AWARD NUMBER: W81XWH-14-2-0190

TITLE: Testosterone Combined with Electrical Stimulation and Standing: Effect on Muscle and Bone

PRINCIPAL INVESTIGATOR(S): GAIL F. FORREST, Ph. D.

CONTRACTING ORGANIZATION: Kessler Foundation
West Orange, NJ 07052

REPORT DATE: October 2015

TYPE OF REPORT: ANNUAL REPORT

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

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The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
The study is a prospective, randomized, double blinded, controlled, multi-site clinical trial to determine the efficacy of a tri combination intervention to improve musculoskeletal gains in men with subacute to chronic SCI with low circulating testosterone levels. Participants will be enrolled at Kessler Foundation (KF), the University of Louisville-Frazier Rehab (UoL), the James J. Peters VA Medical Center (JJPVAMC). During year 1 of the study, the Study Team (Drs. Forrest, Bauman, and Harkema) established a new partnership with a pharmaceutical company (AbbVie) to supply Drug and Placebo for all potential study participants. Each of the study sites submitted to the pharmaceutical company all requested regulatory documentation. Manufacture of the drug/placebo with randomization across the sites for administration of drug/placebo will be completed in early Year 2 of the study. Kessler submitted all required documentation to the FDA to obtain an IND number and approval for the use of drug/placebo and electrical stimulation, as specified in the study protocol. Kessler purchased electrical stimulators for use at the study sites. Local IRB approval at KF was completed. IRB approvals at UoL and JJPVAMC are pending. The Manual of Operation Procedures and the Case Report Forms have also been completed.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Introduction</td>
<td>4</td>
</tr>
<tr>
<td>2. Keywords</td>
<td>4</td>
</tr>
<tr>
<td>3. Accomplishments</td>
<td>4</td>
</tr>
<tr>
<td>4. Impact</td>
<td>7</td>
</tr>
<tr>
<td>5. Changes/Problems</td>
<td>7</td>
</tr>
<tr>
<td>6. Products</td>
<td>9</td>
</tr>
<tr>
<td>7. Participants &amp; Other Collaborating Organizations</td>
<td>9</td>
</tr>
<tr>
<td>8. Special Reporting Requirements</td>
<td>10</td>
</tr>
<tr>
<td>9. Appendices</td>
<td>10</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

This study is a prospective, randomized, double blinded, controlled, multi-site clinical trial to determine the effectiveness of a tri combination Activity-Dependent Rehabilitation Model on improving musculoskeletal gains in men with subacute to chronic SCI who have low serum testosterone levels. A total of 56 research participants will be enrolled across 3 clinical sites: Kessler Foundation Research Center, the University of Louisville-Frazier Rehab and the James J. Peters VA Medical Center (Bronx, NY). Each site will recruit 20 participants over 3 years or 6-7 subjects per year. Eligibility will be determined by the site physician and site PI. Research participants will be randomized into one of four groups: 1) Stand Training only; 2) Stand+Electrical Stimulation; 3) Stand Training+Testosterone; 4) Stand Training+Testosterone+Electrical stimulation. Each research participant will complete 60 sessions of training.

The model involves intense training with testosterone replacement therapy and electrical stimulation on multiple muscles. Our primary focus is to examine the change in muscle, but we will also look at the change in bone. This tri combination Activity-Dependent Rehabilitation Model can easily be adapted to a clinic based model.

2. KEYWORDS

Testosterone, multi muscle electrical stimulation, dynamic standing protocol, muscle volume, MRI, bone mineral density, DXA, QCT scans, blood markers, urine markers, 60 sessions of training, sub acute to chronic SCI.

3. ACCOMPLISHMENTS

- What were the major goals of the project?

Aims of Proposal
The overall aim of this proposal is to determine the interaction of testosterone, ES of multiple leg muscles and stand training or loading (bearing of the body weight) in individuals with sub-acute to early chronic SCI who are wheelchair reliant at least 75% of the time in a phase I/II multi-site randomized clinical trial (n=56, recruited at 3 training sites) on bone and muscle.

Our primary aim is to assess the effects of our novel tri combination Activity-Dependent Rehabilitation model approach on muscle volume of the lower limbs.

Our secondary aims are:

i) To better define the mechanisms that contribute to changes in muscle.
Secondary outcome measures associated with this aim will further assess whether the tri-combination of stand training with TRT and ES will lead to increased muscle strength and contractile elements of muscle as shown by an increase in muscle torque, an increased expression of PGC-1α and its downstream targets in the lower limb and an alteration in myostatin signaling.

Preliminary data from animal studies have shown increased expression of Activin receptor IIB and increased nuclear localization of Smad2 and Smad3 after SCI and that these adverse changes are reversed by androgens. Additional studies will examine mRNA levels for myostatin, its receptor and its inhibitors (e.g., follistatins) and determine nuclear levels of Smad2 and Smad3.

We will also measure resting energy expenditure to confirm that changes in muscles mass correspond to anticipated metabolic effects.

ii) To evaluate the changes in bone and bone structure with Stand Training with TRT and ES.
Secondary outcome measures of this aim will include BMD of the proximal tibia and distal femur; these are the most common sites for fracture and may also respond faster to intervention. Other secondary outcome measures will be BMD at the hip, cortical and trabecular bone with 3-D volumetric measurements, and bone markers for formation and resorption.

- **What was accomplished under these goals?**

In Year 1 we had a significant obstacle where we were informed that Watson Laboratories had been acquired by a company that would not be able to supply drug and placebo - the fill details are described below in Page 4. In addition – the sequential timeline to a positive solution for acquisition of drug/placebo is also explained in Page 5-6. Therefore the major accomplishment in Year 1 was on November 10th, 2015 we received notification from Abbvie that they will provide the drug and placebo at no cost to the study. Drs. Forrest and Bauman contacted Dr. Henry on November 11, 2015 to notify her of our final solution. All of these details are described on Page 4-6.

In year 1 we did accomplish local IRB at Kessler for original protocol but we placed all IRB submissions and resubmissions on hold until we organized a suitable solution for drug acquisition. In Year 2 quarter 1 we received local IRBs at JJPVAMC and Kessler (UoL, pending).

**Specific Aims:**

(1) To examine the effectiveness of stand training with testosterone and electrical stimulation to induce positive changes in muscle volume. **Our secondary aims are:**

i) To better define the mechanisms that contribute to changes in muscle.

ii) To evaluate the changes in bone and bone structure with Stand Training with TRT and ES.

Note we will start **modifying our IRB to show new protocol changes in November/ October 2015.**

<table>
<thead>
<tr>
<th>As per SOW</th>
<th>Timeline</th>
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<tbody>
<tr>
<td><strong>Major Task 1: Adapt TRT to ES protocol: Complete IRB</strong></td>
<td></td>
</tr>
<tr>
<td>Subtask 1: Prepare Regulatory Documents and Research Protocol for Study 1</td>
<td></td>
</tr>
<tr>
<td>Sites for IRB completions submitted</td>
<td>UoL and JJPMC submitted 5/29/15</td>
</tr>
<tr>
<td><strong>Milestone Achieved:</strong> Local IRB approval at Kessler; IRB at UoL, JJPMC is pending after several resubmissions.</td>
<td></td>
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<tr>
<td><strong>Note:</strong> UoL and JJPMC needed to wait for IND number (4/29/1) before submitting to IRB</td>
<td></td>
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**Major Task 2: Training of protocol at Kessler**

<table>
<thead>
<tr>
<th></th>
<th>3-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual of Operations (MOP) and Standard Operating Procedures for TRT and Case Report Forms completed</td>
<td>6/28/14</td>
</tr>
<tr>
<td>Forrest and Harkema trained site PTs on Combination ST+ES.</td>
<td>4/28/15 Kessler UoL</td>
</tr>
<tr>
<td>Dr William Bauman (WB) will train all sites to administer testosterone patch based on Standard Operating Procedures.</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Regular biweekly Conference calls (Kessler, UoL, JJPMC) established to discuss study protocol, training and testing.</td>
<td>Ongoing</td>
</tr>
<tr>
<td><strong>Milestone Achieved:</strong> Kessler and UoL Research staff trained in standing and ES protocol</td>
<td></td>
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- **What opportunities for training and professional development has the project provided?**

Training in Year 1 involved the Kessler PTs working on the Project for preliminary training on using the multi muscle stimulators.
- 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?

In the next reporting period we plan to do the following:

The tasks that we intend to complete in the next year (8.25.16) as per the original SOW submitted are given below.

Note: ***The time line in the SOW (8.25.16) below will be revised in year 2.

<table>
<thead>
<tr>
<th>Major Task 1: Adapt TRT to ES protocol: Complete IRB</th>
<th>Time line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submit amendments, adverse events and protocol deviations as needed</td>
<td>As needed</td>
</tr>
<tr>
<td>Coordinate with Sites for annual IRB report for continuing review</td>
<td>Annually</td>
</tr>
<tr>
<td>Milestone Achieved: Local IRB approval at Kessler, UoL, JIPMC</td>
<td>3 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Task 2: Training of protocol at Kessler</th>
<th>3-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual of Operations will be completed and sent to all sites one month prior to training</td>
<td>80% completed 9.31.15</td>
</tr>
<tr>
<td>Faghi will train all site PI and PTs on Electrical stimulation protocol (ES)</td>
<td>3</td>
</tr>
<tr>
<td>Forrest and Harkema will train all site PIs and PTs on Combination ST+ES</td>
<td>3</td>
</tr>
<tr>
<td>Dr William Bauman (WB) will train all sites on testosterone patch</td>
<td>3</td>
</tr>
<tr>
<td>Forrest, Harkema and Bauman will instruct all sites on protocol description per MOP</td>
<td>3</td>
</tr>
</tbody>
</table>

Milestone Achieved: Research staff trained

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<thead>
<tr>
<th>Major Task 3: Participant Recruitment, Therapy, Participant Evaluation</th>
<th>25-30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtask 1: Data set up with initial subject at each site.</td>
<td></td>
</tr>
<tr>
<td>Coordinate with Sites for all study steps, web data collection and database requirements</td>
<td></td>
</tr>
<tr>
<td>Set up assessment measurements (already established at 2 sites – Kessler, UoL)</td>
<td>4-6</td>
</tr>
<tr>
<td>Milestone Achieved: 1st participant consented, screened and enrolled at all sites</td>
<td>4-6</td>
</tr>
<tr>
<td>Milestone Achieved: At all sites Study begins</td>
<td>4-6</td>
</tr>
<tr>
<td>Begin subject recruitment</td>
<td>4-30</td>
</tr>
<tr>
<td>Screen potential participants</td>
<td>4-30</td>
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<tr>
<td>Evaluate and assign participants to one of the four randomized groups</td>
<td>4-30</td>
</tr>
<tr>
<td>Outcome measures assessment at baseline time frame</td>
<td>4-30</td>
</tr>
<tr>
<td>At all sites: Research participant complete 60 sessions of training frequency of 4 times per week (1.5-hour) followed by post testing and follow up (MRI, DXA)</td>
<td>4-33</td>
</tr>
</tbody>
</table>

Milestone Achieved: Record data for year 1, 2, 3, into ITW database; Report | 4-33 |
4. IMPACT

Nothing to report

5. CHANGES/PROBLEMS

- Changes in approach

No change in protocol in Year 1.

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

During the reporting period there were significant delays associated with acquisition and delivery of drug/placebo. These delays were reported in the quarterly reports. The delays are outlined in detail below:

*As reported in Quarter 1, year 1 report the main problem to address for Quarter 1 in year 1 was that we were informed that Watson Laboratories had been acquired by a company that would not be able to supply drug and placebo for our proposed placebo-controlled RCT. For Quarter Year 2 report 2 (7/14/2015) we proposed a long term solution to the TRT/Placebo issue. For the Year 2, Quarter 1 report we proposed our final solution to the TRT/Placebo issue. All for year 1 is explained below.*

- At the time of submission of our grant, Watson Laboratories had provided a letter of support which stated that this company would provide TRT patch and matching placebo for our study. The support being offered by Watson Laboratories was a continuation of previous collaboration with the company for similar work that was completed by Dr. William A. Bauman, co-principal investigator on the current grant, which addressed the safety and efficacy of TRT patch in a population of persons with chronic spinal cord injury at the James J. Peters VA Medical Center and The Kessler Institute for Rehabilitation, work which was published in *Hormones and Metabolic Research* in 2011. In our Quarter 1, Year 1 report we reported that Watson Laboratories was obtained by Actavis Pharmaceuticals, and management at the new company had informed us that they had decided not to provide study drug for our RCT, nor for any other RCTs at this time. It was inferred that their policy decision was based on a change in philosophy toward research initiatives which took into account the total cost of supplying matching placebo and the assumption of risk for any new study.
After careful consideration and in discussion with Patricia Henry, PhD, Science Officer (discussions: 2/17/2015 and 4/1/2015) Drs. Forrest, Bauman, and Harkema addressed the problem in a satisfactory manner to maintain the study as designed and to make no changes to the SOW.

In Quarter 1, we reported that the FDA approved New York based compound pharmacy “Metro Drugs” would be supplying the drug (Gel) and placebo to the sites, and we provided a letter from the company confirming this agreement. Shortly after we submitted the Quarter 1 report, we were informed by the New York State (NYS) DEA that the only suitable and legal option to supplying drug and placebo to our 3 study sites was FDA approved pharmacy that was located outside NYS because of stringent laws that prohibited the dispensing of any controlled substances by an appropriately licensed NYS pharmacy outside of the state. In actual practice, the testosterone/placebo preparation would be sent by the FDA pharmacy directly to the subjects.

As you may appreciate, identifying a FDA compound pharmacy that has the experience and resources to supply both study drug and placebo, with an appropriate dispensing system in place, was an onerous task, and our main difficulty with initiating this study to date. A pharmacy was located and agreed to provide the investigators with drug and placebo. To do so required the investigators to pay for the cost of topical generic testosterone preparation (at approximately 25% the cost of Androderm) and for a placebo gel. The cost of these preparations had been provided in a previous email, as well as the other associated costs, including those of the cost of dispensing ($10,920), repacking ($6006), and shipping ($24,570), with a total final cost of the pharmacy to provide us with drug/placebo of over $100,000, an expense that were not budgeted prior to Watson Laboratories withdrawing their support for our proposal. Of note, the investigators decided that intramuscular preparations of testosterone were not physiologic (peaks and valleys in pharmacokinetics) and in the SCI population would be associated with a heightened risk of autonomic dysreflexia, potentially a life-threatening complication, if the injection is delivered below the level of lesion; administration of the intramuscular injection above the level of lesion may be associated with pain and discomfort upon transfers, which may limit mobility, reduce drug/placebo compliance, and increase drop-out rates. A total of 56 research participants is proposed to be studied in our proposal.

The source of the drug was Belmar Pharmacies, a licensed non-resident pharmacy (license #30,649) and that is licensed with the DEA. We did supply the letter in the Quarterly report 7/14/15. The pharmacy would have supplied the patient-specific compounded testosterone or placebo, directly to patients based upon a valid prescription. To date, this company had been the only viable option after an exhaustive search of both Clinical Trials.gov and reaching out to other pharmacies. Drs. Forrest and Bauman worked with the company to set up the standard of operation procedures for dispensing the drug/placebo to study participants.

Drs. Forrest and Bauman had been in discussions via email and conference calls (6/9/15; 6/15/15; 6/16/15) with Patricia Henry, Ph.D., Science Officer regarding the potential of additional funds to cover the additional cost of the drug. Based on our discussions, Dr. Henry instructed us to submit a formal request for additional funding (6/18/15).
o Drs. Forrest and Bauman submitted a formal request to the DOD for additional funding on 6/23/15. **Please see letter in report dated 7/14/15.**

o Of note - In January 2015, the investigators submitted a request to Abbvie to provide testosterone gel and matching placebo for our study. We considered this “option” to be a real possibility, albeit somewhat unlikely if one considers the length of time that our request had languished without resolution. However, our proposal continued to be actively considered. We suggested in our previous quarterly report (7/14/2015) if this company approved our request, then the investigators would proceed with the clinical trial without the need for additional financial support from the DoD.

o Fortunately, in November 10th, 2015 we received notification from Abbvie that they had agreed in principle to provide the drug and placebo at no cost to the study. Drs. Forrest and Bauman contacted Dr. Henry on November 11, 2015 to notify her of our final solution. Dr. Henry had requested that Dr. Forrest submit a revised SOW (attached) to Dr Henry on 11/23/15. Based on the revised SOW – we have amended the protocols at all institutions to comply with our proposed changes in drug formulation (e.g., patch to gel application), dosage, and origin of agent/placebo.

o Note: At end of Quarter 2, Year 2 Abbvie Inc have manufactured drug/placebo at no cost to the grant. Final contractual agreement between Kessler Foundation and Abbvie is currently being signed (4/24/16). All details associated with shipping of drug to each site, storage of drug, administration have been addressed in Q2, Year 2.

- **Changes that had a significant impact on expenditures**

  Because of the unanticipated delay in our obtaining of drug/placebo, we have not spent the projected funds for Year 1. **These details were outlined both in our financial and quarterly reports.**

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

    No significant change to human subjects

6. **PRODUCTS**

None to report

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

None to report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **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 individuals have worked on the project?

In the year 1 period individuals’ have worked primarily on setting up the protocol, IRB submissions, Manual of Operation Procedure (MOP) and Case Report Forms (CRF).

**Overall Submitting PI:** Gail F Forrest Ph.D.
**Co- PI:** William Bauman Ph.D.

**Individuals that have worked for at least 1 month (~160 hrs) in year 1.**

Name: Milda Woods  
Project Role: Study Coordinator, consultant  
Nearest person month worked: 2.7months  
Contribution to Project: Ms. Woods has worked continually with Dr Forrest in year 1:  
  i) in setting up initial IRB applications, approvals and resubmission of IRB forms for continual approvals at Kessler  
  ii) on all documents for submission and resubmission for FDA IND approval  
  iii) on all documentation for Abbvie Inc submission approval process,  
  iv) on all case report forms for subject binders for all site and Manual of Operations to be used at all sites.

• What other organizations have been involved as partners?

<table>
<thead>
<tr>
<th>Site 2: University of Louisville (UoL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frazier Rehab Institute</td>
</tr>
<tr>
<td>220 Abraham Flexner Way, Suite 1506</td>
</tr>
<tr>
<td>Louisville, KY 40202</td>
</tr>
<tr>
<td>Site PI: Susan Harkema Ph.D.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site 3: James J. Peters VA Medical Center (JJPVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 West Kingsbridge Road</td>
</tr>
<tr>
<td>Bronx, NY 10468</td>
</tr>
<tr>
<td>Site PI: Ann Spungen, EdD.</td>
</tr>
<tr>
<td>William Bauman.</td>
</tr>
</tbody>
</table>

In year 1 UoL and JJPVA worked on their IRB submission. IRB approval pending.

• 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

8. **SPECIAL REPORTING REQUIREMENTS**

QUAD CHARTS submitted in appendices

9. **APPENDICES**

PIs Bio has been included.
BIOGRAPHICAL SKETCH

NAME: Gail F Forrest
eRA COMMONS USER NAME: gfforrest

POSITION TITLE: Associate Director, Human Performance and Engineering Research (HPER).

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bachelor of Applied Science RMIT, Melb., Australia</td>
<td>B. App. Sc.</td>
<td>1979</td>
<td>Mathematic/Computing</td>
</tr>
<tr>
<td>Temple University, Philadelphia</td>
<td>Ph.D.</td>
<td>1/2001</td>
<td>Biomechanics</td>
</tr>
<tr>
<td>Post Doctoral Fellow, Kessler Foundation</td>
<td></td>
<td>1/2001-12/2002</td>
<td>Biomechanics</td>
</tr>
</tbody>
</table>

A. Personal Statement
I am currently an Associate Professor of Physical Medicine & Rehabilitation Rutgers New Jersey Medical School, Rutgers, NJ, an Assistant Director of the Human Performance and Engineering Laboratory, an Affiliated Faculty Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ, Member of the Graduate Faculty in Biomedical Science, University of Medicine and Dentistry of New Jersey, Newark, NJ. I am currently funded by multiple grants from the National Institute on Disability and Rehabilitation Research (NIDRR), Christopher and Dana Reeve Foundation, Department of Defense, Craig H. Neilson Foundation and New Jersey Commission on Spinal Cord Research. Much of my research and grant funding is directed towards understanding neurological and musculoskeletal and neurological recovery for individuals following spinal cord injury (SCI). This grant is focused directly at understanding the musculoskeletal gains of tri combination activity based rehabilitation intervention to improve musculoskeletal gains in men with subacute to chronic SCI with low circulating testosterone levels.

B. Positions and Honors.

1.1.1 Positions and Employment

Prior to 1989 Mathematics and Computer Science Senior Level Teacher, Australia.
1989-1992 Corporate Consultant to Four Season Hotels (Daikyo Corporation), Australia and Japan.
1991-1992 Victoria University, Melbourne, Australia, Grad Dip. Biomechanics
1995-1997 Teaching Assistant - Human Anatomy and Biomechanics, Temple University.
1997-1998 Biomechanics Lecturer and Coordinator, Temple University.
1998-1999 Teaching Assistant – Physiology, Biomechanics, and Anatomy, Temple University
2000-2002 Post Doctoral Fellow, Kessler Medical Rehabilitation Research and Education Corporation, West Orange, NJ.
2003-2007 Research Scientist II, Kessler Medical Rehabilitation Research and Education Corporation, West Orange, NJ.
2007-2012 Interim Director, HPMAL, Kessler Foundation Research Center, West Orange, NJ.
2007- Date Kessler site Director of the NeuroRecovery Network.
2012-2014 Assistant Director Human Performance Engineering Laboratory, Kessler Foundation.
2012-Present Director Neuroplasticity Laboratory.
2014-Present Associate Director Human Performance Engineering Laboratory, Kessler Foundation.

University Appointments

5/2000-9/2000 Adjunct Professor Biomechanics, Physiology, – Temple University, University of Pennsylvania
1/2001-6/2005 Instructor, University of Medicine and Dentistry of New Jersey / New Jersey Medical School
7/5/05-present Assistant Professor University of Medicine and Dentistry of New Jersey/New Jersey Medical Sc.
2011-Date  Affiliated Faculty Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ
2012- Date  Member of the Graduate Faculty in Biomedical Science, University of Medicine and Dentistry of New Jersey, Newark, NJ.
2013 –Date  Associated Professor of Physical Medicine & Rehabilitation. Rutgers New Jersey Medical School. Rutgers, the State University of New Jersey

Other Professional Experience

1999 - 2000  Research Assistant Dynamic Control of Head Stability, Agency NIH/NIA (RO3); (Ronita Cromwell, Ph.D., Principal Investigator)
2001 - present  Institutional Review Board Member Kessler Foundation
2004 - present  Reviewer for Journal of Neuroengineering and Rehabilitation
2005 - present  Reviewer of Journal of Rehabilitation Research and Development
2005 - present  Reviewer of Journal of Spinal Cord Medicine
2005 - present  Compliance Committee member (subcommittee of IRB)
2005 - present  Committee member for ACRM International task force
2005 - present  Reviewer, RESNA
2009 -present  Adhoc Reviewer NIH (2014/10 ZRG1 BBBP-Y (05),
2013-2014  Motor Function, Speech and Rehabilitation (MFSR) Study Section).
2012-present  Reviewer for Craig H Neilson Foundation
2013-present  Reviewer for Gait and Posture.
2015-2021  Reviewer NIH grants, Permanent study member Motor Function and Rehabilitation Study Section

C. Selected peer-reviewed publications (2012-2015)
Abstracts (2012-2015)


12. **Forrest GF**. (2014, July). Simulation of muscle work during hip/knee exoskeleton-assisted Gait. Presented at the 7th World Congress of Biomechanics, Boston, MA.


We propose that the combination of interventions of the exoskeleton assisted walking (EAW) with transcutaneous lumbosacral stimulation (TLS) would increase the excitability of the cord and afferent input when training in the exoskeleton to increase lower extremity muscle firing and to functionally increase walking speed.

International and National Symposiums (2012-2015)


Ongoing Research Support.

Rehabilitation Engineering Research Centers (RERC) Forrest (project PI) 7/1/2015 – 12/31/2020

National Institute on Disability, Independent Living and Rehabilitation Research Site Project: Exoskeleton and spinal cord stimulation for SCI:

We propose that the combination of interventions of the exoskeleton assisted walking (EAW) with transcutaneous lumbosacral stimulation (TLS) would increase the excitability of the cord and afferent input when training in the exoskeleton to increase lower extremity muscle firing and to functionally increase walking speed.
Testosterone combined with Electrical Stimulation and Stand Retraining.
A Phase I/II prospective, randomized, double blind, controlled, multi-site clinical trial where the primary aim is to
determine the neurological and neuromuscular interaction of testosterone, neuromuscular stimulation of multiple lower
limb muscles and loading in individuals with sub acute to early chronic SCI who are non ambulatory. Ultimately we are
interested in recovery of muscle and bone and the effect on functional motor gain for chronic SCI.

Christopher Dana Reeves Foundation.

BIG Idea Project: Recovery of Autonomic control of cardiovascular and bladder function and the ability to stand
and voluntary leg control movements below the level if injury with epidural stimulation
The objective of the project is to test the hypotheses related to neural control of human movement and cardiovascular
function after human spinal cord injury while also obtaining knowledge for optimizing spinal cord epidural stimulation
(scES) as a therapeutic intervention that can be immediately translated to larger numbers of patients who now have no
treatment options for the secondary consequences of spinal cord injury.

SC140099 Department of Defense PI Bloom; Site PI Forrest 9/1/2015-8/30/2018
USAMRAA/CDMRP/Department of Defense

Biomarkers of Spontaneous Recovery from Traumatic Spinal Cord Injury
The objective is to test the hypothesis that levels of some inflammatory biomarkers correlate inversely with functional
recovery throughout the first year after spinal cord injury (SCI). The project specific aims are to (1) identify the circulating
inflammatory response in patients with SCI, (2) determine the trajectory of spontaneous functional recovery in patients
with SCI, and (3) derive a predictive, multiscale model of functional recovery after SCI.

W81XWH-14-2-0170 PI Spungen – Site PI Forrest 9/1/2014-8/30/2017
USAMRAA/CDMRP. Department of Defense

A Randomized, Crossover Clinical Trial of Exoskeletal-Assisted Walking to Improve Mobility, Bowel Function,
and Cardiometabolic Profiles in Persons with SCI*
The primary objectives of this research is to document how long it will take to reach functional gains, such as speed and
distance after 36 sessions of training with these devices. Preliminary studies support the goals that walking in the
exoskeletons will improve bowel function and body composition.

CSCR14ERG007 Pilkar (PI) Forrest (Co-I) 10/17/2014-9/16/2016
New Jersey Commission on Spinal Cord Research

Development of Signal Processing Toolbox for Assessing Neuromuscular Response during Electrical
Stimulation.
The goal of this study is to develop a robust signal processing algorithm to extract EMG during ES and study the
physiological significance of ES on neuromuscular properties of the stimulated muscle. The outcomes of this study will
help in understanding the direct effects of ES on muscles by getting access to high quality EMG during ES and help the
clinician or researcher to modify and optimize FES training paradigms based on the target muscle response. This could
have a major impact on the field of spinal cord injury research and rehabilitation

Parker Hannifan Site Forrest 10/17/2014-9/16/2016
Indego® Exoskeleton; Assessing Mobility for Persons with Spinal Cord Injury (SCI).
*Two separate protocols are under the one title; *PH-INDO1 (FDA) and *PH-INDO2 (Exploratory)
Description of Project:
The purpose of this project is to evaluate if the Indego® robotic device is both safe and effective at allowing persons with
SCI who are non-ambulatory or poorly ambulatory to stand up and walk under a variety of conditions; indoor surfaces,
outdoor surfaces, elevators, managing doorways, different seat heights and extended distances.

CSCR13IRG013 Forrest (PI) 6/17/2013-6/16/2017
New Jersey Commission on Spinal Cord Research

Non-ambulatory SCI walk using a Robotic Exoskeleton: Effect on bone and muscle
The overall purpose of this pilot study is to assess if 5 hours per week for 20 weeks of exoskeleton-assisted walking over
ground for persons with chronic SCI will positively affect the musculoskeletal system. In addition we will evaluate
the human neuromuscular and mechanic reposne to the robot.

NJCSCR13FEL009 Forrest (Co-I) 10/17/2014-9/16/2016
New Jersey Commission on Spinal Cord Research

Quantitative Measure of Force During Electrical Stimulation: An Exploratory Study
Non-ambulatory SCI walk using a Robotic Exoskeleton: Effect on bone and muscle
The overall purpose of this pilot study is to assess the muscle activation, 3D forces and moments generated at the knee during ES induced contraction during standing for motor complete SCI. Mentor: Forrest GF
Mehmed Bugrahan Bayram (PI)

H133N110020 Forrest (Co-PI) 10/01/2011 – 9/31/17

NIDRR Models Systems Primary Research Project
Restoring Lost Functions after Spinal Cord Injury: Combination Therapy with Dalfampridine and Locomotor Training for Persons with Chronic, Motor Incomplete Spinal Cord Injury.
The primary purpose of this National Institute on Disability and Rehabilitation Research funded project is to examine the effect of combination of Dalfampridine and Locomotor Training on walking distance and musculoskeletal system.

1R21NS095052-01A1 Jiang T (PI) Forrest (Co-I) 04/01/2016-3/31/2017
NINDS. Major goal is to complete Longitudinal Assessment of Spinal Cord Structural Plasticity using DTI in SCI Patients

CSCR15ERG013NJC: Jiang T (PI) Forrest (Co-I) 6/29/2015-6/30/2017
New Jersey Commission on Spinal Cord injury
The major goal is assessing Spinal Cord Structural Changes using Diffusion Tensor imaging in Patients with Incomplete Traumatic Spinal Cord Injury

191152 Forrest (PI) 7/1/2014 – 1/31/2015

Craig H Neilson Foundation
Activity-Dependent Rehabilitation Model to improve Bone and Muscle after SCI.
Note – this is a no cost extension of the original grant ($250,000)
The purpose is to assess the musculoskeletal gains in individuals with subacute to chronic SCI, with bone mineral density as the primary outcome variable and volumetric measures of bone, bone markers for reabsorption and absorption, muscle volume and muscle expression of PGC-1α as secondary outcome measures.

143298 Forrest (Co-PI) 01/01/2007 – 12/31/2017
NIDRR
Advanced Rehabilitation Research and Training Center (ARRTC) on Neuromusculoskeletal Rehabilitation Post-Doctoral Training Grant.
The purpose of this NIDRR funded ARRT project is to provide research training and experience at an advanced level to individuals with doctorates or similar advanced degrees who have clinical or other relevant experience.

SC090246 Behrman (PI) Forrest (Co-I) 10/1/2012-9/30/2016
Department of Defense/University of Florida
A new measure of neurological and behavioral recovery after SCI
The major goal of this project is to Assess the responsiveness of the Phase System for evaluating recovery from SCI over the period of 1) in-patient rehabilitation (sub-acute SCI) receiving usual care and 2) outpatient rehabilitation (chronic SCI) while receiving an intense, activity-based therapy.

07-3063-SCR-E-0 Forrest (Co-PI) 01/01/207 – 1/31/2017
Center For Disease Control and Christopher Dana Reeves Foundation NeuroRecovery Network grant.
The major goal of this project is to develop specialized centers that provide standardized activity-based therapy care based on current scientific and clinical evidence for people with SCI and other selected neurological disorders.
BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: BAUMAN, William A, MD

eRA COMMONS USER NAME (credential, e.g., agency login): WBAUMAN

POSITION TITLE: Professor of Medicine and Rehabilitation Medicine; Director, Center for the Medical Consequences of SCI, Co-Investigator

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>Completion Date</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard College, Boston, MA</td>
<td>B.A.</td>
<td>06/1972</td>
<td>English</td>
</tr>
<tr>
<td>State University of New York, Downstate College of Medicine, New York, NY</td>
<td>M.D.</td>
<td>06/1976</td>
<td>Medicine</td>
</tr>
</tbody>
</table>

2 A. Personal Statement

Since 1990, as Director of the Spinal Cord Damage Research Center, my career has been directed to better define the medical complications of spinal cord injury (SCI). Once these adverse conditions have been more clearly defined, our investigators have intervened to reduce their detrimental impact or to prevent their occurrence. Early in my career, I first described the high prevalence of diabetes, insulin resistance, and adverse changes in lipid profiles in the SCI population, as well as the rapid loss of bone after acute paralysis and subsequent immobilization osteoporosis. The success of my research and my continued dedication to addressing the needs of individuals with SCI led to my establishing the VA RR&D’s National Center of Excellence for the Medical Consequences of SCI in 2001, and I have served as the Center’s Director since its inception. I was Chairman of the VA Cooperative Study entitled “Anabolic Steroid Therapy on Pressure Ulcer Healing in Persons with Spinal Cord Injury (CS #535),” with the primary manuscript published in the Annals of Internal Medicine. Currently, I am Co-Chairman of a VA Cooperative Study entitled “Exoskeletal-Assisted Walking in Persons with SCI: Impact on Quality of Life (CS #2003).”

My efforts have resulted in over 300 peer-reviewed papers, book chapters, and review articles, which have led to nationwide changes in the care of persons with SCI. My work has been honored with multiple awards and invited lectures in the fields of endocrinology and SCI Medicine and Rehabilitation Medicine: Excellence Award from the American Paraplegia Society for outstanding leadership and accomplishments in SCI health care in 2002; Paul B. Magnuson Award from the VA’s RR&D Service, its highest service award, in 2005; the 31st G. Heiner Sell Memorial Lectureship at the Annual Scientific Meeting of the American Spinal Injury Association in 2012; the Donald Monro Lecture at the 2013 Annual Meeting of the American Society of Spinal Cord Injury Professional; the prestigious Samuel J. Heyman Service to America Medal in Science and Environment in 2014.

3 B. Positions and Honors

3.1 Positions and Employment

1982 – 1987 Associate Professor of Medicine, Albert Einstein College of Medicine, Bronx, NY
1983 – 1985 Attending Consultant, Department of Medicine, VA Medical Center, Bronx, NY
1985 – 1989 Physician/Research Associate, Solomon A. Berson Research Laboratory, VA Medical Center, Bronx, NY
1987 – 1989 Associate Professor of Medicine and Rehabilitation, Mount Sinai School of Medicine, New York, NY
1989 – 2003 Director, Spinal Cord Damage Research Center, Mount Sinai Medical Center, New York and VA Medical Center, Bronx, NY
1996 – Present Professor of Medicine, Mount Sinai School of Medicine, New York, NY
1996 – Present Professor of Rehabilitation Medicine, Mount Sinai School of Medicine, New York, NY
2001 – Present Director, VA Rehabilitation Research & Development Center of Excellence for the Medical Consequences of Spinal Cord Injury, James J. Peters VA Medical Center, Bronx, NY
3.2 Other Experience and Professional Memberships

1976 – 1977 Medical Internship, New York University Medical Center, New York, NY
1977 – 1979 Medical Residency, Montefiore Hospital & Medical Center, Bronx, NY
1979 – 1980 Endocrine Fellowship, VA Medical Center, Bronx, NY
1980 – 1982 Endocrine Fellowship, Montefiore Medical Center, Bronx, NY
1982 – 1985 NIH SERCA Recipient, Attending, Departments of Medicine and Endocrinology & Clinical Sciences, Montefiore Medical Center, Bronx, NY

3.3 Honors

1972 Honors graduate in English Literature, Harvard University
1982 Recipient of NIH Special Emphasis Research Career Award
1994 Excellence in Medical Research, Medical Service, VA Medical Center, Bronx, NY
2001 William Dock Award for outstanding teaching ability in Internal Medicine/Endocrinology
2002 Excellence Award in Research (American Paraplegia Society)
2005 Paul B. Magnusson Award, VA RR&D Service
2014 Medalist, Samuel J. Heyman Service to America Award, Science & Environment

4 C. Contribution to Science

1. Osteoporosis and fractures present a major problem for persons with SCI. My contributions include defining calcium metabolism and bone disease in persons with SCI. Our publications first suggested a high prevalence of vitamin D deficiency in persons with SCI and proposed an approach for vitamin D replacement therapy. Despite literature that suggested a value to bisphosphonate therapy in those with SCI, possibly because of the work conducted in those with varying completeness of lesion, our work has demonstrated the limited efficacy of bisphosphonates administration in persons with acute complete motor SCI, necessitating the search for more effective therapeutic approaches. Our work in monozygotic twins, discordant for SCI, has suggested that bone loss continues for decades after initial injury, a new and controversial finding. We have shown that bone mass below the level of lesion is directly associated to body fat, and also directly correlated to the serum estradiol levels. Our group has provided evidence of the cellular, biochemical, and molecular effects of paralysis due to SCI or nerve transaction on bone.


2. Although it would appear intuitive that individuals who have adverse body composition and reside at the lowest end of the activity spectrum would have metabolic problems which predispose to cardiovascular disease, prior to our group's entrance to the field, little had been reported in the literature. My contribution has been to be the first investigator to systematically study carbohydrate and lipid metabolism in persons with SCI and suggest that the abnormalities observed would be anticipated to predispose to premature cardiovascular disease. Prior to this work, it was unclear that persons with SCI had disorders of carbohydrate metabolism, which has since been characterized by a high prevalence of carbohydrate intolerance and diabetes mellitus. The finding of low high-density lipoprotein (HDL) cholesterol in those with SCI was observed by our group and subsequently confirmed by others. By nuclear medicine technology and electron beam computerized tomography, publications demonstrated the likelihood of premature atherosclerotic disease in those with SCI. Recently, we have reported on the blunted action of insulin on the sublesional microvascular.

Persons with SCI immediately lose muscle and gain fat after injury. Our contribution to body composition in persons with SCI has been to compare various methodologies to determine body adiposity, develop or apply innovative methodologies, define body composition changes after acute and in chronic injury, and more clearly delineate the relationship of body composition to metabolic derangements. A portion of this work, which was performed in monozygotic twins, one in each pair discordant for SCI, and in cross-sectional studies that have served to define changes in soft tissue mass over decades of life in persons with SCI, has improved our general knowledge in this area of study. The loss of muscle in those with chronic SCI occurs at an accelerated rate both above and below the level of lesion, suggesting a global, or systemic hormonal, process. Depressed levels of anabolic hormones (testosterone and growth hormone/insulin-like growth factor) may partially explain the general adverse changes in soft tissue body composition in individuals with chronic SCI, which we demonstrated to be depressed in younger individuals with SCI. In our preclinical articles, the influence of androgens on muscle mass and signaling pathways after SCI or nerve transection has been described, as well as the antagonistic effect of androgens on the catabolic effect of glucocorticoids on muscle.


Other than some of my above noted contributions to the endocrinology & metabolism of persons with SCI, my contribution to Spinal Cord Medicine have been wide in scope in both the clinical and pre-clinical areas. In clinical medicine, my publications have been in the following areas: GI motility of the esophagus, stomach, small intestine, and, especially, the colon, with interventions to improve colonic motility and evacuation, including the novel drug combination of neostigmine plus glycopyrrolate, and strategies to improve cleansing preparation for elective colonoscopy; identifying for the first time obstructive airway disease in persons with SCI and interventions to improve function, defining restrictive airway disease in persons with complete motor SCI and strategies to improve respiratory muscle strength; defined cardiovascular autonomic dysregulation in persons with SCI and interventions to improve hemodynamics, as well as the association of cognitive deficits associated with hypotension; pressure ulcer energy requirements, healing, and intervention to heal the wound. Our work has reported the mechanics and benefit of exoskeletal-assisted ambulation.


4.1 Complete List of Published Work in My Bibliography: http://www.ncbi.nlm.nih.gov/sites/myncbi/18Wf9J7w8ZFA/n/library/47313079/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

# VA RR&D #B9212-C Bauman (PI) 07/01/11-06/30/16

National Center Grant $450,000

Center of Excellence for the Medical Consequences of Spinal Cord Injury
To improve health and quality of life in five major program areas: (1) endocrine & metabolic, (2) pulmonary, (3) GI, (4) cardiovascular autonomic, and (5) molecular-musculoskeletal.

Role: Director/Principal Investigator
Grant # 297267     Bauman (PI)
07/01/14 – 06/30/17
Craig H. Neilsen Foundation
$598,818
Title: Prevention of Bone Loss after Acute Spinal Cord Injury
Denosumab will be tested to prevent bone loss in persons with acute/subacute SCI.
Role: PI

VA RR&D #B1392-P     Bauman (PI)
07/014 – 06/16
Merit Review
$199,957
Title: Insulin Resistance and Microvascular Blood Flow in Spinal Cord Injury
In healthy persons with chronic SCI, to determine the effect of insulin to induce vasodilatation of the microvasculature above and below the level of lesion compared to that of heat or other medications.
Role: PI

VA CSP #2003     Bauman & Spungen (Co-Chairman)  10/01/15-
9/30/20
VA CSR&D
$22,000,000
Exoskeletal-Assisted Walking in Persons with SCI: Impact on Quality of Life
To demonstrate that Veterans with chronic SCI plus an exoskeletal-assisted walking device in their home and community environments will have clinically meaningful improvements in QOL measures, including those of the MCS/VR-36 and SCI-QOL bladder, bowel, and pain item banks.
Role: Co-Investigator

Federal #B1313-R     Qin (PI)
10/01/14 – 9/30/18
VA RR&D Service
$885,291
Title: Sclerostin Antagonism and the Osteocyte’s Role: Prevention of Bone Loss
To determine the ability of anti-sclerostin antibody to preserve bone integrity after acute SCI, and to test whether impairment of osteocyte function is one mechanism by which SCI causes bone loss, and whether restoration of normal osteocyte function after anti-sclerostin antibody can prevent or reverse bone loss.
Role: Co-Investigator

VA RR&D #B8048R     Qin (PI)
09/01/13 – 08/31/16
IIR Merit Review
$621,488
Title: FES and Androgens in Bone Loss after SCI: Synergistic Effects and Mechanisms
In a rat model of acute SCI, to determine the ability of mechanical intervention (functional electrical stimulation) or testosterone administration to reduce or prevent bone loss.
Role: Co-Investigator

CDMRP #11235809     Forrest (PI)
9/01/14-8/30/17
Department of Defense CDMRP
$984,976
Title: Testosterone Combined With Electrical Stimulation & Standing: Effect on Muscle and Bone
In collaboration with Kessler, to test whether standing with or without muscle electrical stimulation with testosterone/placebo will improve muscle mass and bone mass.
Role: Co-PI

#CSCR13IRG013     Forrest (PI)
05/17/13 – 03/30/16
New Jersey State Commission
$239,193
Title: Non-ambulatory SCI Walk Using a Robotic Exoskeleton: Effect on Bone and Muscle
In collaboration with Kessler, to test whether exoskeletal ambulation improves muscle and bone.
Role: Co-Investigator
Grant # 284196  Wecht (PI)
03/01/14 – 02/28/17
Craig H. Neilsen Foundation
$593,179
Title: Blood Pressure, Cerebral Blood Flow and Cognition in SCI
To assess the relationships among systemic blood pressure, cerebral blood flow, & cognition in tetraplegia.
Role: Co-investigator

CSCR13IRG018  Wecht & Chiaravolloti (PIs)
06/01/13 – 05/30/16
New Jersey Commission on Spinal Cord Research  $596,954
Title: Impact of Age on Cardiovascular, Cerebral Vascular and Cognitive Health in Spinal Cord Injury
To determine the relationships among blood pressure, cerebral blood flow, and cognition will be determined in persons with spinal cord injury over a range of ages and compared to older, able-bodied individuals.
Role: Co-Investigator

#B1925-P  La Fountaine (PI)
06/2015 - 05/2017
VA RR&D  SPIRE
$200,000
Title: An Open-Label Safety and Efficacy Trial of Fenofibrate in Persons with SCI
To test the use fenofibrate, a PPAR-α agonist, to lower concentrations of triglyceride-rich lipoproteins and that of other lipid particles in persons with SCI.
Role: Co-Investigator

1 I21 RX001734-01A1  Handrakis
06/01/15 – 05/31/17
RR&D Service  $196,289
Title: Effect of Heat Exposure on Cognition in Persons with Tetraplegia
To determine the effect of mild hyperthermia on the ability of persons with tetraplegia to perform cognitive tasks will be determined.
Role: Co-Investigator

1 I21 RX001734-01A1  Handrakis
06/01/15 – 05/31/17
RR&D Service  $168,274
Title: Thermoregulation and Cognition during Cool Ambient Exposure in Tetraplegia
To determine the change in core body temperature and cognitive performance (attention, memory, processing speed, executive function) in persons with tetraplegia.
Role: Co-Investigator

1 I21 RX001915-01  Korsten
06/01/15 – 05/31/17
RR&D Service  $193,849
Title: Bowel Biofeedback Training to Improve Bowel Function in Individuals with SCI
To determine the functional bowel phenotype based on anorectal high-resolution manometry findings in individuals with incomplete motor SCI, and to compare these findings with findings of able-bodied individuals with normal bowel function.
Role: Co-Investigator

1 I21 RX001910-01  Schilero
08/01/15 – 07/31/17
RR&D Service  $193,849
Title: The Effect of an Oral Beta-2 Agonist on Respiratory Muscle Strength in SCI
To determine in individuals with cervical (C3-C8) and high thoracic (T1-T6) SCI who have moderate to severe respiratory muscle weakness (baseline MIP < 90 cmH2O) whether 16-weeks of treatment with an oral beta-2 agonist improves surrogate indices of respiratory muscle strength and cough.
Role: Co-Investigator