AWARD NUMBER: W81XWH-20-1-0449

TITLE: Blood flow Restriction training After patellar INStability (BRAINS Trial)

PRINCIPAL INVESTIGATOR: Caitlin Conley ATC, PhD

CONTRACTING ORGANIZATION: University of Kentucky, Lexington, KY

REPORT DATE: July 2023

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
July 2023	Annual	01Jul2022-30Jun2023

4. TITLE AND SUBTITLE

Blood flow Restriction training After patellar INStability (BRAINS Trial)

5a. CONTRACT NUMBER
W81XWH-20-1-0449

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Kentucky Research Foundation
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8. PERFORMING ORGANIZATION REPORT NUMBER

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)

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

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Patellar dislocations are more common in military personnel and athletes than in the civilian population. In the short-term, muscular impairment after patellar dislocation impacts military readiness and in the long-term, patellar dislocation often leads to posttraumatic osteoarthritis (PTOA) within 5 to 15 years after injury. Physical therapy is the standard of care after patellar dislocation; however, despite the risks of PTOA and functional impairment after patellar dislocation, the conservative treatment of these injuries has remained largely unchanged over the past 20 years. There is no consensus on best practices and current treatment algorithms do not address both biologic and biomechanical mechanisms of PTOA. The purpose of this study is to determine if blood flow restriction training (BFRT) will improve outcomes after patellar dislocation. The proposed study directly relates to the FY19 PRMRP Topic Area of Post-Traumatic Osteoarthritis (PTOA). The proposed multidisciplinary study addresses two Areas of Encouragement related to PTOA: 1) Studies to evaluate and develop best practices for multidisciplinary team approaches and treatment algorithms for post-traumatic osteoarthritis, and 2) Development of innovative rehabilitation approaches for preventing or mitigating PTOA. The results of this study will benefit military personnel and civilian patient populations to improve clinical outcomes after patellar dislocation, promoting a safe return to activity while also reducing degenerative changes to both the cartilage and muscle. The low cost and simplicity of the interventions will allow for immediate implementation in clinical practice in military and civilian settings.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	13	19b. TELEPHONE NUMBER *(include area code)*

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1. Introduction

Patellar dislocations are more common in military personnel and athletes than in the civilian population. In the short-term, muscular impairment after patellar dislocation impacts military readiness and in the long-term, patellar dislocation often leads to posttraumatic osteoarthritis (PTOA) within 5 to 15 years after injury. Physical therapy is the standard of care after patellar dislocation; however, despite the risks of PTOA and functional impairment after patellar dislocation, the conservative treatment of these injuries has remained largely unchanged over the past 20 years. There is no consensus on best practices and current treatment algorithms do not address both biologic and biomechanical mechanisms of PTOA. The purpose of this study is to determine if blood flow restriction training (BFRT) will improve outcomes after patellar dislocation. The proposed study directly relates to the FY19 PRMRP Topic Area of Post-Traumatic Osteoarthritis (PTOA). The proposed multidisciplinary study addresses two Areas of Encouragement related to PTOA: 1) Studies to evaluate and develop best practices for multidisciplinary team approaches and treatment algorithms for post-traumatic osteoarthritis, and 2) Development of innovative rehabilitation approaches for preventing or mitigating PTOA. The results of this study will benefit military personnel and civilian patient populations to improve clinical outcomes after patellar dislocation, promoting a safe return to activity while also reducing degenerative changes to both the cartilage and muscle. The low cost and simplicity of the interventions will allow for immediate implementation in clinical practice in military and civilian settings.

2. Keywords

Patella, dislocation, instability, rehabilitation, strength, cartilage

3. Accomplishments

What were the major goals of the project?

Major Task 1: Acquire revised protocol approvals from local IRB and HRPO (Complete)
Major Task 2: Prepare for data collection (Completed 100% of specific objectives)
Major Task 3: Participant recruitment, evaluation (We have enrolled 19/78 patients to date)

What was accomplished under these goals?

Major Task 1: Acquire approvals for protocol modifications

Regulatory Approvals

- Local IRB approval at the University of Kentucky (01/18/2022, IRB# 56541)
- Updated trial on clinicaltrials.gov (01/21/2022, NCT04554212)
- HRPO approval (03/29/2022)

Major Task 2: Prepare for data collection

REDCap database has been updated to reflect the protocol modifications including the process to record subject information and patient-reported outcomes, randomization module, data management, and quality control prior to enrolling patients

- Timeline (Month 1 of updated SOW); Completed 01/11/2022

Modify existing Manual of Operations to reflect major protocol changes data collection methods and intervention specifics

- Timeline (Month 1 of updated SOW); Completed 01/11/2022

Updated existing Physical Therapy recording file (MS Excel)

- Timeline (Month 1 of updated SOW); Completed 01/11/2022

Updated procedures for collection and processing blood and urine specimens

- Timeline (Month 1 of updated SOW); Completed 01/11/2022

Finalize procedures for biomechanical data collection (these methods were not affected by the major protocol change)

- Original Timeline (Months 1-2); Completed 09/17/2020

Finalize MRI collection and transfer process (these methods were not affected by the major protocol change)

- Original Timeline (Months 1-3); Completed 07/30/2020

Milestone Achieved: Manual of Operations updated

- Timeline (Month 1 of updated SOW); Completed 01/11/2022

Milestone Achieved: All research staff trained on updated procedures

- Timeline (Month 1 of updated SOW); Completed 01/24/2022
    - Benjamin Wilson, MD was added to the protocol as a sub-investigator. Dr. Wilson is an orthopaedic surgeon at the University of Kentucky and routinely treats patients with patellar instability.

Major Task 3: Participant recruitment, evaluation

Milestone Achieved: Patient enrollment initiated

- Timeline (Month 15 of updated SOW); screening resumed immediately following HRPO approval (approved on 03/29/2022, screening resumed on 03/30/2022)

Continue subject recruitment (Target accrual rate: 1.1 participants/week)

- We have enrolled 19 patients to date and are actively working to improve recruitment.

Meetings with full research team (Quarterly)

- The PI met individually with Co-Investigators at both sites to discuss implementation of data collection and difficulties with enrollment. In addition, the PI meets weekly with clinic-based research coordinators to discuss enrollment and other day-to-day study administration. The Co-PI, Brian Noehren, PT, PhD also meets weekly with the physical therapy team.

Create DSMB report (Every 4 months)

- The initial DSMB report was reviewed by the DSMB on 10/28/2020 and approved on 12/02/2020.
- The most recent DSMB report was reviewed and approved by the DSMB on 06/07/23

Major Task 4: Data analysis and dissemination of results
Process biomechanics assessments with existing Matlab and Labview batch programs (scheduled to begin in month 4)

- We have continued to analyze biomechanical data for the subjects that have been enrolled to date.

Analyze MRI scans (scheduled to begin in month 4)

- We have implemented the MRI file transfer process that allows UK to upload de-identified scans.

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

Nothing to Report

How were the results disseminated to communities of interest?

Nothing to Report

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

The primary concern is the lack of enrollment. We have continued our efforts of recruitment with electronic IRB-approved recruitment flyers and have leveraged social media to improve enrollment (paid Facebook blasts, lab Twitter and Facebook posts, etc.). However, we are actively seeking other locations where we can expand this recruitment to other sites in the community (such as the local soccer referring community and adult sport and activity clubs). Lastly, we have a contact we are working with in our local ER to determine if there are recruitment opportunities there.

We will also continue our meeting with UK HealthCare certified athletic trainers (ATCs) that cover local area high schools and small colleges regarding the study. Additionally, there have been multiple contracts acquired by our institution increasing the number of athletic trainers in these meetings. We will also reach out to athletic trainers who work on an as-needed basis for coverage through our institution to ensure they are also informed of the study.

We will continue our weekly local team meetings as well as our quarterly meetings involving all study investigators at both sites.

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

- We underwent a change of PI from Cale Jacobs to Caitlin Conley, initiated Fall 2022 or a PI departure from our university on 10/01/2023. The PI change was officially approved on 03/28/2023. During this time, we continued our day to day study procedures but were also heavily focused on the administrative needs to execute the PI change.

- Additionally, we initiated a subcontract with Cale Jacobs' new institution, Mass General Brigham, for his continued work on the project. Once this contract is executed it will be listed in the "*What other organizations are involved as partners?*" section of the report.

- In the Fall of 2022, our study physical therapist, Benjamin Brightwell, took a new job. There were 2 other physical therapists in our lab working on other studies who had some bandwidth to help treat patients currently enrolled in the study, but we were unable to enroll new patients during this time. We have since hired 2 additional physical therapists who will be assisting on the study, 1 therapist has been added to the study. The other therapist suffered an unexpected injury requiring surgery in the Fall of 2022 and limited their ability to see patients. They will be added to the protocol once they are cleared to see patients again. After the start of the new year, we were able to conduct enrollment without any limitations.

- Additionally stating in January Mrs. Spach, the research coordinator on the study dually trained in phlebotomy left the institution. The new research coordinator, Mr. Long, who took over her position is not dual trained in phlebotomy. Thus, we contracted with our local Clinical and Translational Science unit to have them perform the blood draws.

6. Products

Nothing to Report

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name: Caitlin Conley, ATC, PhD
Project Role: PI (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): 0000-0001-9874-5200
Nearest person month worked: 1
Contribution to Project: Dr. Conley has worked on all aspects of project including regulatory approvals, staff training, data collection procedures, and enrollment and screening procedures.

Name: Cale Jacobs, PhD
Project Role: C-PI (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): 0000-0002-9300-5550
Nearest person month worked: 1
Contribution to Project: Dr. Jacobs has worked on all aspects of project including regulatory approvals, staff training, data collection procedures, and enrollment and screening procedures

Name: Brian Noehren, PT, PhD
Project Role: Co-I (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Dr. Noehren has worked on all aspects of project including regulatory approvals, staff training, data collection procedures, and enrollment and screening procedures.

Name: Austin Stone, MD, PhD
Project Role: Co-I (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): 0000-0002-9406-7884
Nearest person month worked: 1
Contribution to Project: Dr. Stone is the medical director for the project and has been involved with finalizing the inclusion/exclusion criteria and screening and enrollment procedures.

Name: Katherine Thompson, PhD
Project Role: Co-I (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Dr. Thompson is the team's biostatistician and has been involved with the study design and implementing the randomization procedures. She will be involved throughout the project and will be responsible for all analyses performed at the conclusion of the trial.

Name: Xiaojuan Li, PhD
Project Role: Site PI (Cleveland Clinic)
Researcher Identifier (e.g. ORCID ID): 0000-0002-0567-9935
Nearest person month worked: 1
Contribution to Project: Dr. Li has worked on all aspects of MRI image collection and transfer, and will be involved with the analysis and interpretation of imaging results.

Name: Megan Graham, PT, DPT, SCS, FAAOMPT
Project Role: Graduate Assistant, Physical Therapist
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Mrs. Graham is directly involved with the day-to-day administration of the physical therapy program.

Name: Emily Sagsetter, PT, DPT, ATC
Project Role: Physical Therapist
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Mrs. Graham is directly involved with the day-to-day administration of the physical therapy program.

Name: Lauren Erickson, PT, DPT, PHD, SCS, CSCS
Project Role: Physical Therapist
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Mrs. Graham is directly involved with the day-to-day administration of the physical therapy program.

Name: Doug Long
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Mr. Long has participated in staff training and finalizing data collection and enrollment procedures. She will be actively involved with coordinator research testing and physical therapy sessions in the Biomotion Lab.

Name: Jennifer Douyere
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Ms. Douyere has participated in staff training and finalizing data collection and enrollment procedures. She has been involved with patient recruitment, collection of biospecimens, and preparation of regulatory and DSMB reports.

Name: Tereza Janatova
Project Role: Biomechanist
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Ms. Janatova has participated in staff training and is responsible for biomechanical and strength testing being done as part of the trial.

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

Yes, the PI was changed from Cale Jacobs to Caitlin Conley (additional information outlined in section 3.5)

Caitlin Conley, ATC, PhD

Active support that has been initiated since the last report (6)

Title: MOntelukast as a Potential CHondroprotective Treatment Following Anterior Cruciate Ligament Reconstruction (GRANDE MOCHA Trial): Study Protocol for a Double-Blind, Randomized, Placebo-Controlled Clinical Trial
Role: Co-Investigator
Supporting Agency: Arthritis Foundation
Performance Period: 01/2023 - 12/2025

Title: Marines SpeCial Operations PrEparedness (M-SCOPE)
Role: Co-Investigator
Supporting Agency: Office of Naval Research
Performance Period: 08/2022 - 01/2025

Title: CR Toolkit for Optimal Recovery after Orthopedic Injury; A Multi-Site Feasibility Study to Prevent Persistent Pain and Disability
Role: Site PI
Supporting Agency: Massachusetts General Hospital/NCCIH
Performance Period: 01/2022 - 04/2024

Title: Sex-based Muscular Adaptations, Capillary dysfunction and functional decline impact Knee-related psychosocial outcomes after acute knee injury (SMACK)
Role: Co-Investigator
Supporting Agency: NIAMS
Performance Period: 07/01/2021 - 06/30/2026

Title: Development of a Mind Body Program to Reduce Cartilage Breakdown and Knee Pain in Obese Osteoarthritis Patients with Comorbid Depression
Role: PI
Supporting Agency: NCCIH
Performance Period: 01/2020 - 12/2023

Title: Myostatin Alters Muscle Composition as a Result of an ACL Injury
Role: Co-Investigator
Supporting Agency: NIAMS
Performance Period: 07/2019 - 02/2024

Previous support that has been completed since the last report (1)

Title: The Arthritis Foundation OA Virtual Center of Excellence Clinical Trial Network Site Charter Agreement - PTOA Platform
Role: Co-Investigator
Supporting Agency: Arthritis Foundation
Performance Period: 01/2020 – 02/2023

Cale Jacobs, PhD

Active support that has been initiated since the last report (1)

Title: BWH CTU for Preventing Injured Knees from Osteoarthritis Severe Changes (PIKASO)
Role: Co-PI
Supporting Agency: Arthritis Foundation
Performance Period: 01//2023 - 12/2024

Previous support that has been completed since the last report (1)

Title: OACTN Clinical Trial Unit (CTU)
Role: Co-Investigator
Supporting Agency: Arthritis Foundation
Performance Period: 01/02/2023 – 12/31/2024

Brian Noehren, PT, PhD

Active support that has been initiated since the last report (1)

Title: Leveraging Wearables to Transform Patient Recovery After Tibial Fracture Surgery
Role: PI
Supporting Agency: NIH/NIAMS
Performance Period: 04/2023 – 03/2028

Previous support that has been completed since the last report (2)

Title: Optimizing Musculoskeletal Health Outcomes through High Resolution Peripheral Quantitative Computed Tomography (HR-pQCT)
Role: Co-Investigator
Supporting Agency: Office of Naval Research
Performance Period: 10/01/2021 - 09/30/2022

Title: Pilot, Patient Blinded Randomized Gait Study on InterTan
Role: Co-Investigator
Supporting Agency: Smith & Nephew
Performance Period: 07/01/2021 - 06/30/2023

Austin Stone, MD, PhD

Active support that has been initiated since the last report (2)

Title: MOntelukast as a Potential CHondroprotective Treatment Following Anterior Cruciate Ligament Reconstruction (GRANDE MOCHA Trial): Study Protocol for a Double-Blind, Randomized, Placebo-Controlled Clinical Trial
Role: PI
Supporting Agency: Arthritis Foundation
Performance Period: 01/2023 - 12/2025

Title: OACTN Clinical Trial Unit (CTU)
Role: PI
Supporting Agency: Arthritis Foundation
Performance Period: 01/02/2023 – 12/31/2024

Previous support that has been completed since the last report (1)

Title: The Arthritis Foundation OA Virtual Center of Excellence Clinical Trial Network Site Charter Agreement - PTOA Platform
Role: PI
Supporting Agency: Arthritis Foundation
Performance Period: 01/2020 – 02/2023

Katherine Thompson, PhD

Active support that has been initiated since the last report (4)

Title: Participant Support: The SROCS Summer Research Conference in Statistics and Biostatistics
Role: PI
Supporting Agency: NSF
Performance Period: 08/01/2022-07/31/2023

Title: Participant Support: The SROCS Summer Research Conference in Statistics and Biostatistics
Role: PI
Supporting Agency: NSF
Performance Period: 06/01/2023-05/31/2024

Title: The Impact of Insulin Sensitivity on the Potential of Metformin to Delay Age-related Inflammation
Role: Co-Investigator
Supporting Agency: NIA
Performance Period: 08/01/2022-04/30/2026

Title: The Local Infiltration Therapy (LIT) Trial for Pain Control Following Hip Fracture Fixation
Role: Co-Investigator
Supporting Agency: NIAMS
Performance Period: 08/01/2022-07/31/2023

Previous support that has been completed since the last report (3)

Title: The Biological Mechanisms of Metformin Effects on Aging-Associated Inflammation
Role: Co-Investigator
Supporting Agency: NIH/NIA
Performance Period: 09/15/2020-08/31/2022

Title: Efficacy of a Narrative Comprehension Intervention for Elementary School Children At- Risk for Attention-Deficit Hyperactivity Disorder
Role: Co-Investigator
Supporting Agency: Institute of Education Sciences
Performance Period: 07/01/2017-06/30/2023

Title: Macrophage Phenotype Orchestrates Mammalian Tissue Regeneration
Role: Co-Investigator
Supporting Agency: NIAMS
Performance Period: 03/01/2017-02/29/2023

Peter Hardy, PhD

Active support that has been initiated since the last report (0)

Previous support that has been completed since the last report (0)

Xiaojuan Li, PhD (Cleveland Clinic)

Active support that has been initiated since the last report (2)

Title: OACTN Clinical Trial Unit (CTU)
Role: PI
Supporting Agency: Arthritis Foundation
Performance Period: 01/02/2023 – 12/31/2024

Title: OACTN Clinical Trial Unit – Imaging Core
Role: PI
Supporting Agency: Arthritis Foundation
Performance Period: 01/02/2023 – 12/31/2024

Previous support that has been completed since the last report (0)

What other organizations are involved as partners?

Organization Name: Cleveland Clinic Foundation

Location of Organization: 9500 Euclid Ave, ND20
Cleveland, OH 44195

Partner's contribution to the project:

Collaboration: Xiaojuan Li, PhD is the Director of the Program in Advanced Musculoskeletal Imaging (PAMI) at the Cleveland Clinic. She will be directly involved with the analysis of the MRI images that are collected as a part of this trial. Her research program aims at developing novel quantitative imaging techniques to improve early diagnosis and prognosis for musculoskeletal diseases, and translating these advanced techniques to clinical practice to ultimately improve patient care. She has served as the PI of basic research and clinical research studies sponsored by NIH (K25, R21, R01, U01), private foundations, industry companies and universities, and has served as the imaging core director/chair for multicenter studies. Currently, she served as the Co-Chair of the quantitative imaging alliance (QIBA) subcommittee for cartilage compositional MRI biomarkers, sponsored by Radiologic Society of North America (RSNA), and serves on the Executive Committee of the Arthritis Foundation OA Center of Excellence Initiative. In August 2017, she moved from UCSF to Cleveland Clinic to expand her research program. She has served as the Founding Director of the Program of Advanced MSK Imaging (PAMI), CCF. PAMI is a multi-institutional joint program between Lerner Research Institute, Imaging Institute, and Orthopaedics and Rheumatology Institute at Cleveland Clinic. Currently PAMI has more than 40 members and holds a monthly meeting for discussing ongoing collaborative research and planning strategic program development with new collaborations. With her expertise in this topic area, she is an invaluable member of the research team.

8. Special Reporting Requirements

Nothing to Report

9. Appendices

None