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TITLE: The Effects of Vibration on Indicators of Post-Traumatic Knee Osteoarthritis Risk Following Anterior Cruciate Ligament Injury

PRINCIPAL INVESTIGATOR: Troy Blackburn

CONTRACTING ORGANIZATION: University of North Carolina at Chapel Hill

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14. ABSTRACT

The purpose of this study is to determine the effects of whole body vibration (WBV) and local muscle vibration (LMV) on quadriceps function, gait biomechanics, patient-reported outcomes, imaging markers of knee joint health, and the incidence of post-traumatic knee osteoarthritis in individuals with anterior cruciate ligament reconstruction (ACLR). Patients will be randomized to 1 of 3 study arms: standard rehabilitation, standard rehabilitation + WBV, or standard rehabilitation + LMV, and the study outcomes we be assessed prospectively over the first year following ACLR. Patients will be recruited from the UNC Orthopaedics and Womack Army Medical Center. We hypothesize that both forms of vibration will enhance quadriceps function and gait biomechanics more effectively than standard rehabilitation, thus resulting better patient-reported outcomes and knee joint health, and a lower risk of post-traumatic knee osteoarthritis.

To date we have 1) hired and trained all study personnel, 2) received local IRB and HRPO approval, 3) engaged with Womack Army Medical Center to establish IRB rely-on approval, 4) procured vibration devices for the rehabilitation clinics, 5) developed a laboratory standard operating procedures manual, and 6) enrolled the first 9 patients.

15. SUBJECT TERMS
Knee, Osteoarthritis, Anterior Cruciate Ligament, Quadriceps, Muscle Dysfunction, Gait Biomechanics, Rehabilitation, Cartilage

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1. **INTRODUCTION:**
Post-traumatic knee osteoarthritis (PTOA) is a leading cause of medical separation from military service. Anterior cruciate ligament injury and surgical reconstruction (ACLR) incurs a high PTOA risk and is an ideal model for evaluating PTOA prevention strategies. Aberrant gait biomechanics are a primary contributor to PTOA development and are attributable in part to quadriceps muscle dysfunction. Vibration acutely improves quadriceps function and gait biomechanics in individuals with ACLR, but its effects on joint health and PTOA risk are unknown. Therefore, the purpose of this randomized clinical trial is to evaluate the effects of whole body vibration (WBV) and local muscle vibration (LMV) embedded in ACLR rehabilitation on quadriceps function, gait biomechanics, patient self-report outcomes, knee cartilage composition, and PTOA incidence over the first year post-ACLR.

2. **KEYWORDS:**
Quadriceps, Muscle Dysfunction, Gait, Rehabilitation, Cartilage, Neuromuscular, Biomechanics, Imaging, Composition, T1 rho MRI, T2 MRI, KOOS, IKDC, Kinesiophobia, Quality of Life

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

- **Major Task 1:** Ethics Approval
    - **Subtask 1:** Local IRB approval & non-significant risk IDE determination
    - **Subtask 2:** Office of Research Protections HRPO approval

- **Major Task 2:** Establish Study Staff and Procedures
    - **Subtask 1:** Hire study staff
    - **Subtask 2:** Train staff on study procedures
    - **Subtask 3:** Coordinate recruitment, enrollment, and intervention procedures at participating clinics
    - **Subtask 4:** Coordinate reporting plans with Research Monitor and Clinical Trials Quality Assurance Program
    - **Subtask 5:** ClinicalTrials.gov registration

- **Major Task 3:** Clinical Trial Operations
    - **Subtask 1:** Patient recruitment, enrollment, and interventions
    - **Subtask 2:** Data collection

- **Major Task 4:** Data Processing & Analysis

- **Major Task 5:** Dissemination

- **Major Task 6:** LMV Device Commercialization

What was accomplished under these goals?

- **Major Task 1:** Ethics Approval (70% complete)
  - **Subtask 1:** Local IRB approval & non-significant risk IDE determination
    - Local (UNC-CH) IRB approval and the non-significant IDE risk determination were obtained on May 3, 2021
    - We have not yet been able to establish Womack Army Medical Center (WAMC) as a study site due to minor logistical hurdles. The general, broad rely-on agreement between UNC-CH and WAMC has been enacted, and we are awaiting approval of the WAMC site-specific submission. The process of subcontracting with Geneva Foundation and ethics approval at WAMC has certainly taken longer than we anticipated. However, our collaborators at WAMC indicated on 10/4/2022 that "It is safe to assume that the WAMC site will receive local approval by the end of this calendar year, but we hope to have it approved sooner". As such, we anticipate being able to begin enrolling patients at WAMC in the near future.
  - **Subtask 2:** Office of Research Protections HRPO approval
    - HRPO approval was obtained on September 21, 2021

- **Major Task 2:** Establish Study Staff and Procedures (75% complete)
  - **Subtask 1:** Hire study staff
    - The postdoctoral research fellow and GRAs at UNC-CH have been hired and onboarded. Additionally, the WAMC subcontract with WAMC has been executed, and all WAMC study staff have been hired.
  - **Subtask 2:** Train staff on study procedures
    - All data are being collected on the UNC-CH campus. The UNC-CH study team has been trained on all data capture and processing procedures.
  - **Subtask 3:** Coordinate recruitment, enrollment, and intervention procedures at participating clinics
    - We have completed training on all procedures for the two UNC-affiliated rehabilitation clinics, both of which are actively enrolling patients. We have also established clear communication and procedures with the participating orthopaedic surgeons at UNC-CH for identifying and recruiting patients and confirming inclusion criteria that are obtained from surgical notes.
    - We have conducted initial remote trainings with the study team at WAMC regarding the scope of the study and the use of the investigative devices. Once WAMC site-specific IRB approval is obtained, we will conduct in-person trainings with the WAMC study team.
  - **Subtask 4:** Coordinate reporting plans with Research Monitor and Clinical Trials Quality Assurance Program
    - Per correspondence with HRPO during the original review process (see Appendix 1), a Research Monitor is no longer required for our project.
    - We have developed the clinical trial monitoring process with the UNC-CH Clinical Trials Quality Assurance Program. Per this process, we have completed the scheduled review following enrollment of the first 5 patients. We are awaiting their formal report, but have received verbal confirmation that there are

no major problems to be addressed. Audits are scheduled for every 6 months of the trial.

- **Subtask 5:** ClinicalTrials.gov registration
  - The study was registered with ClinicalTrials.gov on May 12, 2021.

- **Major Task 3:** Clinical Trial Operations 5%)
  - **Subtask 1:** Patient recruitment, enrollment, and interventions
    - **Milestone 1:** enrollment of 1st cohort of 57 patients
      - To date we have enrolled 14 patients. One of these individuals was withdrawn from the study due to complications arising from her knee surgery (details provided below). Nine of the enrolled individuals have been randomized, and the remaining four have agreed to participate but are either awaiting randomization at 1 month post-surgery (3) or are awaiting surgery (1).
      - Enrollment is occurring at a slower rate than anticipated. This is due in part to the timing of the study launch. Specifically, we began recruiting patients in October 2021 and had initial success, but the summer period from late May to September typically represents a down time in ACL injury prevalence, as high school and collegiate sports participation (i.e. the most common population in whom ACL injuries occur) is paused. Additionally, our enrollment plan is for at least 1/3 of the sample to be composed of active duty military from WAMC, yet that site has not yet been activated due to the logistical issues noted above for Major Task 1. However, we have created an efficient and effective recruitment process at UNC-CH. We have also received local IRB approval to recruit 1) patients from the participating UNC-CH clinics who received ACLR through surgical providers other than UNC Orthopaedics and 2) other local orthopaedic providers who refer their patients to UNC Therapy Services for rehabilitation. I am confident that these developments and the fact that WAMC will be activated as a site before the end of the calendar year will increase enrollment substantially in the near future.
    - **Milestone 2:** enrollment of 2nd cohort of 57 patients
      - Not applicable at this early point in the trial
  - **Subtask 2:** Data collection
    - **Milestone 3:** Baseline testing completed for 1st cohort
      - Of the enrolled patients, 9 have completed the Baseline/1-month post-surgical assessment.
    - **Milestone 4:** 6-month testing completed for 1st cohort
      - Of the enrolled patients, 3 have completed the 6-month post-surgical assessment.
    - **Milestone 5:** 1-year testing completed for 1st cohort
      - The first 1-year post-surgical assessment will take place in December 2022.

- **Major Task 4:** Data Processing & Analysis (30% complete)
    - Data processing (e.g. deriving gait biomechanics and MRI outcomes) is being performed in an ongoing manner by GRAs and the postdoctoral fellow (all blinded to group assignment) throughout the study period. The custom software pipelines necessary to process the data have all been developed.
    - While data for the majority of the outcomes resulting from the Baseline/1-month post-ACLR assessment have been processed for the first 9 patients, the MRI image processing is highly time-intensive and is not yet complete. Once this step is complete, we will conduct a quality check to ensure fidelity.
    - All of the study aims will be evaluated via the same prospective clinical trial design that will follow patients over the first year following surgery. As such, no statistical analyses have been conducted to date.

- **Major Task 5:** Dissemination (0% complete)
    - Nothing to report

- **Major Task 6:** LMV Device Commercialization (20% complete)
    - We have engaged with multiple potential commercial licensees, but have not yet started "serious" discussions with any of them. However, our project/device was recently selected for the Market Testing Program that is a collaboration between UNC-CH, the North Carolina Translational and Clinical Sciences Institute, and RTI International, an independent nonprofit research institute. This program will provide in-depth market analysis and focus group interviews with stakeholders in both the clinical and commercial spaces to identify the most appropriate commercialization route(s). The program administrators plan to carry out their analyses throughout October and November 2022 and provide a summary report by the end of the calendar year. We will use this information to inform our next steps with commercialization.

In summary, the study is running very well as planned. With the exception of the delays in activating WAMC as a study site and slower than expected enrollment, we have established an efficient process for identifying, recruiting, and enrolling patients in the trial. Though we've experienced minor protocol deviations (e.g. one patient did not feel comfortable walking at the Baseline assessment without a post-surgical brace, one patient was unable to complete the 1-month MRI assessment due to COVID-19 restrictions at the imaging center), data collection is running very smoothly and the study team at UNC-CH is adept and cross-trained for all aspects of the trial.

HRPO STATUS: Approved (9/21/2021)

			Enter information regarding number of subjects					
HRPO Protocol Number	**Protocol PI Name**	**Organization (Site)**	**# Target**	**# Enrolled**	**# Completed**	**# Screened**	**# Recruited**	**Other**
E02126.1a	Troy Blackburn	UNC-CH	114	14	0	22	22	N/A

Participant Demographic Data

Randomized Group*	Age (yr)	Sex	Height (m)	Mass (kg)	ACLR Graft Type
1 (n = 4)	21 ± 5	1 M, 3 F	1.73 ± 12	65.9 ± 12.9	3 PT, 1 QT
2 (n = 1)	20	1 F	1.66	53.8	1 QT
3 (n = 4)	24 ± 7	2 M, 2 F	1.72 ± 15	72.3 ± 17.5	4 PT

These data reflect mean ± sd or frequency counts where applicable.

*The PI and all members of the UNC-CH study team involved in data collection are blinded to group assignment, thus these data are dummy coded.

One patient enrolled in the study developed a deep vein thrombosis in the first week following her ACL reconstruction surgery. While this problem is not unheard of, it is rare in younger patients. Given the unknown implications of vibration for blood clot dynamics, her surgeon and the research team consulted with her hematologist and decided to withdraw her from the trial. She had not yet been randomized to an intervention arm (randomization occurs at 1 month post-surgery), so the design of the trial was not impacted. This unanticipated problem was deemed by the UNC-CH IRB to be a consequence of the patient's surgery, and not be related to study participation, thus no formal changes to human subjects protection were required.

One patient enrolled in the study experienced an audible "pop" during rehabilitation, raising concern that either the ACLR graft had ruptured or a patellar fracture had occurred. Follow up orthopaedic examination revealed that there was no fracture and that the graft was intact and "normal". The diagnosis was "release of scar tissue", and it was recommended that the patient continue his current rehabilitation as tolerated. The patient's symptoms (e.g. pain and swelling) quickly subsided, and he resumed "typical" rehabilitation. We filed a Promptly Reportable Information report with the UNC-CH IRB, and this unanticipated problem was deemed to be a consequence of the patient's surgery, and not be related to study participation. This individuals has continued participation in the trial as randomized.

What opportunities for training and professional development has the project provided?
Though the project was not specifically intended to provide training or professional development opportunities, the GRAs and postdoctoral fellow have gained invaluable experience with data collection and processing, patient recruitment, and general clinical trials management.

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?
Our primary focus in the next reporting period will be to increase the rate of enrollment. We plan to achieve this goal in large part by activating WAMC as a study site as noted above. Secondly, we have received local IRB approval to recruit 1) patients from the participating UNC-CH clinics who received ACLR through surgical providers other than UNC Orthopaedics and 2) other local orthopaedic providers who refer their patients to UNC Therapy Services for rehabilitation, and we will begin these efforts in earnest during the next reporting period. Thirdly, we are seeking local IRB approval to employ social media recruitment materials that will broaden our outreach capacity.

4. IMPACT:

Given that we are early in the overall study timeline and that the study outcomes will all be derived from the same prospective clinical trial, we do not yet have tangible results to report that would impact the discipline, technology transfer, or society.

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:

Changes in approach and reasons for change
When we originally drafted the grant proposal more than two years ago, we planned to control for ACLR graft type by only including patients who received patellar tendon grafts. However, since that time there has been changeover at WAMC in terms of personnel and surgical preferences such that their surgeons now utilize quadriceps tendon grafts rather than patellar tendon grafts at a 40:1 ratio. Pending a conversation with the original Science Officer (see Appendix 2) we are now also recruiting patients with quadriceps tendon grafts. This modification does not change the risks or safety concerns associated with the study.

Actual or anticipated problems or delays and actions or plans to resolve them
As noted above, the primary limitation we have faced is in activating WAMC as a study site. These delays are due in part to "red tape", but were also influenced by changes in the leadership at WAMC. Specifically, the initial WAMC PI for the project was the head of PT line, but as active duty, she was reassigned soon after the project began. Her replacement as head of the PT line agreed to serve as PI, but was limited in her capacity to do so due to being newly assigned to the site. We have now established Col. Don Goss (ret) as the site PI and have hired the WAMC study team. The subcontract has been executed and the general UNC-WAMC IRB rely-on agreement has been signed, and we are awaiting WAMC local IRB approval to begin study procedures there in earnest. Recent communications with the study team a WAMC suggest that this process will be resolved in the near future such that we will be able to begin recruiting active duty military patients in early 2023 at the latest.

Additionally, UNC Orthopaedics has recently hired a fourth sports medicine surgeon, and we anticipate that this change will result in a larger volume of potential patients for recruitment at UNC-CH.

Changes that had a significant impact on expenditures
As noted above, the initial HRPO review indicated that the study does not require a Research Monitor. Removing this individual (Dr. David Berkoff) from the study personnel "saved" $62,382 that was originally allocated to his salary support over the 3-year study period. Additionally, the postdoctoral fellow funded by the project received an NIH postdoctoral fellowship that will support his salary for the remaining two years of the study, thus saving $137,756.

A revised budget was submitted on 9/12/2022 in which reallocation of the funds recouped from these personnel changes was requested to support the following:

- $1,650 was reallocated to Y1 Equipment to cover an increase in shipping costs from the time when the original budget was drafted and the actual purchase date.
- Our protocol for processing MRI outcomes in the study aims has changed since the time that the grant was originally submitted and requires longer scanning times at the UNC-CH Biomedical Research Imaging Center to obtain the requisite images. A total of $27,325 (Y2 = $20,100; Y3 = $7,225) was reallocated to cover the cost of the longer scanning times.
- $21,749 was reallocated to replace equipment necessary for the study aims (electromyography [EMG] system).
- $5,959 (Y2 = $3,980; Y3 = $1,979) was reallocated to Supplies to afford expendable research supplies, data processing software, and software technical support.
- $116,007 was reallocated to increase GRA support (%effort) and support an additional GRA in Y2 and Y3.

We have not yet received feedback from DoD regarding these budgetary changes, but will provide any relevant information in the next Quarterly report after we receive notification of approval/disapproval.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report

Significant changes in use or care of human subjects
Nothing to report

Significant changes in use or care of vertebrate animals
Not applicable

Significant changes in use of biohazards and/or select agents
Not applicable

6. PRODUCTS:

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

  Journal publications.
  Nothing to report

Books or other non-periodical, one-time publications.
Nothing to report

Other publications, conference papers and presentations.
Nothing to report

Website(s) or other Internet site(s)
Nothing to report

Technologies or techniques
Nothing to report

Inventions, patent applications, and/or licenses
We filed a patent for our prototype local muscle vibration device on 9/23/2022 (see Appendix 3).

Other Products
Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	Project Role	ORCID ID	Nearest Person Month Worked	Contribution to Project
Troy Blackburn	Principal Investigator	0000-0003-0878-9432	3	Dr. Blackburn is responsible for the overall coordination of and primary duties associated with the project including data collection, reduction, analysis, and interpretation; software development; patient recruitment; and supervision of study personnel.
Brian Pietrosimone	Co-investigator	0000-0002-7202-7718	1	Dr. Pietrosimone has assisted with patient recruitment; data collection, quality control, reduction, analysis, and interpretation. He is also the contact point for the participating physical therapsits in the event of logistical challenges (e.g. device malfunction) to preserve blinding of the PI and members of the study team involved with data collection.
David Lalush	Co-investigator	0000-0002-7240-929X	1	Dr. Lalush has provided expertise regarding evaluation of cartilage composition (T1ρ and T2 MRI relaxation times) including custom software development and establishing processing protocol.
Todd Schwartz	Co-investigator	0000-0002-0232-2543	1	Dr. Schwartz developed and implemented the randomization scheme for the project.
Jeff Spang	Co-investigator	0000-0003-3610-7339	1	Dr. Spang has served as a clinical liaison and provides oversight of the recruitment

				of ACLR patients at UNC-CH. He also reviews surgical notes to confirm patients meet the inclusion criteria.
Daniel Nissman	Co-investigator	0000-0002-6022-7288	1	Dr. Nissman has provided oversight of the process for evaluating MRIs for the presence of post-traumatic knee osteoarthritis, and has provided "expert" values against which the results obtained by other members of the study team are validated.
Tom Birchmeier	Postdoctoral Research Fellow	0000-0003-1494-331X	12	Dr. Birchmeier has provided daily coordination of the project including patient recruitment and enrollment; managemement of rehabilitation remuneration; scheudling of MRI asssessments; and data collection and reduction.
Alex Nilius	Graduate Research Assistant	0000-0002-0022-3533	7	Ms. Nilius has assisted with patient recruitment and data collection and analysis.

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

Drs. Blackburn (PI) and Pietrosimone (Co-I) have recently received an award from the National Science Foundation as outlined below, but this award does not impact their FTE or salary support.

Franz/Pietrosimone/Blackburn (Co-PIs) (7/2022 – 6/2024)
Acquisition of a High-Speed Biplanar X-Ray System for Non-Invasive Quantitative Imaging of Human Movement
National Science Foundation
Major Research Instrumentation Program
Person Months: 0

Dr. Schwartz (Co-I) has received additional support since the beginning of the study as outlined below:

Adams (PI) (10/2021 – 10/2022)
Validation of the Roche cobas h 232 Point of Care system for NT-proBNP Determinations Compared to Standard Platform Assay Results Utilized in Guided Therapy of Patients with Heart Failure Start Up Activities
Roche Diagnostics Corporation
Person Months: 2.86

Nelson (PI) (5/2020 – 4/2025)
Assessment of Ultrasound Features of Knee Osteoarthritis in a Population-Based Community Cohort
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Person Months: 0.54 (2023), 0.60 (2024), 0.60 (2025)

Bryant (PI) (3/2021 – 2/2023)
A Nurse-Led Palliative and Supportive Care Intervention for Newly Diagnosed Adults with Acute Myeloid Leukemia
National Institute of Nursing Research
Person Months: 0.36 (2023)

Allen (PI) (12/2021 – 11/2023)
Optimizing Osteoarthritis Care through Clinical and Community Partnership
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Person Months: 0.90 (2022), 0.90 (2023)

Franz (PI) (9/2022 – 8/2027)
A Framework for Feasible Translation to Enhance Foot and Ankle Function in Aging and Mobility
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Person Months: 1 (2023, 2024, 2025, 2026, 2027)

What other organizations were involved as partners?
As noted above, we are in the process of establishing WAMC as a study site.

8. SPECIAL REPORTING REQUIREMENTS
Please see attached Quad Chart

9. APPENDICES
- **Appendix 1:** Research Monitor Update
- **Appendix 2:** ACLR Graft Type Update
- **Appendix 3:** Patent Application