Orthopaedic Section of the APTA
Grant Program
Annual Progress Report Form

Date: April 15, 2009

Name of Investigators: Todd E. Davenport, PT, DPT, OCS; Kornelia Kulig, PT, PhD; Beth E. Fisher, PT, PhD

Name of Grant: ANKLE MANUAL THERAPY FOR INDIVIDUALS WITH POST-ACUTE ANKLE SPRAINS: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Award Period: June 2008 to June 2010 (Initial award date is the date that the award was made to your institution)

Current Year of Award completed (circle one): 1st, 2nd, no-cost extension year (3rd)

Progress reports are due no later than 1 year plus 10 days after the initial award date. Failure to submit a timely progress report may result in the termination of your award.

1. Summary of accomplishments in the past year:
    - Completed the manual of procedures for randomized clinical trial (Experiment #1) and pre-clinical transcranial magnetic stimulation study (Experiment #2)
    - Acquired study personnel for Experiment #1 and #2
    - Recruit clinical sites and clinic coordinators for Experiment #1 and #2
    - Purchased equipment for Experiment #1 and #2
    - Standardized investigational therapists for Experiment #1 and #2
    - Standardized study procedures for Experiment #1 and #2
    - Repeated feasibility study for Experiment #2 in n=1 subject with post-acute ankle sprain
    - Obtained Institutional Review Board approval for Experiment #1 (Appendix 1) and Experiment #2 (Appendix 2)
    - Registered Experiment #2 with www.clinicaltrials.gov (NCT00847769)
    - Completed and submitted methodology paper for Experiment #2

2. Provide a one-paragraph summary of results or abstract suitable for posting on the Orthopaedic Section website.

BACKGROUND: Up to 2 million ankle sprains are reported annually. Although the prognosis for functional recovery in individuals with ankle sprains is generally favorable, a subgroup of individuals with ankle sprains is predisposed to continued pain and additional incidence of re-injury. Limited ankle mobility is associated with an elevated risk for ankle sprains. Therefore, some individuals with ankle sprains may benefit from graded mobilization to address ankle mobility deficits that may predispose them to future sprains. However, the clinical effects of graded mobilization have yet to be convincingly demonstrated as part of a comprehensive physical therapy rehabilitative program. In addition, the mechanism of observed clinical improvements remains unknown. **PURPOSES:** (i) Determine the effects of thrust and non-thrust ankle manual therapy procedures combined with a home exercise program on lower extremity dysfunction in individuals with post-acute ankle sprains (Experiment #1), and (ii) Document the effect of ankle manual therapy procedures on corticospinal in patients with post-acute ankle sprains (Experiment #2). **DESIGN:** Randomized, placebo-controlled multicenter clinical trial. **METHODS:** In **Experiment #1,** subjects (n=189) with post-acute ankle sprains who meet inclusion and exclusion criteria will be recruited to participate from multiple clinical sites. After informed consent is obtained, subjects will receive baseline measures from a blinded investigator, including the demographic questionnaire, lower extremity dysfunction indices, and a standardized physical examination. Subjects subsequently will be randomized to receive talocrural long-axis thrust procedure (n=63), talocrural long-axis traction mobilization (n=63), or hands-on control intervention (n=63), followed by a range of motion exercise. Study-related intervention will be provided over 5 visits during a 4-week period, with 2 visits occurring during the first week and 1 visit weekly for the subsequent 3 weeks. Manual therapy procedures will be provided during the first 2 visits, and subjects will receive instruction in a standardized exercise program during the final 3 visits. After the 5th visit, patients and clinicians will be free to pursue any additional treatments of choice. Post-treatment measurement will occur at 4 weeks, 6 months, 1 year, and 2 years following enrollment, involving re-administration of the demographic and disability questionnaires. In **Experiment**

#2, subjects (n=18) with post-acute ankle sprains who meet inclusion and exclusion criteria will be recruited to participate. After informed consent is obtained, subjects will receive baseline measurements, consisting of transcranial magnetic stimulation over the tibialis anterior and gastrocnemius somatotopic representation while recording from each respective muscle, star balance excursion lower extremity reach test, and ankle dorsiflexion range of motion measurement. From standardized and blinded examiners. Following baseline measurements, patients will be randomized to receive either talocrural long-axis thrust procedure (n=9) or talocrural long-axis traction mobilization procedure (n=9) from a standardized and blinded investigator. Baseline measurements will then be repeated. **INTERIM RESULTS:** For **Experiment #1**, a multicenter cohort of investigative clinicians has been recruited and standardized, consisting of n=42 physical therapists (19 women) in n=18 clinics across n=4 states. All study investigators have achieved criterion level of standardization for study-related examination and intervention, and are prepared to begin enrollment. For **Experiment #2**, a pilot study confirmed the study methodology and data analysis are feasible in the study sample. **CONCLUSION:** Preliminary work to develop study infrastructure and establish feasibility will support ongoing subject enrollment and data collection.

3. Attach a list of your publications published or accepted during the past year, or currently being written. Send reprints when available. List presentations made and abstracts accepted for presentation based on this work. Indicate with an asterisk (*) those publications supported by Orthopaedic Section funding.

   * Fisher BE, Davenport TE, Kulig K, Wu AD (2009). Identification of potential neuromotor mechanisms of manual therapy in patients with musculoskeletal disablement: rationale and description of a clinical trial. BMC Neurology, in press.

4. Provide a budget, using the original approved budget. Indicate total funds spent to date per major categories. If there was $\geq$ 25% deviation (greater or less spent) of use of funds for any of the budget category, please BRIEFLY indicate the rationale.

   Please see attached budget (Appendix 3).

5. Objectives for the next year:

   - Recruit subjects with post-acute ankle sprains at all participating clinical sites
   - Begin enrollment of 189 subjects across participating clinical sites for randomized clinical trial (Experiment #1)
   - Begin enrollment of 18 subjects for pre-clinical TMS study (Experiment #2)
   - Continue recruitment and retention efforts through periodic conference calls and emails to clinic coordinators
   - Analyze short-term data to ensure the safety of the procedures under study
   - Register Experiment #1 with www.clinicaltrials.gov
   - Complete and submit methodology paper for Experiment #1
   - Analyze initial data to ensure the accuracy of initial sample size calculations

Your Signature

April 15, 2009

Date

Return to:

Tara Fredrickson, Executive Associate
Orthopaedic Section, APTA, Inc.
2920 East Avenue South, Suite 200
LaCrosse, WI 54601-7202

Appendix 1. NOTIFICATION OF RENEWAL OF IRB APPROVAL FOR EXPERIMENT #1

November 14, 2008

Dr. Todd Davenport
Long School of Pharmacy & Health Science
Physical Therapy

Re: IRB Review of Continuing Project #08-45

Dear Dr. Davenport:

Your proposal for a continuing project, entitled "Ankle Manual Therapy for Individuals with Post-Acute Ankle Sprains: A Randomized, Placebo-Controlled Trial," has been approved.

This approval is good for one additional calendar year, through November 30, 2009. If you are not finished with data collection by that time, we request that you file another renewal form prior to the new deadline.

If you have any questions, please feel free to contact me at 209-946-7367.

Best wishes for continued success.

Sincerely,

Carol Brodie
Manager, Research Administration & Compliance

Appendix 2. NOTIFICATION OF IRB APPROVAL FOR EXPERIMENT #2

Proposal #HS-08-00192

University of Southern California Health Sciences Campus
Institutional Review Board
LAC+USC Medical Center, Intern's Residence Dorm #425
2020 Zonal Avenue. Los Angeles, CA 90033
(323) 223-2340 phone
(323) 224-8389 fax
irb@usc.edu

Date: Fri Aug 08 08:33:34 2008

To: Beth Fisher
BIOKINESIOLOGY AND PHYSICAL THERAPY (DIVISION 6)

Todd Davenport
BIOKINESIOLOGY AND PHYSICAL THERAPY (DIVISION 6)

From: **Health Science Institutional Review Board Vice Chair**
Norman Kachuck, M.D.
Interns Residence Dorm, Room #425
2020 Zonal Avenue
Los Angeles, CA 90033
(323) 223-2340

TITLE OF PROPOSAL:
Effect of manual therapy intervention on corticospinal excitability in individuals with post-acute ankle sprains (Ankle sprains and corticospinal excitability)

Action Date: **8/7/2008** Action Taken: **APPROVED**

Committee: **Health Science Institutional Review Board Vice Chair**

Note: Your correspondence dated and received on 8/4/08 and attachments were reviewed by Dr. Kachuck on 8/7/08.

The proposed changes qualify for expedited review according to 45CFR46.110 (b) 2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized. The proposed changes were APPROVED.

The Following documents have received final IRB Approval:

1. Revised Research Protocol #HS-08-00192, dated 8/4/08
2. Magstim ® Model 200 (USA Only) Operating Manual, dated March 28, 2006
3. Magstim Manufacturer Statement regarding device risks, dated 9/22/06
4. Investigator Statement regarding study device as NSR, undated
5. Revised Recruitment Flyer, dated 8/4/08
6. TMS Screening Questionnaire, undated
7. Eligibility Screening Checklist, undated
8. NCI Human Subjects Training Completion Report for T. Davenport (completed on 9/18/06)
9. Revised iStar Application dated 8/4/08
10. Revised Informed Consent dated 8/4/08

NOTE TO PI:

NON-SIGNIFICIANT RISKS DEVICE 1) The IRB has made the determination that the device is a non-significant risk. An IDE application is not required. This study must be conducted in accordance with the "abbreviated requirements" of the IDE regulations (21 CFR 812.2(b)): (1) An investigation of a device other than a significant risk device, if the device is not a banned device; (2) An investigation of a device other than one subject to paragraph (e); (3) A diagnostic device, if the sponsor complies with applicable requirements in Sec. 809.10(c) and if the testing: (i) Is noninvasive, (ii) Does not require an invasive sampling procedure that presents significant risk, (iii) Does not by design or intention introduce energy into a subject, and (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure; (4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk; (5) A device intended solely for veterinary use; (6) A device shipped solely for research on or with laboratory animals and labeled in accordance with Sec. 812.5(c); (7) A custom device as defined in Sec. 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

2) IRB approval is required and must be maintained throughout the investigation and informed consent must be obtained and documented.

3) This research study with human subjects involves a medical device that must comply with FDA regulations for informed consent (21 CFR 50) and Institutional Review Board (21 CFR 56) regulations. Investigational devices are medical devices undergoing clinical study to test the effectiveness and/or safety of the device which must be conducted according to the requirements of the Investigational Device Exemption (IDE) regulations (21 CFR 812).

Based on expedited review of your response, contingencies of 5/22/08 and 7/24/08 have been fully satisfied.

In approving this research the IRB determined that all of the following requirements (45CFR 46.111) were satisfied: (1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, only those risks and benefits that may result from the research are considered (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). (3) Selection of subjects is equitable (the purposes of the research and the setting in which the research will be conducted were take into account). (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45CFR 46.116. (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by 45CFR 46.117. (6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

As the Principal Investigator you are required to ensure that this research and the actions of all project personnel involved in conducting the study will conform with the research project and its modifications approved by the IRB; HHS regulations (45CFR46); FDA regulations (21CFR50,56); International Conference on Harmonization Good Clinical Practice Consolidated Guideline; IRB Policies and Procedures and applicable state laws. Failure to comply may result in suspension or termination of my research project, notification of appropriate governmental agencies by the IRB, and/or suspension of your freedom to present or publish results. Any proposed changes in the research project must be submitted, reviewed and approved by the IRB before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB should be promptly informed of the change following its implementation for IRB review. You must inform the IRB immediately if you become aware of any violations of HHS regulations (45CFR46), FDA regulations (21CFR50,56), applicable state laws or IRB Policies and Procedures for the protection of human subjects. You are required to notify the IRB office in the event of any action by the sponsor, funding agency or FDA, including warnings, suspension or termination of your participation in this trial. You must maintain all required research records and recognize the IRB is authorized to inspect these records.

Approval of your study will expire at the end of the day (i.e. midnight) on 7/23/2009. IRB approval is valid for a maximum period of one year with continuing review by the IRB required at least annually in order to maintain approval status. You may not enter subjects on the study before IRB approval or if IRB approval expires. In the latter case you must immediately contact the IRB to obtain permission to continue subjects on the trial. You must submit a progress report using the Continuing Review activity in iStar sufficiently (one to two months) prior to your study expiration date to permit IRB review before the expiration date.

You must inform the IRB of any unanticipated adverse event or injury no later than two (2)

business days following the time it becomes known that a subject suffered an adverse event/injury. To report adverse events you must use the Report Event activity in iStar. Furthermore you must inform the IRB immediately of any significant negative change in the risk/benefit relationship of the research as originally presented in the protocol and approved by the IRB.

The Revised Informed Consent Document, dated 8/4/2008, was APPROVED.

Please inform current enrolled research participants of the updated information using the revised informed consent. The investigators should be careful to point out to the research participants the new information and solicit their agreement to continue in the study. In the future, the investigators should consider submitting a statement of significant new findings/information for existing participants and a revised informed consent for future participants.

This informed consent is located at the "Documents" tab in the iStar study and in the iStar application under item 29. The IRB has placed an "Approval Stamp" on a copy of this consent (after using the accept changes feature) and placed it at the top of the "Documents" tab under the Approved Consent Forms (With IRB Approval Stamp). This is considered the APPROVED informed consent. You must utilize a copy of the Approved informed consent that bears the IRB Approval Stamp.

Informed consent must be obtained by the investigator or person authorized to obtain informed consent from all research subjects or their legally authorized representatives. You must ensure that all project personnel involved in the process of consent/assent are trained properly and are fully aware of their responsibilities relative to the obtainment of informed consent/assent according to the IRB guidelines and applicable federal regulations.

The IRB office has stamped the approved informed consent form(s) for use in this research project. It should be photocopied, as appropriate, onto the correct letterhead for the hospital or institute. You may not use this informed consent form document to consent new subjects after its expiration date. A photocopy of this IRB approved informed consent form document(s) bearing this stamp must be used for consenting and/or reconsenting the study subjects. The study subject must sign and date the informed consent document. The person obtaining informed consent must also sign the study consent form at the time consent is obtained. One copy of the informed consent should be given to the study subject, one copy placed in the medical record, and the investigator should retain one copy.

The California Health and Safety Code provides the (minimum) statutory protection for residents of California with regard to human experimentation. The LAC/USC Medical Center subject's demographic information was obtained and according to that information the California Experimental Subject's Bill of Rights has been translated to the main languages used by the target population. The English, Spanish, Korean, Farsi, Armenian, Thai, Russian, Chinese and Vietnamese versions of the California Experimental Subject's Bill of Rights are now available on the IRB website.

Informed consent is obtained in the research participant's language. If the participant speaks

Spanish and the informed consent document has been translated into Spanish, you must utilize the Spanish informed consent document, the Spanish Experimental Subject's Bill of Rights and the Spanish HIPAA Authorization form. For participants who speak other languages, you must have a translator verbally translate the English informed consent document into those languages for the participants. The English informed consent serves as a summary. The translator, the person obtaining informed consent and the witness sign the English informed consent document. The participant and witness sign the Short Form informed consent document, which must be in the participant's language. The IRB has translated the Short Form consent into multiple languages, which are available on the IRB website. In addition, the participant signs the Experimental Subject's Bill of Rights in the participant's language. The IRB has translated the Experimental Subject's Bill of Rights into multiple languages which are also available on the IRB website (http://www.usc.edu/admin/provost/oprs/hsirb/forms).

Attachments:

Appendix 3. DAVENPORT, KULIG, and FISHER - YEAR 1 FINAL BUDGET

	Year 1 Projected Expenses	Year 1 Actual Expenses	Item subtotal
Salaries and Wages			
Principal Investigator salary assumes .05FTE. Graduate Assistant salary assumes .05FTE level; position created for database management and assistance with coordinating subject recruitment.			
Principal Investigator*	$3000.00	($2994.86)	$5.14
Graduate Assistant	$1500.00	$0	$1500.00
Total Salaries and Wages	$4500.00	($2994.86)	**$1505.14**
Equipment			
Materials include: Experiment 1 - 6" goniometer, 12" goniometer, bubble inclinometer, and foot volumeter for up to 20 clinics. Experiment 2 - lycra swim caps, coupling agent, and surface electrodes.			
Experiment 1	$6500.00	($6500.00)	$0
Experiment 2	$500.00	($226.02)	$273.98
Total Equipment	$7000.00	($6726.02)	**$273.98**
Travel and Lodging			
Expenses associated with travel that will ensure an appropriate level of investigator standardization, data management, subject/clinician recruitment and retention, and data collection.			
Automobile Travel	$850.00	($127.68)	$722.32
Airline Travel	$600.00	($936.70)	($336.70)
Lodging and Meals	$1700.00	($150.67)	$1549.33
Total Travel and Lodging	$3150.00	($1215.05)	**$1934.95**
Miscellaneous Operating Expenses			
Materials to facilitates communication among PI, collaborators and study clinicians, confidential and accurate recordkeeping, secure electronic and physical storage of data, and secure transmission of electronic data. Examples include file folders, paper, copy costs, postage, and portable computer memory cards.	$750.00	($132.82)	**$617.18**
Grand Total	**$15400.00**	**($11068.75)**	**$4331.25**

* Includes Federal Insurance Contributions Act withholdings for Principal Investigator