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AWARD NUMBER: W81XWH-21-2-0039

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

PRINCIPAL INVESTIGATOR: CAPT Scott M. Tintle, MC, USN

RECIPIENT: Henry M Jackson Foundation,
6720a Rockledge Dr, Suite 100,
Bethesda, MD 20817

REPORT DATE: Oct 2023

TYPE OF REPORT: FINAL

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

REPORT DOCUMENTATION PAGE

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1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
Oct 2023	FINAL	09/30/2021-10/30/2023

Oxandrolone Supplementation in Trauma: The Post-Injury Trial

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-21-2-0039

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
CAPT Scott M. Tintle, MC, USN

E-Mail: scott.m.tintle.mil@health.mil

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Henry M. Jackson Foundation, for the Adv. of Mil. Med.
6720-A Rockledge Dr. STE 100
Bethesda, MD 20817

8. PERFORMING ORGANIZATION REPORT NUMBER

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

U.S. Army Medical Research and Materiel 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

To conduct a multi-center randomized, single blind, placebo-controlled pilot clinical trial (phase II/III) to evaluate the feasibility and safety of oxandrolone supplementation to increase muscle mass recovery in the lower extremities of patients who have suffered high energy trauma

15. SUBJECT TERMS
High-energy, Trauma, Musculoskeletal injury, anabolic steroids, male

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

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Currently there is no truly effective adjuvant treatment to physical therapy that has been shown to improve the quality of life and functional limitations in patients with high energy. We propose that there may be a role for direct pharmacologic modulation of a patient's metabolism to induce an anabolic state and/or offset the known catabolic state to support more complete and faster muscle recovery as has been used by our team in similar patient populations at our institution. The primary aim of this study is to examine the effect of Oxandrolone supplementation after lower extremity high energy fracture on muscle volume recovery. As Oxandrolone supplementation has never been examined in this patient population, the primary null hypothesis is that there will be no difference in measured thigh muscle mass volume between Oxandrolone supplementation and placebo administration groups

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

High-energy, Trauma, Musculoskeletal injury, anabolic steroids, male

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

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.

Major Task 1	% Complete	Complete Date
Subtask 1: Prepare Regulatory Documents and Research for Study	100	
Submit to Health Canada	100	
Major Task 2: Prepare Research Protocol for Approval		
Subtask 1: Prepare Regulatory Documents and Research Protocol for Study		
Finalize consent form and human subject protocol	100	2021-10-22
Submit IRB protocol submission to WRNMMC	100	Nov 2022
Submit IRB protocol submission to Sunnybrook	100	2021-07-21(IRB approval received 2022-08-04
Major Task 2: Coordinate Study Staff for Clinical Trials		
Subtask 1: Hiring and Training of Study Staff		
Create job descriptions design	100	Aug 2021
Advertise and interview for project related staff	100	Aug 2021
Coordinate for space allocation for new staff	100	Sept 2021
Major Task 3: Patient Recruitment, Enrollment, and Follow-up	0	
Subtask 1: Conduct Patient Recruitment, Enrollment and Follow-up		
Analyze, measure and determine the feasibility and safety of Oxandrolone supplementation to increase muscle mass recovery	0	
Screen potential participants at SHSC and WRNMMC with high-energy lower extremity fractures and consent (n=86)	0	
Evaluate all participants at the 6 and 12 month timeframe		
Major Task 4: Data Analysis		
Subtask 1: Evaluate and measure the feasibility and safety of Oxandrolone supplementation to increase muscle mass	0	
Perform all analyses according to specifications, share output and finding with all investigators	0	
Work with data core and dissemination of findings (abstracts, presentation, publications, DoD)	0	

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Walter Reed National Military Medical Center (WRNMMC)

- Submitted the protocol to WRNMMC's IRB for review on 30 November 2022. It is under review administrative review.
- Working on revisions requested in the administrative review
- Reached out to the FDA to inquire if an IND is required

Sunnybrook Research Institute

- Provincial Approval from IRB received
- Regulatory Authority approval [Health Canada] received
- Preparing study tools and templates, study documents for the study.
- The protocol has received OHRO second level approval.
- HFJ Grant Regulatory protocol review approval received.
- Site initiation visit for Sunnybrook site done on 3rd Mar, 2023.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

WRNMMC: Nothing to report

Sunnybrook: Dr. Wasserstein obtained experience as the PI of a multi-centre trial including aspects of coordination, regulatory submissions, etc.

Dr. Catapano was a student during the trial proposal and set up and he gained extensive experience in grant writing, RCT development and study set up.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

- Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

- Nothing to report

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

The FDA has asked the drug manufactures to pull the drug from the market.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

The FDA has asked the drug manufactures to pull the drug from the market. Since there isn't a comparable drug and we reached out to our Science Officer to explain the situation. It was determined that we are closing the award.

Changes that had a significant impact on expenditures

WRNMMC: Nothing to report

Sunnybrook: The study had to be terminated prematurely because the FDA requested the drug manufacturers of oxandralone voluntarily remove their marketing authorization, therefore the budget has been amended to only include costs up to August 2023.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

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: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

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

  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Not applicable

  Books or other non-periodical, one-time publications.

Nothing to report.

  Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Not applicable

- **Website(s) or other Internet site(s)**

  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Not applicable

- **Technologies or techniques**

  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

• Nothing to report.

- **Inventions, patent applications, and/or licenses**

  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. .

- **Other Products**

• Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Name: Scott M. Tintle, MD
Project Role: Principle Investigator and Director
Researcher Identifier (e.g. ORCID ID): 0000-0003-0887-7600
Nearest person month worked: 1
Contribution to Project:

Name: Toby Perkins
Project Role: Clinical Research Manager
Nearest person month worked: 1
Contribution to Project: Mrs. Perkins is working on getting the protocol approved.

Name: Qingfeng Liu
Project Role: Regulatory Affairs Specialist
Nearest person month worked: 1
Contribution to Project: Mr. Liu is working on getting the protocol submitted.

Sunnybrook Research Institute.
Name: David Wasserstein, MD
Project Role: Sunnybrook – subaward Site PI
Nearest person month worked: No change
Contribution to Project:. Oversight of Project at SRI

Name: Rao, Pujitha
Project Role: Project Manager
Nearest person month worked: No change
Contribution to Project: Ms. Jamil will be managing the clinical trial from the Sponsor perspective. She has gotten the IRB approval, prepared study tools and templates and is now working on getting the Health Canada application approved.

Name: Gail Klein
Project Role: Senior Manager
Nearest person month worked: No Change
Contribution to Project: Oversight of Project at SRI.

Name: Shirley Xu
Project Role: Quality Assurance Specialist
Nearest person month worked: No Change
Contribution to Project: Oversight of Project at SRI.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

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: $1,500,000

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, March 2023

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 100%
- ❑ 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: $ 431,822

Projected Expenditure: $ 1,500,000

Actual Expenditure: $431,821.52