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TITLE: Oxandrolone Supplementation in Trauma: The Post-Injury Trial

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14. ABSTRACT
The POST-Injury Trial addresses the rehabilitation techniques and outcomes after high-energy, lower extremity fractures. These injuries require extensive rehabilitation and often multiple surgeries and typically result in permanent limitations of physical function. Furthermore, unlike low-energy fractures, these patients incur multiple insults to their soft tissues from both the initial injury and as a result of treatment. This is further compounded by any post-operative immobilization and associated volumetric muscle loss. The process of recovery is long, and the result is often an incomplete functional recovery with residual disability. Within the United States military, musculoskeletal injuries account for 53-76% of medically nondeployable Service Members, of which 65%-92% are due to volumetric muscle loss after high-energy trauma and fracture. There have been a lack of efficacious interventions available to offset the metabolic and mechanical sequalae associated with high-energy trauma and prolonged immobilization. Oxandrolone has been successfully utilized to reduce muscle loss, accelerate muscular recovery, and improve physical function in large surface area burns in similar populations and may be translatable to high-energy, lower-extremity fracture patients.

15. SUBJECT TERMS
Post-injury, oxandrolone, high-energy trauma

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1. INTRODUCTION:

The POST-Injury Trial addresses the rehabilitation techniques and outcomes after high-energy, lower extremity fractures. These injuries require extensive rehabilitation and often multiple surgeries and typically result in permanent limitations of physical function. Furthermore, unlike low-energy fractures, these patients incur multiple insults to their soft tissues from both the initial injury and as a result of treatment. This is further compounded by any post-operative immobilization and associated volumetric muscle loss. The process of recovery is long, and the result is often an incomplete functional recovery with residual disability. Within the United States military, musculoskeletal injuries account for 53-76% of medically nondeployable Service Members, of which 65%-92% are due to volumetric muscle loss after high-energy trauma and fracture. There have been a lack of efficacious interventions available to offset the metabolic and mechanical sequalae associated with high-energy trauma and prolonged immobilization. Oxandrolone has been successfully utilized to reduce muscle loss, accelerate muscular recovery, and improve physical function in large surface area burns in similar populations and may be translatable to high-energy, lower-extremity fracture patients. The proposed trial will be a multi-centered randomized, single-blind, placebo-controlled pilot clinical trial (phase II/III). Included patients will consist of those with an acute high-energy, lower-extremity fracture within 2-weeks of enrollment. Those meeting inclusion and exclusion criteria will be randomized via a block randomization technique to receive either standard-of-care rehabilitation with placebo medication versus standard of care rehabilitation with oral Oxandrolone. Those in the experimental group will receive standard dosing for Oxandrolone at 20mg/day orally divided into two doses for a total of 6 months. Patients will be evaluated at 6 months and 1 year by MRI with quantified volumetric vastus medialis and total thigh muscle mass, short form 36 health survey, VAS, PROMIS, and activity counter by a wearable tracker via the ActiGraph GT3X-BT.

2. KEYWORDS:

Post-injury, oxandrolone, high-energy trauma

3. ACCOMPLISHMENTS:

What were the major goals of the project?

This is a 3-year Multi-centered, double-blind, randomized control trial. We are examining the effect of Oxandrolone supplementation after lower extremity high energy fracture on muscle volume recovery. In addition, examining the effect, of Oxandrolone supplementation with respect to both functional and patient reported outcomes, determining if Oxandrolone supplementation reduces the length of hospital stay, establish the safety and barriers to compliance.

Statement of Work – Tasks and Subtasks	% Complete
Major Task 1: Prepare Regulatory Documents and Research for Study	
Subtask 1.1 Submit to Health Canada (Sunnybrook)	50
Major Task 2: Prepare Research Protocol for Approval	
Subtask 2.1 Finalize consent form and human subject protocol	100
Subtask 2.2 Submit IRB protocol submission to WRNMMC	50
Subtask 2.3 Submit IRB protocol submission to Sunnybrook	100
Subtask 2.5 Submit IRB protocol submission to HRPO for WRNMMC	0
Subtask 2.6 Submit IRB protocol submission to HRPO for Sunnybrook	100
Major Task 3: Coordinate Study Staff for Clinical Trials	
Subtask 3.1 Hiring and Training of Study Staff (Sunnybrook)	100

Statement of Work – Tasks and Subtasks	% Complete
Subtask 3.2 Create job description for project related staff (Sunnybrook)	100
Subtask 3.3 Advertise and interview for project related staff (Sunnybrook)	100
Subtask 3.4 Coordinate or space allocation for new staff (Sunnybrook)	100
Major Task 4: Patient Recruitment, Enrollment and Follow-Up	
Subtask 4.1 Analyze, measure and determine the feasibility and safety of Oxandrolone supplementation to increase muscle mass recovery	0
Subtask 4.2 Screen potential participants at Sunnybrook and WRNMMC with high-energy lower extremity fractures and consent (n=86)	0
Subtask 4.3 Evaluate all participants at the 6- and 12-month timeframe	0
Major Task 5: Data Analysis	
Subtask 5.1 Evaluate and measure the feasibility and safety of Oxandrolone supplementation to increase muscle mass	0
Subtask 5.2 Perform all analyses according to specifications, share output and finding with all investigators	0
Subtask 5.3 Work with data core and dissemination of findings (abstracts, presentation, publications, DoD)	0

What was accomplished under these goals?

Major Task 1: Prepare Regulatory and Administrative Documentation

Walter Reed National Military Medical Center (WRNNMC)
Scientific review was completed on 18 July 2022
Protocol has been submitted to the IRB and is under review

Sunnybrook Research Institute (SRI)
Provincial Ethics Approved
Application sent to Health Canada
Study tools and templates have been created
Submitted the HRPO for second level review on 10 August 2022
Clinicaltrials.gov registration completed

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?

WRNMMC:

- We will continue to work on IRB approval at WRNMMC.
- We will submit for HRPO approval
- We will work on the appropriate agreements (CRADA, DSAA)

Sunnybrook Research Institute:

- We will await Health Canada approval to use Oxandrolone in a clinical trial.
- We are working with a supplier to import study drug, formulate placebo pills and prepare IP kits for the study.
- We will be contracting with study sites to activate the clinical trial at the three 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:

Changes in approach and reasons for change
Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
Sunnybrook Research Institute

- Challenges with supply chain issues for placebo at Sunnybrook pharmacy
    - Resolved by engaging a vendor we have previously worked with
- Vendor needed time to add Oxandrolone to their dealer license with Health Canada
- Challenges with contacting the Oxandrolone manufacturer that previously supplied Oxandrolone to another study in Canada.
    - Resolved by finding another manufacturer who has agreed to provide us with the Oxandralone and act as the exporter
- Costs of Onxadralone have increased significantly since the grant was submitted, we have reviewed the budget to find other areas where we can save money.
    - We submitted a request for supplemental funding which we was approved.

Changes that had a significant impact on expenditures
The delays in regulatory approvals have caused corresponding delays in spending for this project. However, we anticipate that the effect of this will be neutral on the budget over the life of the project.

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
Nothing to report.

Journal publications.
Nothing to report.

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

Other publications, conference papers and presentations.
Nothing to report.

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

Technologies or techniques
Nothing to report.

Inventions, patent applications, and/or licenses
Nothing to report.

Other Products
Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Walter Reed National Military Medical Center (WRNMMC)	
Name:	CAPT (sel) Scott Tintle, MD
Project Role:	Initiating PI at WR
ORCID ID:	0000-0003-0887-7600
Nearest person month worked:	2
Contribution to project:	CAPT(sel) oversees all aspects of the project-related activities.

Name:	Toby Perkins, CCRP
Project Role:	Program/Regulatory Manager
ORCID ID:	none
Nearest person month worked:	1
Contribution to project:	Mrs. Perkins oversees the management of the study to include regulatory. Mrs. Perkins is working on IRB approval at WRNMMC.

Sunnybrook Research Institute (SRI)

Name:	David Wasserstein, MD
Project Role:	Subaward Site PI
ORCID ID:	none
Nearest person month worked:	1
Contribution to Project:	Dr. Wasserstein oversees all aspects of the project-related activities at SRI.

Name:	Pujitha Rao
Project Role:	Project Manager
ORCID ID:	none
Nearest person month worked:	1
Contribution to Project:	Ms. Rao is managing the clinical trial from the Sponsor perspective. She oversees the study to include the regulatory oversight.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report.

What other organizations were involved as partners?
Sunnybrook Health Science Center

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS: See Appendix A

9. APPENDICES: See Appendix A for Quad Chart.

POST-Injury Trial – Placebo versus Oxandrolone Supplementation in Trauma

Peer Reviewed Orthopedic Research Program Transitional Science Award

Log Number: OR200144, **Award Number**: W81XWH2120039

PI: Dr. Scott Tintle

Org: Henry Jackson Foundation

Award Amount: $1,481,600

Sites: WRNMMC; Sunnybrook Health Sciences Center

Study/Product Aim(s)

- Understand the effect of Oxandrolone on soft-tissue injury and muscle atrophy after high-energy lower extremity fractures
- Improve short-term and long-term function after high-energy lower extremity fractures
- Improve soft-tissue recover after high-energy lower extremity fractures
- Decrease muscle atrophy after high-energy lower extremity fractures
- Decrease days in hospital and rehabilitation after high-energy lower extremity fractures

Approach

Patients with high-energy lower extremity fractures and significant soft-tissue injury will be randomized to receive either Oxandrolone or Placebo.

In the last year Sunnybrook Orthopaedic Trauma group has participated in 4 multi-center & 2 single-center surgical RCTs. Drs Wasserstein have garnered >1.5M combined peer-reviewed funding in <4 years practice.
Walter Reed National Military Medical Center has consistently been one of the largest DoD funded Orthopedic Research Centers in the world

Timeline and Cost

Activities CY	21-22	22 -23	23-24
Prepare Research Protocol			
Coordinate Staff for Clinical Trial			
Recruitment, enrollment & follow-up			
Data Analysis (mid f/u & final)			
Estimated Budget ($K)	**$500**	**$500**	**$500**

Updated: Sunnybrook Health Science Center and Walter Reed National Military Medical Center

Goals/Milestones

CY21-22 Goal –

- ❑ Production readiness, study initiation and data collection 50%
- ❑ Apply for and receive Health Canada approval for the use of Oxandrolone 50%
- ❑ Initiate the trial with initial patient recruitment and data collection

CY 22-23 Goal – Data collection

- ❑ Finish patient recruitment and data collection

CY 23-24 Goal –study completion, analysis and result dissemination

- ❑ Finish data collection
- ❑ Analyze study data

Budget Expenditure to Date: $ 11,106