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TITLE: Eccentric Motor Training with Neuromodulation and Biomarkers for Rehabilitation Readiness in Subacute SCI

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14. ABSTRACT
Spinal cord injury (SCI) results in severe consequences. Two interventions show promise for functional improvements but have never been tried together are downhill treadmill training which works muscles in with an eccentric control challenge and surface electrical stimulation. The expectation is that combining these two treatments together will bring improvements beyond what each can deliver alone. Interventions delivered too early actually interfere rather than assist recovery. Therefore, we are investigating genetic and imaging biomarkers as Go/No Go thresholds to determine readiness for rehabilitation. The expression of genes as quantified from cerebrospinal fluid will indicate whether the spinal cord environment is inflammatory, which would show a condition in which exercise training is likely to be less effective, a No Go indicator. For an image-based Go biomarker, we will quantify the amount of myelin around the nerve cells in the brain and spinal cord using MRI. Individuals with complete or incomplete SCI (neurologic level C4-T10) are being enrolled at 2-4 months after SCI, a period when we hypothesize that inflammation will be declining (ie not too early) and myelin loss may still be limited. We will compare these individuals with age-matched, healthy controls. The primary focus in Year 2 has been 3-fold. Focus 1: Developing and testing statistical analytics and data visualization for biomechanical data using previous data with the same structure and outcome measures as the current study. Focus 2: On-boarding new personnel (GRA, bioinformatician) to continue working on biomarker processing pipeline and genetic data analysis of the blood biomarker data collected previously. Focus 3: Upgrades to MRI software has been completed and validation of measurements against phantoms and University of British Columbia (UBC) are underway.

15. SUBJECT TERMS
Spinal cord Injury, biomarkers (blood, CSF), MRI, neuromodulation, electrical stimulation, eccentric training, treadmill, rehabilitation, biomechanics (kinetics, kinematics, EMG)

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1. INTRODUCTION:

The investigators are studying a new rehabilitation treatment for individuals trying to recover walking after spinal cord injury (SCI). The investigators will test conditions in the blood and spinal fluid to determine the best time to start this new training program. This will include checking for certain features called biomarkers by testing participants' spinal fluid and blood and compare these features to individuals without SCI. These features will help investigators determine when to start the new training program, either right away or waiting for 3 months. The new training program uses walking downhill on a slight slope on a treadmill while muscles that are not working normally are stimulated to contract using low levels of electricity. Adding this stimulation will allow people to practice walking and other skills even though full muscle control has not recovered. This new program will be in addition to any other rehabilitation therapy and will not replace standard rehabilitation. The hope is to see if downhill training with muscle stimulation, when delivered at the most ideal time, will improve trunk and leg movement, walking, and overall function. This recovery of movement and function will be compared to people with SCI receiving standard rehabilitation alone. Certain regions of the brain and spinal cord will also be studied using MRI scans to determine if these are affected by the training and compare to individuals without SCI. The total length of the study for SCI participants will be up to 16 weeks if in the standard of care group and up to 33 weeks if in the trained group. Healthy control participants will be involved for 1-2 visits.

2. KEYWORDS:

Spinal Cord Injury
SCI
Biomarkers
MRI
Locomotor Training
Downhill
Neuromodulation
Electrical Stimulation
Cerebral Spinal Fluid
Rehabilitation
Physical Therapy
Eccentric
Treadmill

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Overall Objective

	Timeline	OSU	UBC	ND	Progress
Major Task 1: Implement protocols for study	Months				
IRB submission for OSU/ND; UBC	1-6	Basso	Boyd		Complete OSU/ND #2021H0209 Initial Approval: 9/27/2021 UBC #H21-03222 Initial Approval: 6/22/2022
USAMRMC ORP HRPO submission	1-6	Basso	Boyd		Complete OSU and UBC
Milestone Achieved: Protocols and approvals established	6	Basso	Boyd		Complete OSU and UBC
Major Task 2: Recruit subjects who will participate in Aims 1-3					
Study registration with NIH clinical trial registry (clinicaltrials.gov)	6-27	Basso			Complete #NCT05337982
Subject recruitment and enrollment (n=49) SCI Immediate start/Go n=9; SCI delayed start/No Go n=9; SOC n=9; Healthy control n=11. One individual added to each group to account for the possibility of drop-outs	6-27	Basso			In progress 5%. UBC and OSU are receiving inquiries from potential participants with and without SCI via clinicaltrials.gov, ResearchMatch, scitrials.org and scitrialfinder.net.
Meeting with Lived Experience Consultants – Quarterly; 2-3 meetings with Dr. Basso and at least one meeting a year with collaborators at UBC and Notre Dame for input on but not limited to the following: recruitment, solution finding, status of data collection, strategic focus.	6-27	Basso, Angold, Johnson, Mann	Boyd, Kwon	Schmieeler	In Progress 30%. Lived Experience Consultant meeting May 2023.
Milestone Achieved: Enrollment completed	27				In Progress

Aim 1. Identify biomarkers of SCI for a receptive microenvironment for augmented rehabilitation

	Timeline	OSU	UBC	ND	Progress
Major Task3: Implement protocols for study	Months				
Coordination with physicians, OSUMC on CSF collection protocol	1-6	Schwab, Rajneesh, Basso			Complete
Coordinate sample processing pipelines for lcRNAseq and/or scRNAseq	1-6	Kirby, Basso			Complete

Milestone Achieved: Experimental Processing Algorithms created at OSUMC and Nationwide Children's Hospital	6				Complete. Trained PhD student in biomarker protocols. Manualized the biomarker processing protocol using blood sample. Awaiting bioinformatics analysis to determine success of pilot.
Major Task 4: Collection of CSF samples					
Cerebrospinal fluid collection (n=29: SCI Immediate start/Go n=9; SCI delayed start/No Go n=9; Healthy control n=11). Approximately n=4-6 quarterly (2-3 healthy control, 2-3 SCI). CSF (20ml) will be collected, FAC sorted and processed at OSU, then analyzed for RNAseq at Nationwide Children's Hospital.	6-27	Rajneesh			Not yet initiated
Milestone Achieved: Sample collection completed	27				Not yet initiated
Major Task 5: Collection of blood samples					
Blood collection (n=29: SCI Immediate start/Go n=9; SCI delayed start/No Go n=9; Healthy control n=11). Approximately 4-6 quarterly (2-3 healthy control, 2-3 SCI). Whole blood (8 ml) will be collected, FAC sorted and processed at OSU, then analyzed for RNAseq at Nationwide Children's Hospital.	6-27	Rajneesh			In Progress: 5% Pilot blood biomarker data collected, processed through Nationwide Children's Hospital labs, and began bioinformatics data processing
Milestone Achieved: Sample collection completed	27				In progress
Major Task 6: Analysis of samples					
Cerebrospinal fluid analysis will include but is not limited to lcRNAseq or scRNAseq to determine levels of gene expression including but not limited to hybrid microglia/monocyte cells, CCL2/CCr2, L-selectin, ADAM8, MMP9, IL1B, ADAM 9, ADAM 17, Chi3l1, IL1B, L-selectin, Tlr4.	6-30	Kirby, Pietrzak			Not yet initiated
Blood analysis will include but is not limited to lcRNAseq or scRNAseq to determine levels of gene expression including but not limited to hybrid microglia/monocyte cells, CCL2/CCr2, L-selectin, ADAM8, MMP9, IL1B, ADAM 9, ADAM 17, Chi3l1, IL1B, L-selectin, Tlr4.	6-30	Kirby, Pietrzak			In Progress: 5% Several pilot samples of blood collected and processed to train PhD student and validate biomarker measures. Began bioinformatics analysis to determine quality.
Milestone Achieved: Sample analysis for biomarkers completed	30				In progress
Identification of biomarkers including but not limited to levels of hybrid microglia/monocyte cells, CCL2/CCr2, L-selectin, ADAM8, MMP9, IL1B, ADAM 9, ADAM 17, Chi3l1, IL1B, L-selectin, Tlr4.	7-36	Basso, Kirby, Pietrzak	Kwon		In Progress: 1% Pilot samples for blood biomarker data have been processed, now awaiting bioinformatics analysis to identify biomarkers in healthy controls.
Statistical analysis including but not limited to correlations between pro-inflammatory gene	9-30	Brock, Yu			In Progress: 10%. Testing of naming

expression and severity of motor impairments and neuropathic pain will be exploratory in nature. Model-based analyses using generalized linear mixed models (GLMMS) to explore these associations, will be summarized using descriptive statistics.					structures and file structures are underway with the statisticians to reduce errors and simplify analyses. Development of new data visualization techniques.
Milestone Achieved: CSF & Blood data set completed	30-36				In progress
Milestones Achieved: Aim 1 completed	36	Basso			
• Deliverables: presentation of Aim 1 data at national meetings and 1 peer reviewed paper		Basso Kirby Brock, Schwab, Rajneesh, Yu, Pietrzak	Kwon		Not yet initiated

Aim 2: Identify SCI myelin response at subacute using MRI

	Timeline	**OSU**	**UBC**	**ND**	**Progress**
Major Task7: Implement protocols for study	Months				
Subject recruitment at UBC	1-6		Boyd		In Progress: 2%. UBC recruitment will begin immediately after OSU scan protocol is validated. The transition of the collection protocol from UBC MRI to OSU has continued with the assistance of Dr. Boyd and her collaborators at UBC. Troubleshooting software alignment remains the focus.
Major Task 8: Collection of MRI data					
Myelin water fraction MRI data collection in healthy controls (n=11) at least 2-3 participants quarterly. Each participant will undergo one scan therefore requiring a single visit.	6-30	Pending MRI scientist	Boyd		Not yet initiated. OSU will run same protocols as pilot tested at UBC on same 2 individuals to determine accuracy/feasibility between UBC and OSU scanners.
Milestone Achieved: Neuroimaging collection completed	30				Not yet initiated
Major Task 9: Analysis of MRI data					
Myelin water fraction (MWF) MRI data analysis including but not limited to the white matter parcellation map used to extract mean MWF from a	6-30		Boyd		Not yet initiated

priori identified regions of interest including motor and non-motor learning regions and whole brain.					
Milestone Achieved: Neuroimaging data analysis completed	30				Not yet initiated
Statistical analysis will include but is not limited to between group and individual comparisons of mean MWF measures for motor learning regions, non-motor learning regions and whole brain. The purpose is to identify Go/NoGo conditions for individuals with SCI as compared to healthy controls (individually or as a group). Metrics and aggregate from Non-injured healthy controls (e.g., PCA) will be plotted and explored visually for each participant using boxplots, dotplots (for e.g. means and medians) and spaghetti plots. The same metrics and aggregate metrics will be derived for individuals with SCI to determine the GO/No Go condition.	9-30	Brock, Yu			Not yet initiated
Milestone Achieved: MRI data set completed	30-36				Not yet initiated
Milestones Achieved: Aim 2 completed 1. Deliverables: presentation of Aim 2 data at national meetings and 1 peer reviewed paper	36	Basso, pending MRI scientist	Boyd		Not yet initiated

Aim 3: Combining eccentric locomotor training with neuromodulation in the subacute phase in a pilot study

	Timeline	**OSU**	**UBC**	**ND**	**Progress**
Major Task 10: Implement protocols for study	Months				
Training of study personnel	1-6	Basso, Kirby		Schmeideler	In Progress: 25% Trained PhD student in subject recruitment process, obtaining informed consent; continuing training in biomarker analysis techniques. Oriented Dr. Pietrzak to research design, biomarker objectives. Greater training requirements will be needed once the new equipment and new clinical coordinator are on board.
Major Task 11: Perform rehabilitation and outcome measures					
Augmented rehabilitation for early start cohort (dhSTIM Go group n=9, 2-3 per quarter). **D**own**H**ill treadmill training with **STIM**ulation (dhSTIM) will include but not limited to downhill treadmill stepping on a 10-20% grade with electrical stimulation of the legs and trunk (Xcite), 3 times a	6-33	Basso			Not yet initiated

week for 12 weeks. Up to 4 trainers will provide the intervention.					
Augmented rehabilitation for late start cohort (dhSTIM No-Go group n=9, 2-3 per quarter). **D**own**H**ill treadmill training with **STIM**ulation (dhSTIM) will include but not limited to downhill treadmill stepping on a 10-20% grade with electrical stimulation of the legs and trunk (Xcite), 3 times a week for 12 weeks. Up to 4 trainers will provide the intervention.	12-33	Basso			Not yet initiated
Collect kinematics, kinetics, EMG and clinical outcomes – **dhSTIM groups** (n=18) pre training, 12 weeks later (post training), and at 1 month follow-up. Go and No Go groups will have these testing procedures. Biomechanics Procedures will include but not limited to placing reflective spheres to the skin of participants for recording motions of their arms, legs and trunk. We will examine muscles of the legs and trunk. Collection of EMG with at least 16-channel surface or indwelling electrodes (indwelling for iliopsoas) will occur while participants walk, with assistance as needed, on a treadmill with embedded force plates to detect kinetics. Clinical outcomes will include but are not limited to: • ASIA Impairment scale (AIS), International standards for neurological classification of spinal cord injury (ISNCSCI) • Autonomic Standards Assessment Form • Spinal Cord Injury Independence Measure (SCIM3) • Neuropathic Pain Symptom Inventory • Pain Numeric Rating Scale (also collected each training session) Additional outcomes completed by therapists during outpatient visit and accessed via medical record: • Neuromuscular Recovery Scale • 6 minute walk test • 10 Meter walk test	9-33	Basso		Schmeideler	Not yet initiated
Collect kinematics, kinetics, EMG and clinical outcomes – **SOC group** (n=9, 2-3 per quarter) at enrollment, 3 months, and at 1 month follow-up. Biomechanics Procedures will include but not limited to placing reflective spheres to the skin of participants for recording motions of their arms, legs and trunk. We will examine muscles of the legs and trunk. Collection of EMG with at least 16-channel surface or indwelling electrodes (indwelling for iliopsoas) will occur while participants walk, with assistance as needed, on a treadmill with embedded force plates to detect kinetics. Clinical outcomes will include but are not limited to:	6-30	Basso		Schmeideler	Not yet initiated

• ASIA Impairment scale (AIS), International standards for neurological classification of spinal cord injury (ISNCSCI) • Autonomic Standards Assessment Form • Spinal Cord Injury Independence Measure (SCIM3) • Neuropathic Pain Symptom Inventory • Pain Numeric Rating Scale (also collected each training session) Additional outcomes completed by therapists during outpatient visit and accessed via medical record: • Neuromuscular Recovery Scale • 6 minute walk test • 10 Meter walk test					
Milestone Achieved: Rehabilitation completed for all participants	33				Not yet initiated
Major Task 12: Collect MRI post augmented rehabilitation					
MRI for GO (early) and No Go (late) start cohorts (n=18) including 2 scans, one pre and one post dhSTIM intervention	9-33	Pending MRI scientist	Boyd		Not yet initiated
MRI for SOC group (n=9) including 2 scans, one at enrollment and one 3 months later	6-33	Pending MRI scientist	Boyd		Not yet initiated
Milestone Achieved: MRI collection completed for all participants	33				Not yet initiated
Major Task 13: Analysis of data					
Analysis of kinematics, kinetics and EMG including but not limited to biomechanical variables of interest such as anterior-posterior ground reaction forces, and lower extremity joint angles, moments and powers. EMG outcomes will include but not limited to burst duration, amplitude, timing of eccentric activation during weight acceptance and co-contractions.	9-36			Schmieder	Not yet initiated
Analysis of post rehabilitation MRI by methods including but not limited to the white matter parcellation map used to extract mean MWF from a priori identified regions of interest including motor and non-motor learning regions and whole brain.	12-36		Boyd		Not yet initiated
Analysis of relationship between pre-rehabilitation blood biomarkers and functional changes post rehabilitation including but not limited to levels of hybrid microglia/monocyte cells, CCL2/CCr2, L-selectin, ADAM8, MMP9, IL1B, ADAM 9, ADAM 17, Chi3l1, IL1B, L-selectin, Tlr4 correlated with biomechanics change after completing augmented dhSTIM rehabilitation	12-36	Kirby, Pietrzak			Not yet initiated
Statistical analysis including but not limited to the following techniques for biomechanics: principle component analysis, comparison of peak values	30-36	Brock, Yu			Not yet initiated

during select phases of the gait cycle using group x time repeated measures MANOVA and Tukey's posthoc tests, correlational analysis between clinical outcomes and the biomechanics outcome measures, Non-responder analyses with chi-square testing, timing measures of eccentric EMG activation patterns. Treated groups (GO, No Go) will be compared to SOC and healthy controls, and pre-post training. Mixed effects models with a random effect for participant and leg nested within a participant will be used when appropriate. MRI. The change in MWF before and after augmented rehabilitation (GO, No Go groups) or the change relative to SOC will be compared. Metrics and aggregate metrics (e.g., PCA) will be plotted and explored visually for each participant using boxplots, dotplots (for e.g. means and medians) and spaghetti plots. Comparisons between control and intervention groups and between Go/No-Go from pre- to post-training will use mixed effects models. Clinical outcomes. Changes in sensorimotor function will be assessed using a predictive linear mixed model. Least absolute shrinkage and selection operator (LASSO) will be used to derive models including significant factors. Interactions of the predictors will be tested and retained if $p<0.05$. Adjusted R2 and prediction error will calculated. Due to small sample size, internal bootstrap validation will occur. Biomarkers. Correlations between pro-inflammatory gene expression and severity of motor impairments and neuropathic pain will be exploratory in nature. Model-based analyses using generalized linear mixed models (GLMMS) to explore these associations will be summarized using descriptive statistics.					
Milestones Achieved: Aim 3 completed 1. Deliverables: presentation of Aim 3 data at national meetings and 1 peer reviewed paper	36	Basso, Kirby, Pietrzak	Boyd	Schmieder	Not yet initiated
Major Task 14: Completion of study					
Milestones Achieved: Final study report	36	Basso	Boyd	Schmieder	Not yet initiated

Enrollment

	Year 2							
Quarter	**Q1**		**Q2**		**Q3**		**Q4**	
Enrollment	**Target**	**Actual**	**Target**	**Actual**	**Target**	**Actual**	**Target**	**Actual**
OSU- People with SCI	3	**0**	3	**0**	3	**0**	3	**0**
OSU- Healthy controls – Blood/CSF	2	**0**	2	**0**	2	**1**	1	**0**
UBC- Healthy controls -MRI	2	**0**	2	**2**	2	**0**	1	**0**
Target Enrollment (cumulative)	21	**1**	28	**3**	35	**4**	40	**4**

What was accomplished under these goals?

Major Activities

- Develop Protocols
    - MRI: As of July, Dr. Lara Boyd was successful in working with imaging staff at OSU and coordinating software upgrades to have the MRI guidelines and capabilities at OSU match UBC. Phantom runs at OSU are being initiated. These accomplishments were more difficult due to the unexpected departure of Dr. Knopp (MRI Physician Scientist) from OSU in Quarter 2.
    - Biomarker analysis: In September our new bioinformatics expert at OSU, Dr. Pietrzak, was onboarded by Drs. Basso and Kirby after a multiple month delay for DOD approval to add him to the project. Test runs of the blood biomarker collection protocol were completed, the graduate student who will be performing the processing of the samples has been trained on the procedures, and analysis of pilot study data was implemented. Dr. Pietrzak is currently confirming the quality of the blood biomarker data collected in pilot studies.
    - Clinical procedures: Drs. Rajneesh, Schwab and Basso resolved questions that would impact enrollment by adopting clinical screening guidelines to address the impact of medications on cerebrospinal fluid (CSF) draws. A submission to OSU IRB is underway to implement the changes. Progress on integrating into the clinic were impacted and delayed by the departure of our clinical research coordinator in the 2nd quarter.
    - Data analysis: This year we have confirmed many processes which will create smoother data processing going forward. A simple and consistent file naming structure was implemented at the time of file creation to be compatible with future statistical computations. Data analyses techniques for the complex large data structures we will have in this study have been tested. New data analytics and visualization techniques have been adopted which show both the group effects and individual responses in people with SCI. This plotting strategy is important because of the large heterogeneity that exists across people with SCI. Dr. Schmiedeler, Dr. Brock, biostatistician, study coordinator, biomechanics engineer and the PI have established twice monthly meetings to design and refine our biomechanics acquisition and processing pipeline. Using preliminary data submitted in the grant, we have completed testing analysis approaches for sensitivity in detecting differences in movement patterns in people with chronic SCI that completed downhill treadmill training.

- Data transfer and storage: We have engaged the OSU IT Leader for options to solve the lack of a functional file transfer protocol between UBC, Notre Dame and OSU. The process in place at the time of the grant initiation was lost because of the removal of equipment related to the departure of Dr. Knopp. In the 4th quarter, a data storage structure was implemented in the OSU Supercomputer Center.

- Pilot Techniques
  - In quarter 1, UBC ran pilot MRI scans on 2 healthy adults using the protocol established for this study.
  - In quarter 2, new Standard Operating Procedures were developed for Xcite stimulation in optimal muscle locations to maximally activate muscles of interest.
  - The study engineer, Dan Richie, in conjunction with the OSU Clinical Research Coordinator made fine wire EMG sensors required for indwelling Iliopsoas muscle in quarters 1-2.

- Recruit Participants
  - In quarter 1, the study was registered with clinicaltrials.gov and UBC was added to as a location.
  - Recruitment of healthy controls is underway has begun. Some individuals are on hold until our biomarker data processing SOPs are validated.
  - For SCI participant recruitment, multiple inquiries have come through from scitrials.org and scitrialfinder.net, among other similar recruitment sites. Most participants have not met the inclusion criteria due to chronicity of their injury and location outside of central Ohio.

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

- Biomarker and Genomics
  - Both under Dr. Kirby's supervision and independently, Jeremy Beales, the MD/PhD student in the lab, has performed biofluid processing and genomic protocols. He has developed detailed SOP manuals to facilitate training of future individuals.
  - Dr. Basso and Dr. Kirby onboarded Dr. Pietrzak, bioinformatics expert, to study design, grant objectives for biomarkers and genomics and established access to blood pilot data for analysis.

- Locomotion and Biomechanics
  - Jeremy Beales has continued to train in application of the EMG electrode system and collected data. Training on the data analysis of EMG will need to wait until a required piece of equipment (Motion Monitor) is available to synchronize signals.
  - Training for accuracy of Neuromuscular Recovery Scale scores given by trained clinician raters, was carried out in quarter 1 of this year. The training is computer-based and lengthy so the clinicians' full work schedules delayed the training until Year 2.

How were the results disseminated to communities of interest?

Dr Basso presented a description of the study and our recruitment criteria and timeframe on June 30th at the Spinal Cord Injury Research, Rehab, Care & Community event at OSU.

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

MRI

- Complete pilot testing of MRI protocols on participants from tests completed at UBC
- UBC to begin recruitment for healthy control participants for MRI when OSU MRI is operational and validated
- Conduct MRI myelin water fraction analyses as healthy control scans are collected. Two scans have been collected and can be analyzed once the collection protocol is validated at OSU.

Biomarker Development

- Complete bioinformatics analysis of blood biomarkers from pilot sample, now that bioinformatics expert is approved and finalize the SOP for blood biomarker analysis based on the quality of the data.
- Once blood biomarker analysis confirms that our processes are successful we will begin pilot tests with CSF to confirm SOP and high quality data
- Begin recruitment of healthy control participants for fluid biomarker collection.
- Begin biomarker data analysis as it is collected and processed for healthy controls

Training Intervention, Biomechanics Collection & Analysis

- Finalize neuromodulation application protocol and use during downhill treadmill training
- Finalize protocol for Xsens placement and collections for biomechanics data collection, run pilot tests through the processing pipeline at Notre Dame University

Protocol and Analysis Objectives

- Establish a data file sharing systems between OSU and external universities
- Continue to refine SOPs for all aspects of the project as pilot testing and initiating recruitment takes place
- Purchase motion monitor for biomechanics data collection
- Finalize CSF biomarker processing at OSU and at Nationwide Childrens Hospital
- Continue analyzing and modelling previous biomechanical data for markers of motor skill development and motor relearning in SCI

4. IMPACT:

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

The biomechanics team and statisticians have considered several analytical approaches for complex data sets which our project will generate. We used previous data with similar measures to test and model effective statistical approaches. Unlike several published approaches for EMG alone or kinetics with kinematics combined, we are taking a novel approach which identifies inherent combinations between the three disciplines relative to healthy controls. To our knowledge, this statistical approach has not been used for studying the motor control of locomotion or the training effects of downhill treadmill walking after SCI. If this model continues to prove sensitive to dyscontrol and recovery, we will publish this work.

We are also testing whether a decrease in movement variability reflects recovery of locomotor skill in people with SCI. We are using previous data but applying new analytics that will be used for the new data collected in this grant. This work is in the preliminary stages, and we are considering statistical approaches to examine changes in variance for EMG, kinematic and kinetic variables before and after training. If successful, these approaches could impact the fields of disability research, rehabilitation, motor learning and motor control.

What was the impact on other disciplines?
Nothing to report for this period.

What was the impact on technology transfer?
Nothing to report for this period.

What was the impact on society beyond science and technology?
Nothing to report for this period. As stated in the last annual report, we expect to improve quality of life for people living with SCI by increasing independence and health. If successful, our project may produce new screening tools for myelin loss, inflammation, and gradations in neuropathology. All of which may be signify GO or NO GO conditions for specific forms of neurorehabilitation.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
No changes in approach

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

- In May 2023, it was identified that our Feb 2023 request for bioinformatics expert Dr. Pietrzak and LEC Paul Mann to be approved on the project was sent to the wrong email address by the Ohio State SPO. Once this was corrected, Dr. Gross requested an updated SOW to complete the staff additions, which was submitted in May 2023. We waited for approval until Quarter 4 when we were alerted that this appointment did not require approval. Dr. Pietrzak was appointed to the grant as of September 1, 2023 and began analyzing pilot study blood samples. The postponement in his appointment resulted in delays in biomarker development for blood and CSF. Therefore, recruitment of healthy controls did not occur in Quarter 4. Without the baseline levels of biomarkers, people with SCI could not be recruited.
- Clinical Research Coordinator: Our study coordinator, Raquel Minarsch, left in Quarter 2 for another study coordinator position offering full time employment. Documentation to post the position and hire another coordinator was approved by OSU in Quarter 3. I screened individuals in Quarters 3 and 4 but as yet has not yielded any applicants with required skills of being a Physical Therapist. I continue to screen candidates as they are submitted.
- Establishing the MRI scanning protocols to quantify myelin at OSU occurred during Quarters 3 and 4. With the departure of Dr. Knopp from OSU, the Radiology Department at Wexner Medical Center had to engage new radiological physicians to support research studies and dedicate technicians/physicists to update and operate the scanner. In Quarter 4, the system had the required software upgrades to begin testing myelin protocols. We rely on expertise at UBC to help resolve software incompatibility between OSU and UBC. Dr. Boyd and the team at UBC have developed and tested a new myelin analysis collection protocol, determined the necessary patches required for the OSU scanner to perform the protocol. They have been in contact with the manufacturer to secure the patch for OSU. Because the

UBC and OSU scanners use slightly different software, we need to validate that the collected data from each scanner are within acceptable ranges. We also identified that the file transfer protocols from OSU to UBC is non functional after Dr. Knopp's departure as the equipment relocated with him. I have asked for University support to establish data transfer pipelines between OSU and UBC and Notre Dame.

- The funding source for Motion Monitor equipment will come from unused salary support for the interim period before appointing a new MRI physician scientist and a new study coordinator.
- Due to biomechanical equipment failure discussed in previous reports, we identified the Xsens IMU systems as an excellent replacement because it resolved barriers such as line of sight issues. This system was not part of our budget and deep budget adjustments would have been required. Fortunately, in Quarter 2, I was able to identify an Xsens system for our use at no cost.
- Study Recruitment: We expected to begin enrollment into the study in Quarter 2 contingent on successful biomarker development. We did not advance this during Quarter 3 because of delays in approving Dr. Pietrzak. In Quarter 4, he began analysis on pilot study samples for blood. Work on CSF biomarkers is contingent on accurate, viable processing of blood samples.
- Mr. Ken Johnson, one of our Lived Experience Consultants confirmed our meeting for May 19, 2023 but he did not attend. I reached out to him and confirmed his commitment to continue working with us as a consultant with lived experience.
- Mr. Paul Mann has replaced Mr. Chris Balance as a Lived Experience Consultant. Mr. Mann was a military policeman, US Army 1989-1993 and served one combat tour in Somalia, Africa. He is currently Board member and Sports Director of Buckeye PVA. He began his consulting duties in May 2023.

Changes that had a significant impact on expenditures

- Personnel changes for an MRI physician expert and clinical research coordinator have not yet been filled so salary expenditures were not made.
- The funding source for Motion Monitor equipment will come from unused salary support for the interim period before appointing a new MRI physician scientist and a new study coordinator.
- Dr. Pietrzak's salary was paid by an honorarium fund for Dr. Basso.
- The paperwork to pay Lived Experience Consultants has been delayed due to adoption of Workday system at OSU. The steps to pay external consultants is at least a 4 step process. The fourth step was only recently shared with me at the end of Quarter 4. The consultant fees are now moving through the 4th step of the processing pipeline.
- The stipend for Jeremy Beales, GRA was assigned to the grant August 15th, 2023. His work on biomarker development is greater than originally considered so his FTE was increased from half to full. The full-time FTE is considered 6 months for GRAs at OSU. Jeremy Beales worked on biomarker processes beginning April 1, 2023 and his stipend was covered by an MD/PhD fellowship.

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

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS:

Publications, conference papers, and presentations

Journal publications

Nothing to Report

Books or other non-periodical, one-time publications

Nothing to Report

Other publications, conference papers and presentations

Nothing to Report

Website(s) or other Internet site(s)

Study Record | ClinicalTrials.gov
https://www.clinicaltrials.gov/study/NCT05337982?locStr=Columbus,%20Ohio,%20USA&country=United%20States&state=Ohio&city=Columbus&distance=50&cond=spinal%20cord%20injury&aggFilters=status:rec&rank=4

Technologies or techniques

Nothing to Report

Inventions, patent applications, and/or licenses

Nothing to Report

Other Products

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	Study Role	Person Months	Contribution to Project
D Michele Basso, EdD, PT The Ohio State University ORCID: 0000-0002-2274-9130	Principal Investigator	2	Maintains compliance with all OSU protocol regulations. Manages funding planning for equipment. Directs discussion with OSU IT to create a new file sharing plan with UBC and NDU. Coordinates OSU Radiology Dept, OSU MR physicists and UBC MRI team to establish MRI scans at OSU. Manages staffing hiring and performance.
Elizabeth Kirby, PhD The Ohio State University ORCID: 0000-0001-9313-3790	Co-Investigator	2	Specializes in CSF and blood analysis and associated gene mapping. Created SOP for blood biomarker processing.
UBC Subcontract Lara Boyd, PT, PhD University of British Columbia ORCID: 0000-0002-2828-4549	Co-Investigator	2	Specializes in MRI image acquisition and analysis. Working with OSU MRI team to trouble shoot software errors at OSU.
Notre Dame Subcontract James Schmiedeler, PhD University of Notre Dame ORCID: 0000-0002-1692-4414	Co-Investigator	1	Specializes in biomechanics data analysis. Working with team to trouble shoot file transfers between OSU and NDU and develop optimal data visualization for large data sets.
Raquel Minarsch The Ohio State University	Study coordinator *This role is currently unfilled.*	5 *before her departure*	Developing SOP with each co-I for implementation to conduct biomarker collection and analysis, neuromodulation delivery, MRI collection specifics between OSU and UBC, biomechanics collection and analysis, downhill treadmill training, participant screening and recruitment. Assisting with IRB & HRPO application and submission.
Daniel Richie The Ohio State University	Study engineer, motion analysis lab manager	4	Assisted with lab set up for preparation for data collection. Participated in meetings/practice sessions with equipment. Beginning process for purchase of motion monitor.
Jeremy Beales The Ohio State University	Graduate Research Assistant	6	On-boarded and trained in blood biomarker processing. Carried out trouble-shooting of individual steps in the process. Developed the processing manual. Previous funding provided by OSU MD/PhD program.

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

New Grant Funding:
Funding: 2022 – 2027W81WH2211083

Title: **A User-Friendly, Portable, and Non-Invasive Hand-Grasp Neuro-Orthosis That Restores Volitionally Controlled Grasp Functions for Those with Tetraplegia at Home**

Funding Mechanism: DOD, SCIRP

MPI: David Friedenberg and Lauren Wengerd

CO-I: **DM BASSO**

Amount: **OSU**

Grants that Ended:
NIH R01 NS074882 2011 – 2023

Title: **Behavioral and cellular determinants of treadmill training and recovery after SCI**

Mechanism: NIH R01 Competitive Renewal

PI: **DM BASSO**

Co-I's: Godbout J, McTigue D, Popovich P, Sheridan J

What other organizations were involved as partners?

Organization Name: University of British Columbia
Location of Organization: Vancouver, British Columbia, Canada
Partner's contribution to the project

- Dr. Lara Boyd, PT, PhD. Co-Investigator. MRI image acquisition, MRI data analysis, MRI data interpretation; train personnel in image acquisition and data processing
- Dr. Brian Kwon, MD, PhD, FRCSC. Co-Investigator. Biomarker analysis

Organization Name: University of Notre Dame
Location of Organization: Notre Dame, IN
Partner's contribution to the project

- Dr. James Schmiedeler, PhD. Co-Investigator. Biomechanics Data analysis (kinematics, kinetics, EMG); train personnel in biomechanics data acquisition and analysis

Organization Name: Nationwide Children's Hospital

Location of Organization: Columbus, OH
Partner's contribution to the project

- Facilities for sample processing and analysis for biomarkers

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS: An updated quad chart has been included with this submission.