

AWARD NUMBER: W81XWH-14-2-0191

TITLE: A Multicenter, Randomized Controlled Trial of Cerebrospinal Fluid Drainage in Acute Spinal Cord Injury

PRINCIPAL INVESTIGATOR: Nicholas Theodore, MD

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14. ABSTRACT The purpose of this randomized clinical trial is to evaluate the safety and efficacy of cerebrospinal fluid drainage (CSFD) and to provide a preliminary clinical efficacy evaluation of the combination of CSFD and elevation of mean arterial pressure (MAP) in patients with acute spinal cord injury. This study is currently screening and enrolling patients at all three active centers, which include: Barrow Neurological Institute/Dignity Health (the main study site) in Arizona, the University of Arizona in Tucson and the University of Alabama in Birmingham. Steps have been initiated to add a high-volume spinal cord injury site from the East Coast to help drive the recruitment efforts which have jeopardized the project timelines. An Investigator Meeting is taking place in Q4 2017 to discuss barriers to recruitment and potential solutions.					
15. SUBJECT TERMS acute spinal cord injury, cerebrospinal fluid drainage, mean arterial pressure, intrathecal pressure, improving neurologic motor outcomes					
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1. INTRODUCTION

In the United States, 10,000-14,000 people per year suffer acute spinal cord injuries. These injuries incur significant costs to the individual and society that are expected to increase with better long term care technologies. The purpose of this randomized clinical trial is to evaluate the safety and efficacy of cerebrospinal fluid drainage (CSFD) and to provide a preliminary clinical efficacy evaluation of the combination of CSFD and elevation of mean arterial pressure (MAP) in patients with acute spinal cord injury. This investigational method for treating acute spinal cord injury patients aims to reduce cell death and axonal damage leading to improved neurological function in patients.

2. KEYWORDS

Acute spinal cord injury, cerebrospinal fluid drainage, mean arterial pressure, intrathecal pressure, improving neurologic motor outcomes.

3. ACCOMPLISHMENTS

What Were the Major Goals of the Project?

- *Prepare Research Protocol & Study Documents*
 - *Projected Completion: March 2015*
 - *Actual Completion: March 2015*
- *Contract the Sites and Vendors*
 - *Projected Completion: February 2015*
 - *Actual Completion: April 2016*
- *Obtain Regulatory Approvals*
 - *Initial Approvals*
 - *Projected Completion: March 2015*
 - *Actual Completion: February 2016*
 - *Continuing Approvals*
 - *Ongoing throughout study*
- *Develop & Validate eCRF*
 - *Projected Completion: March 2015*
 - *Actual Completion: April 2015*
- *Program Clinical Data in SAS®*
 - *Projected Completion: February 2016*
 - *Actual Completion: July 2016*
- *Initiate Sites*
 - *Projected Completion: March 2015*
 - *Actual Completion: April 2016*
- *Enroll Subjects, Deliver Study Treatment, Perform Evaluations*
 - *Projected Completion: through June 2018*
 - *Actual Completion: Ongoing*
- *Monitoring & Data Management*
 - *Projected Completion: through June 2018*
 - *Actual Completion: Ongoing throughout study*

- *Close the Study & Lock the Database*
 - *Projected Completion: June-July 2018*
 - *Actual Completion: Not Started*
- *Analysis & Reporting*
 - *Projected Completion: August-September 2018*
 - *Actual Completion: Not Started*

What Was Accomplished Under These Goals?

- *Prepare Research Protocol & Study Documents*
 - *Research Protocol and Study Documents finalized.*
- *Contract the Sites and Vendors*
 - *Barrow Neurological Institute, University of Arizona, University of Alabama and Nor Consult (CRO) have fully executed Clinical Trial Agreements and/or Service Agreements.*
- *Obtain Regulatory Approvals*
 - *Initial Approvals*
 - *Barrow Neurological Institute has received initial and continuing IRB approvals (annual renewal) for this study.*
 - *University of Arizona has received initial and continuing IRB approvals (annual renewal) for this study.*
 - *University of Alabama has received initial and continuing IRB approvals (annual renewal) for this study.*
 - *Continuing Reviews / Amendments*
 - *All three sites are enrolling patients per version 2.0 of the Clinical Study Protocol.*
 - *University of Alabama has received IRB approval for a revised consent form.*
 - *University of Arizona has received approvals for English and Spanish consent forms.*
- *Develop & Validate eCRF*
 - *The Electronic Data Capture (EDC) system that is being utilized for this study has been developed and validated. It is online and maintenance is regularly performed to ensure that the EDC remains up to date. All new site staff who are assigned to enter data are remotely trained by the CRO.*
- *Initiate Sites*
 - *All three Site Initiation Visits (SIV) have been completed. A fourth visit will be conducted if the newly identified site receives approval to join the study.*
- *Monitoring & Data Management*
 - *Data management data checks and risk-based data checks (i.e. "edit checks") have been written and are actively supporting the ongoing data reviews.*
- *Enroll Subjects, Deliver Study Treatment, Perform Evaluations*
 - *All three sites have successfully enrolled a patient and are continuously performing prescreening and screening to evaluate new potential trial subjects. Follow-up assessments/visits have been/are performed at all three sites as required by the protocol.*

What Opportunities for Training and Professional Development Has the Project Provided?

The project has provided training and professional development opportunities to the neurosurgery residents, fellows and other spinal cord injury clinicians at the three sites. The residents and fellows have had an opportunity to learn about the clinical research process and Good Clinical Practice (GCP) expectations for conducting clinical trials. From a clinical perspective this study has given them an opportunity to learn about how the cerebrospinal fluid drainage and MAP elevation procedures are administered immediately post-injury to spinal cord injury patients.

How Were the Results Disseminated to Communities of Interest?

Nothing to Report. Results postings and publications will follow the final study analysis.

What Do You Plan to Do During the Next Reporting Period to Accomplish Goals?

During the next reporting period we plan to continue pre-screening, screening and enrolling subjects at the three participating sites. Monitoring, data management, including data checks and query resolution, and training of new site staff will continue to ensure the safety of the patients and the integrity of the data. Annual IRB renewals will be obtained as needed to keep all three sites open-for-enrollment throughout the next reporting period. A fourth site has been identified to join the study and our suggested approach for including them within the scope of the grant will be presented to the DoD in Q4 2018. Also, an Investigator Meeting will take place in Q4 2018 with the aim of discussing barriers to recruitment and potential solutions. The result of this meeting may be a protocol amendment with revised inclusion/exclusion criteria.

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:

The initial delay in this study was related to a longer-than anticipated USAMRMC ORP HRPO Administrative Review. Subsequently, there was a change to the Clinical Study Protocol/Investigational Protocol (version 2.0) and the Informed Consent Form. Once these changes were made, it required re-approval from the local IRB at the main study site. Following these initial administrative delays, the screening and enrollment activities were put into action which resulted in the enrollment of the first subject in the trial. However, as witnessed by the slower-than-anticipated enrollment and the lower-than-anticipated spinal cord injury cases presenting to the sites – the study timelines have been jeopardized and it is unlikely that the study will meet its recruitment goal on time. The investigators are again meeting in Q4 to discuss potential changes to the study protocol that may help to promote the recruitment efforts. They will discuss whether revisions to the inclusion/exclusion criteria may be appropriate to help make more patients eligible for the study while maintaining the ability to meet the study's research objectives. In November 2017 we will be suggesting the addition of a new study site which has already passed a site feasibility process. The site is a high volume spinal cord injury center with a proven research track record. Concurrently, we will also request a project extension through September 2019.

Changes that had a significant impact on expenditures:

Nothing to Report.

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

Nothing to Report.

6. PRODUCTS

Publications, conference papers, and presentation

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 another Internet site(s).

<https://clinicaltrials.gov/ct2/show/NCT02495545>

Technologies or techniques.

Nothing to Report.

Inventions, patent applications, and/or licenses.

Nothing to Report.

Other Products.

Nothing to Report.

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name:	Nicholas Theodore, MD, no change
Name:	Nikolay Martirosyan, MD, no change
Name:	Branko Kopjar, MD, no change
Name:	Bridget Dancs, no change
Name:	Anna McCann, no longer on study
Name:	Stan Abramov, no change
Name:	Veljko Kopjar, Project Manager, no change
Name:	Alexis Kosmin, Study Assistant, no longer on study
Name:	Wasinee Opal Sriapha, no longer on study

Name: Samyukta Erabati, Associate Project Manager, no longer on study
Name: Christina Lo, Study Assistant, new to study
Name: Kevin Beverly, Clinical Data Programmer, new to study
Name: Allan Levi, MD, Medical Safety Officer
Name: Site Principal Investigators, Sub-Investigators, Study Coordinators and other staff at the various clinical centers.

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

Dr. Kakarla took over the Principal Investigator responsibilities at Barrow Neurological Institute/St. Joseph's Medical Center.

What other organizations were involved as partners?

Organization Name: University of Arizona, Tucson
Location of Organization: 1501 N. Campbell Ave, LSN 416 Bldg 221, Tucson, Arizona 85724
Partner's Contribution: Other (Investigational Site)

Organization Name: University of Alabama, Birmingham
Location of Organization: 510 20th Street South, FOT 1030, Birmingham, Alabama 35233
Partner's Contribution: Other (Investigational Site)

Organization Name: University of Miami, Miami
Location of Organization: 1321 NE 14th St. Suite 306, West, Miami, FL 33125
Partner's Contribution: Other (Medical Monitor's site)

Organization Name: Nor Consult, LLC
Location of Organization: 677 Strander Blvd, Suite F, Seattle, WA 98188
Partner's Contribution: Other (Contract Research Organization)

8. Special Reporting Requirements

Quad Chart:

A Multicenter, Randomized, Controlled, Trial of Cerebrospinal Fluid Drainage in Acute Spinal Cord Injury

CDMRP Log Number: SC130237

Grants.gov ID Number: GRANT11501120

PI: Nicholas Theodore, MD

Org: St. Joseph's Hospital & Medical Center Award Amount: \$1,653,993

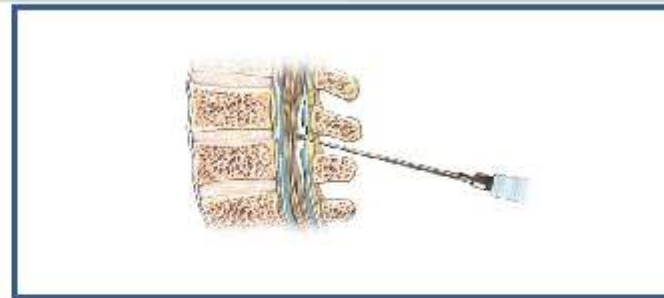


Study/Product Aim(s)

• The purpose of this RCT is to evaluate the safety and efficacy of cerebrospinal fluid drainage (CSFD) and to provide a preliminary clinical efficacy evaluation of combination of CSFD and elevation of Mean Arterial Pressure (MAP) in patients with acute spinal cord injury.

Approach

Subjects randomized to the Control Arm will receive elevation of MAP. Subjects randomized to the Experimental Arm will receive an intensive regimen of CSFD and elevation of MAP. The duration of the study treatments will be 120 hours in both arms counting from the time when the study treatment has been initiated.



Accomplishments: All three sites have enrolled a subject in this trial. Prescreening and screening efforts are ongoing at all sites.

Timeline and Cost

Activities	CY	14	15	16	17
Study Start Up					
Enrollment and Follow-up					
Enrollment and Follow-up					
Trial Termination and Analyses					
Estimated Budget (\$K)		504	310	308	339

Updated: October 31, 2017

Goals/Milestones

Quarter 3, 2016 – Quarter 3 2017:

- Pre-Screen, Screen and Enroll Subjects, Deliver Study Treatment(s), Perform Evaluations, Enter Data (ongoing)
- Obtain Regulatory Approvals (renewals)
- Monitoring & Data Management (ongoing)
- Adjudication of Safety Events (ongoing)
- Training of new site personnel (ongoing)

Comments:

Budget Expenditure to Date \$1,072,156

Estimated Projected Expenditure: \$1,124,404

9. Appendices

None