implementing the research activities, you are responsible for complying with IRB decisions, conditions and requirements. The research procedures should be implemented as approved in the IRB protocol. It is the principal investigator's responsibility to ensure any changes planned for the research are submitted for review and approval by the IRB prior to implementation. Protocol changes made without prior IRB approval to eliminate apparent hazards to the subject(s) should be reported in writing immediately to the IRB. Furthermore, discontinuing a study or completion of a study is considered a change in the protocol's status and therefore the IRB should be promptly notified in writing.

For information describing investigator responsibilities after obtaining IRB approval, download and read the document "PI Guidance to Responsibilities, Qualifications, Records and Documentation of Human Subjects Research" available in the online Office of Research Integrity's IRB Survival Handbook. Additional information regarding IRB review, federal regulations, and institutional policies may be found through ORI's web site. If you have questions, need additional information, or would like a paper copy of the above mentioned document, contact the Office of Research Integrity at 859-257-9428.

seeblue.
405 Kinkead Hall | Lexington, KY 40506-0057 | P: 859-257-9428 | F: 859-257-8995 | www.research.uky.edu/ori/
An Equal Opportunity University

Gribble, Phillip A.

From: Kilmon, Kelsey A CTR USARMY HQ USAMRDC (USA) <kelsey.a.kilmon.ctr@mail.mil>
Sent: Tuesday, December 7, 2021 2:57 PM
To: Gribble, Phillip A.; Wikstrom, Erik A.; Stoute, Shawn M MAJ USARMY MEDCOM WBAMC (USA)
Cc: kcarter.1@uky.edu; Office of Sponsored Projects Administration; Bennett, Jodi H CIV USARMY FUTURES COMMAND (USA); IRB Reliance; Adosci, David N CIV USARMY USAMRAA (USA); Ghannadian, D Jason CIV USARMY CDMRP (USA); Odam, Kimberly L CIV USARMY HQ USAMRDC (USA); Kline, Andrea J CIV USARMY HQ USAMRDC (USA)
Subject: A-20657.1a, A-20657.1b, and A-20657.1c, Continuing Review Acknowledgement Memorandum (Proposal Log Number DM170430, Award Number W81XWH-18-1-0083)

SUBJECT: Acknowledgement of the Continuing Review Documents for the Protocol, "Addressing Neuromuscular Deficits for Improved Outcomes in Ankle Rehabilitation," Submitted by Phillip Gribble, PhD, University of Kentucky (UK), Lexington, Kentucky, Erik Wikstrom, PhD, University of North Carolina (UNC), Chapel Hill, North Carolina, and CAPT Shawn Stoute, William Beaumont Army Medical Center (WBAMC), El Paso, Texas, Proposal Log Number DM170430, Award Number W81XWH-18-1-0083, HRPO Log Numbers A-20657.1a (UK Site), A-20657.1b (UNC Chapel Hill Site), and A-20657.1c (WBAMC Site)

1. The U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) approved the subject protocol on 5 July 2019.

2. The USAMRDC ORP HRPO received the University of Kentucky (UK) Institutional Review Board (IRB) approval on 26 October 2021. The UNC, Chapel Hill and the WBAMC are relying on the review provided by the UK Institutional Review Board (IRB). The UK IRB approved continuation of the subject protocol on 26 October 2021; this approval will expire on 25 October 2022.

3. This correspondence serves to acknowledge the HRPO receipt of the continuing review documents for the protocol. No further action related to this continuing review is needed. The documents in support of this continuing review will be placed in the HRPO file.

4. The Principal Investigator must provide the following post-approval submissions to the HRPO via email to usarmy.detrick.medcom-usamrdc.other.hrpo-cr-documents@mail.mil. Failure to comply could result in suspension of funding.

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRDC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change in the IRB of Record, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

d. The following study events must be promptly reported to the HRPO by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrdc.other.hrpo@mail.mil), by facsimile (301-619-7803), or mail to the U.S. Army Medical Research and Development Command, ATTN: FCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to subjects or others.

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.

(3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

(6) Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRDC ORP HRPO. The report must include actions taken by the institution and the IRB.

e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

5. Please note: The USAMRDC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRDC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

6. Do not construe this correspondence as approval for any contract or grant/cooperative agreement funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds by notice of official award documentation. It is recommended that you contact the appropriate contract/grants specialist or Contracting/Grants Officer regarding the expenditure of funds for your project.

7. The HRPO point of contact for this study is Kelsey Kilmon, B.S., Human Subjects Protection Scientist, at 301-619-2166, DSN 343-2166, or Kelsey.a.kilmon.ctr@mail.mil.

Regards,

Kelsey Kilmon, B.S.
Human Subjects Protection Scientist
Human Research Protection Office
Office of Research Protections
U.S. Army Medical Research and Development Command