AWARD NUMBER: W81XWH-16-2-0023

TITLE: Advancing Clinical Outcomes, Biomarkers, and Treatments for Severe TBI

PRINCIPAL INVESTIGATOR: Theresa Pape, DrPH

CONTRACTING ORGANIZATION:
Chicago Association for Research and Education in Science
Edward Hines, Jr. VA Hospital
5000 S. 5th Ave, MC151H
Hines, IL 60141

REPORT DATE: August 31, 2018

TYPE OF REPORT: Annual

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

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| 08/31/2018 | Annual | 08/01/17 – 07/31/18 |

**4. TITLE AND SUBTITLE**

Advancing Clinical Outcomes, Biomarkers, and Treatments for Severe TBI

**5a. CONTRACT NUMBER**
W81XWH-16-2-0023

**5b. GRANT NUMBER**
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**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**

Dr. Theresa Pape

E-Mail: Theresa.Pape@va.gov

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

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

Chicago Association for Research and Education
5000 South 5th Avenue
Bldg. One C347
Hines, IL 60141

**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

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**12. DISTRIBUTION / AVAILABILITY STATEMENT**

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**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

This study is a ***double blind randomized placebo-controlled clinical trial using repeated measures***. The ***objective*** is to improve recovery of functional skills for persons living in states of seriously impaired consciousness 3 to 12 months after severe TBI. This will be achieved by determining the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS), which is a non-invasive technique to stimulate the brain. The evidence of therapeutic efficacy from the literature in non-TBI related neurologic populations combined with our preliminary findings with severe TBI, indicate that rTMS merits investigation as a neurotherapeutic for severe TBI and that the proposed repetitive TMS protocol should be examined to determine effectiveness in inducing structural and functional neural plasticity and improving neurobehavioral recovery after severe TBI. ***Specific Aims***: Aim I will determine presence, direction and sustainability of rTMS-induced neurobehavioral effects measured with the Disability Rating Scale. Aim II will determine the presence, direction and sustainability of rTMS-induced changes in functional neural activation and whether or not these changes correlate with improving neurobehavioral function. Aim III will examine the effect of rTMS on white fiber tracts and whether or not the rTMS-related effects correlate with improving neurobehavioral function. Aim IV addresses the need to confirm rTMS safety for severe TBI.

**15. SUBJECT TERMS**
Disability Rating Scale (DRS), Neurobehavioral, Repetitive Transcranial Magnetic Stimulation (rTMS), Traumatic Brain Injury (TBI), Vegetative (VS), Minimally Conscious (MCS)

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

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

## Table of Contents

1. **INTRODUCTION:** Based on published evidence and pilot data from three subjects, repetitive Transcranial Magnetic Stimulation (rTMS) holds promise as a treatment for severe Traumatic Brain Injury (TBI). TBI alters the lives of the patient, their family, and society. Severe TBI is particularly devastating with some survivors recovering full consciousness swiftly while others remain in states of seriously impaired consciousness (SIC). Both recovery trajectories involve complex and potentially chronic cognitive and physical impairments. Evidence that cortical processing can occur even while unconscious and evidence of late recoveries continues to accumulate suggesting that SIC is a modifiable condition. Advanced medical care saves and sustains the lives of persons incurring severe TBI and there is a growing body of evidence indicating that this devastating injury is modifiable but there are few to no treatments that induce or accelerate functional and adaptive recovery for survivors of severe TBI. Optimal functional recovery after severe TBI, without targeted treatments, is unlikely. To address the need for targeted treatments that induce functional and structural changes in the brain, ultimately improving neurobehavioral functioning, we propose examining the therapeutic effectiveness of rTMS. The objective is to improve functional recovery for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI. The approach is to determine the neurobehavioral effect of rTMS, the relationship between neurobehavioral changes and net neural effects, and to identify and define the neural mechanisms related to neurobehavioral improvements by providing 30 active or placebo rTMS sessions. The Disability Rating Scale (DRS), Coma Recovery Scale-Revised (CRSR), Disorders of Consciousness Scale-25 (DOCS-25), and Coma/Near Coma Scale (CNC) will be used at four time points to measure neurobehavioral recovery slopes. Net neural effects will be measured at three time points using fcMRI, resting state EEG (EEG-Rest), a language fMRI task and changes in EEG power spectrum when listening to a semantic processing task (EEG-Task). We will examine changes in structural integrity of fiber tracts using DTI. Measures are collected prior to, during, after and at follow up from active and placebo rTMS treatments. Subsequently, the JWMRP allows the study design to collect the Glasgow Outcomes Scale-Extended (GOS-E) at all four time-points. Further, the addition of paired ratings for all five neurobehavioral function measures creates an opportunity to examine these widely used assessments and establish key indices of change. This pivotal information will enable us to generate effect sizes and meaningful measures of change from which researchers can power clinical trials and better quantify the patient's improvement. Additionally, we will identify the micro-Ribonucleic acids (miRNA) within whole blood and microparticles that are altered by the rTMS intervention and correlated with the neurobehavioral and neurophysiological outcomes. We think that we can identify specific miRNA because evidence shows that severe TBI results in cellular damage and dysregulation of signaling pathways and structural proteins and also that miRNA play a critical role in translational regulation of cellular pathways in the recovery of TBI.. Furthermore, evidence from animal models demonstrate that rTMS promotes miRNA regulation involved with neural repair. Collectively, the evidence suggests that specific miRNA represent potentially useful biomarkers for therapeutic responsiveness to rTMS.

2. **KEYWORDS:**

Disability Rating Scale (DRS)

Coma Recovery Scale-Revised (CRSR)
Disorders of Consciousness Scale-25 (DOCS-25)
Coma/Near Coma Scale (CNC)
Glasgow Outcomes Scale-Extended (GOS-E)
MicroRNA (miRNA)
Neurobehavioral
Repetitive Transcranial Magnetic Stimulation (rTMS)
Traumatic Brain Injury (TBI)
Vegetative State (VS)
Minimally Conscious State (MCS)

## 3. ACCOMPLISHMENTS:

| Supplemental Project #2<br>Advancing Clinically Reported TBI Outcomes using Modern Psychometrics |
|---|

**What were the major goals of the project?**

Major Goal 1: Development and testing of meaningful change anchors (Months 1-6)
*Milestones: Valid hierarchy of anchor descriptors*; **45% completed**
Major Goal 2: Create patient video cases and collection of linking data (Months 6-12)
*Milestones: Complete standardize case videos;* **15% completed**
*Collect data on these videos;* **0% completed**
Major Goal 3: Examine basic psychometrics for each assessment (Months 13-18)
*Milestones: Complete rating scale, item, and person analyses;* **25% completed**
Major Goal 4: Conduct the Rater Severity/Leniency analyses (Months 19-25)
*Milestones:* Item and rating scale anchors with effect of Rater Severity/Leniency removed; 1**0% completed.**
Major Goal 5: Conduct Minimally Detectable Change, Minimally Clinically Important Difference, & Effect Size analyses (Months 26-32)
*Milestones: Indices of change for each neurobehavioral functional assessment;* **30% completed**
Major Goal 6: Complete deliverables including conversion tables, crosswalks, and change indices tables (Months 33-36)
*Milestones: Co-calibration tables/crosswalks;* **10% completed**
*Milestones: Tables of change indices for each of the assessments;* **0% completed**
Major Goal 7: Dissemination activities (Months 33-36); **0% completed**

**What was accomplished under these goals?**

To develop and test meaningful change anchors, we have started with a qualitative inquiry for clinicians and caregivers of patients with DoC. During this reporting period IRB and HRPO approvals have been secured for Northwestern, Hines, and Minneapolis VA. At this time, 20 clinician interviews have been completed. Transcription and preliminary analysis have been completed for 6 of the clinician interviews. Transcription is underway for the remaining 14 interviews. Research staff has received NVIVO training to assist with data analysis. An IRB revision has been submitted to Hines VA to add interviews with caregivers. This same revision is in the process of being submitted to Northwestern & Minneapolis VA IRB. We recognized in

order to advance TBI outcome measurement, we need to address the content and construct validity of the five widely used measures for NBF in patients with severe TBI. Therefore, we have undertaken two systematic reviews that are registered with PROSPERO. The first seeks to broadly describe each of the content areas addressed by intervention studies examining recovery of consciousness in patients with severe TBI and the trends in these content areas over time; the second review aims to describe the domains and constructs specifically related to NBF for patients with DoC following sTBI. We have developed our search strategy, searched databases, and we are currently screening the articles for the eligibility criteria.

To create patient case videos we have recorded one patient when assessed using the DOCS-25. Evaluation of the current video is underway to improve the process and determine next steps.

To examine the psychometric properties of each NBF assessment tool, the DOCS-25 is published and the CNC has been analyzed with a manuscript describing the psychometric properties of the tools currently under review. A second manuscript, reporting the responsiveness of the CNC is under development and will be submitted shortly. To conduct the rater severity/leniency analyses, we have been examining the extent to which methods comparison approaches can be applied in this novel context. A manuscript describing this approach is in development and will be submitted shortly. A presentation on the proposed methods has been accepted the International Outcomes Measurement Conference (IOMC) in Chicago, IL, September 15, 2017.

We have been collaborating with ICON Inc. to develop a letter of intent for submission to the FDA to request that the DOCS-25 be considered for review as a federally qualified endpoint. To date, we have drafted the entire LOI and are in the process of revising the conceptual model and incorporating best reporting practice guidelines for clinician reported outcomes. We anticipate submitting this LOI in the next two months. A poster describing this process has been accepted at the MHSRS conference in August, 2017.

Dissemination activities are an iterative process and to maximize our effort we are using personal and non-personal approaches. A non-personal approach includes publishing manuscripts and we have one under review and another in progress. Additionally, we include personal approaches for dissemination such as presenting at conferences. We have a poster scheduled for the Military Health System Research Symposium, two abstracts at IOMC, and conference abstracts under review for the American Congress of Rehabilitation Medicine Annual Conference, American Occupational Therapy Association Annual Conference, World Federation of Occupational Therapists Congress, and the Academy Health Dissemination and Implementation Annual Conference.

**What opportunities for training and professional development has the project provided?** Nothing new to report.

**How were the results disseminated to communities of interest?** Nothing to report.

**What do you plan to do during the next reporting period to accomplish the goals?**

We are working to acquire additional data that will advance our work on the assessment psychometrics while we are waiting for additional patients to be recruited. We will continue to

work on acquiring video-based cases for scoring. We will use existing data to advance techniques for examining rater severity/leniency to improve the precision of NBF measurement for patients in DoC.
We also plan to continue transcription and analysis of the clinician interviews and plan to start crafting vignettes to work towards Major Goal 1.

4. **IMPACT:** Nothing to report.

5. **CHANGES/PROBLEMS:** Nothing to report.

6. **PRODUCTS:** Nothing to Report

7. **PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:**

**What individuals have worked on the project?**

*Name: Theresa Pape. Dr. PH*
*Project Role: Principal Investigator*
*Nearest person months worked: 4*
*Contribution to project: Dr. Pape has overseen protocol development, staffing at each site, and overall project flow.*

*Name: Lisel Kwartnik*
*Project Role: Project Manager*
*Nearest person months worked: 8*
*Contribution to project: Ms. Kwartnik is responsible for the development and monitoring of study budgets and ensuring all financial allocations and expenditures are in accordance with the grant and VA requirements for the currently funded research clinical trial and the three supplemental projects. She provides daily operational assistance to project staff. No Change.*

*Name: Ann Guernon, MS*
*Project Role: Clinical Research Manager*
*Nearest person months worked: 4*
*Contributions to project: Ms. Guernon is responsible for the oversight of regulatory submissions and clinical data collection. She works closely with Dr. Walsh, Mallinson and Pape to insure the quality of the data collected in these projects. No change.*

*Name: Elyse Walsh, DPT*
*Project Role: Research Therapist*
*Nearest person months worked: 4*
*Contributions to project: Dr. Walsh managed the specific IRB submission for the Clinician Language Protocol at all three submission sites. She also manages screening of potential participants for both protocols and schedule of research procedures. No change.*

*Name: Jen Weaver, OTR/L*
*Project Role: Research Associate:*
*Nearest person months worked: 7*
*Contributions to project: Ms. Weaver has now created two systematic review protocols which are published on PROSPERO, an international database for prospectively registered systematic reviews. The initial search strategy yielded 8,612 and the title review phase is 100% complete. The abstract review process is 50% complete. She is in the process of finalizing a draft for a letter of intent to the FDA to discuss the DOCS-25 as an endpoint. She is an active participant in coding the qualitative interviews and has completed a psychometric analysis of the Coma-Near-Coma scale with a manuscript under review. The analysis of the CNC meaningful indices of change has been initiated.*

*Name: Trudy Mallinson, PhD*
*Project Role: PI of Supplemental Project # 2*
*Nearest person months worked: 2*
*Contributions to project: Trudy Mallinson directly oversees Jen Weaver, building capacity for the team to examine the psychometric properties of each outcome measure and complete systematic reviews to strengthen the content validity of the DOCS-25. Additionally she worked closely with Dr. Pape, Ms. Ann Guernon, Dr. Walsh, Ms. Weaver, & Dr. Papadimitriou on revising the caregiver interview guide and protocol. She is involved in the data analysis of the transcribed interviews and is working on the rater severity/leniency analyses plan and overseeing the CNC analyses.*

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

The following changes have occurred in the active other support of the PI and key personnel:

**Trudy Mallinson**

New Support

TEFT (PI Mallinson) 04/04/2017-03/31/2018 4.8 Calendar Months

"Testing Experiences and Functional Assessment Tools (TEFT) in Community-Based Long Term Services and Supports Demonstration" Truven Health Analytics

This proposal was extended from the original performance period of 04/01/2015-03/31/2017. The goal of this project is to develop, test, and validate standardized functional status items, including self-care and mobility for beneficiaries in Home and Community-based Services waiver programs.

**What other organizations were involved as partners?**

Organization Name: George Washington University
Location of Organization: Washington, DC, USA
Partner's Contribution to the Project: Collaboration

8. **SPECIAL REPORTING REQUIREMENTS:** None.

9. **APPENDICES:** None

**QUAD CHART:** See attached Quad Chart.

AWARD NUMBER: W81XWH-16-2-0023

TITLE: rTMS: “Advancing Clinical Outcomes, Biomarkers and Treatments for Severe TBI”
**Subproject: “miRNA as Biomarkers for Severe TBI and rTMS Mediated Gains in Neurobehavioral Activity”**

PRINCIPAL INVESTIGATOR: Theresa Pape, DrPH

CONTRACTING ORGANIZATION:
Chicago Association for Research and Education in Science
Edward Hines, Jr. VA Hospital
5000 S. 5th Ave, MC151H
Hines, IL 60141

REPORT DATE: August 31, 2018

TYPE OF REPORT: Annual

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**4. TITLE AND SUBTITLE**

"Advancing Clinical Outcomes, Biomarkers and Treatments for Severe TBI"

**5a. CONTRACT NUMBER**
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**5b. GRANT NUMBER**
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**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**

Dr. Theresa Pape

E-Mail: Theresa.Pape@va.gov

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

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

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**12. DISTRIBUTION / AVAILABILITY STATEMENT**

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**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

This study is a ***double blind randomized placebo-controlled clinical trial using repeated measures***. The ***objective*** is to improve recovery of functional skills for persons living in states of seriously impaired consciousness 3 to 12 months after severe TBI. This will be achieved by determining the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS), which is a non-invasive technique to stimulate the brain. The evidence of therapeutic efficacy from the literature in non-TBI related neurologic populations combined with our preliminary findings with severe TBI, indicate that rTMS merits investigation as a neurotherapeutic for severe TBI and that the proposed repetitive TMS protocol should be examined to determine effectiveness in inducing structural and functional neural plasticity and improving neurobehavioral recovery after severe TBI. ***Specific Aims***: Aim I will determine presence, direction and sustainability of rTMS-induced neurobehavioral effects measured with the Disability Rating Scale. Aim II will determine the presence, direction and sustainability of rTMS-induced changes in functional neural activation and whether or not these changes correlate with improving neurobehavioral function. Aim III will examine the effect of rTMS on white fiber tracts and whether or not the rTMS-related effects correlate with improving neurobehavioral function. Aim IV addresses the need to confirm rTMS safety for severe TBI.

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| 16. SECURITY CLASSIFICATION OF: Unclassified | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
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**Standard Form 298 (Rev. 8-98)**
**Prescribed by ANSI Std. Z39.18**

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1. **INTRODUCTION:** Based on published evidence and pilot data from three subjects, repetitive Transcranial Magnetic Stimulation (rTMS) holds promise as a treatment for severe Traumatic Brain Injury (TBI). TBI alters the lives of the patient, their family, and society. Severe TBI is particularly devastating with some survivors recovering full consciousness swiftly while others remain in states of seriously impaired consciousness (SIC). Both recovery trajectories involve complex and potentially chronic cognitive and physical impairments. Evidence that cortical processing can occur even while unconscious and evidence of late recoveries continues to accumulate suggesting that SIC is a modifiable condition. Advanced medical care saves and sustains the lives of persons incurring severe TBI and there is a growing body of evidence indicating that this devastating injury is modifiable but there are few to no treatments that induce or accelerate functional and adaptive recovery for survivors of severe TBI. Optimal functional recovery after severe TBI, without targeted treatments, is unlikely. To address the need for targeted treatments that induce functional and structural changes in the brain, ultimately improving neurobehavioral functioning, we propose examining the therapeutic effectiveness of rTMS. The objective is to improve functional recovery for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI. The approach is to determine the neurobehavioral effect of rTMS, the relationship between neurobehavioral changes and net neural effects, and to identify and define the neural mechanisms related to neurobehavioral improvements by providing 30 active or placebo rTMS sessions. The Disability Rating Scale (DRS), Coma Recovery Scale-Revised (CRSR), Disorders of Consciousness Scale-25 (DOCS-25), and Coma/Near Coma Scale (CNC) will be used at four time points to measure neurobehavioral recovery slopes. Net neural effects will be measured at three time points using fcMRI, resting state EEG (EEG-Rest), a language fMRI task and changes in EEG power spectrum when listening to a semantic processing task (EEG-Task). We will examine changes in structural integrity of fiber tracts using DTI. Measures are collected prior to, during, after and at follow up from active and placebo rTMS treatments. Subsequently, the JWMRP allows the study design to collect the Glasgow Outcomes Scale-Extended (GOS-E) at all four time-points. Further, the addition of paired ratings for all five neurobehavioral function measures creates an opportunity to examine these widely used assessments and establish key indices of change. This pivotal information will enable us to generate effect sizes and meaningful measures of change from which researchers can power clinical trials and better quantify the patient's improvement. Additionally, we will identify the micro-Ribonucleic acids (miRNA) within whole blood and microparticles that are altered by the rTMS intervention and correlated with the neurobehavioral and neurophysiological outcomes. We think that we can identify specific miRNA because evidence shows that severe TBI results in cellular damage and dysregulation of signaling pathways and structural proteins and also that miRNA play a critical role in translational regulation of cellular pathways in the recovery of TBI. Furthermore, evidence from animal models demonstrate that rTMS promotes miRNA regulation involved with neural repair. Collectively, the evidence suggests that specific miRNA represent potentially useful biomarkers for therapeutic responsiveness to rTMS.

2. **KEYWORDS:**

Disability Rating Scale (DRS)

Coma Recovery Scale-Revised (CRSR)
Disorders of Consciousness Scale-25 (DOCS-25)
Coma/Near Coma Scale (CNC)
Glasgow Outcomes Scale-Extended (GOS-E)
MicroRNA (miRNA)
Neurobehavioral
Repetitive Transcranial Magnetic Stimulation (rTMS)
Traumatic Brain Injury (TBI)
Vegetative State (VS)
Minimally Conscious State (MCS)

## 3. ACCOMPLISHMENTS:

| Supplemental Project #3<br>rTMS: miRNA as biomarkers for severe TBI and rTMS mediated gains in neurobehavioral activity |
|---|

Major Goal 1: Regulatory Requirements (Months 1-6)
*Milestones: Local IRB and safety approval;* **100% completed**
Major Goal 2: Coordinate Study Staff and Logistics for Study (Months 1-36)
*Milestones: Milestone Achieved: Study staff hired and trained;* **100% completed**
Major Goal 3: Validation of sample collection, shipment, processing and storage
*Milestones: Validation and standardization of sample collection, shipping, processing and storage;* **100% completed.**
Major Goal 4: Validation of miRNA in severe TBI patients
*Milestones: Validation of target miRNA to follow in TBI patients*; **4.2% completed**
Major Goal 5: Assessment of miRNA in entire study population
*Milestones: All study participants recruited and completion of research participation;* ***14.6*****% completed**
Major Goal 6: Data Analysis (Months 37-48); **3% completed**

**What was accomplished under these goals?**

To date, we have enrolled and collected both blood samples from 20 of the 20 healthy controls. Total blood cell RNA has been collected from these 20 patients and has been sent to the Loyola Genomics facility for quality control testing before proceeding to small RNA library construction and next generation miRNA sequencing. New to this quarter, we have collected blood samples from an additional 6 severe TBI participants for a total of 9 TBI participants. Blood samples from 4 have been taken to the Loyola Genomics facility to extract the miRNA and processed 6 samples from each TBI participants along with 2 samples from sex and age matched control patients. Once the data is obtained, we will have data from 6 severe TBI participants.

**What opportunities for training and professional development has the project provided?**
Nothing new to report.

**How were the results disseminated to communities of interest?** Nothing to report.

**What do you plan to do during the next reporting period to accomplish the goals?**

For the next reporting period, the goals are to continue subject recruitment at all sites for microRNA. We anticipate enrollment and study of 2 to 3 subjects during the next quarter.

We plan to analyze preliminary data that we will obtain for the first 6 TBI participants to determine whether there are miRNA that change in the TBI patients over time, and whether these miRNA patterns are significantly different compared to the sex and age matched healthy control patients. We also plan to take the remaining two patients' samples over to Loyola Genomics facility to have the miRNA extracted and processed.

4. **IMPACT:** Nothing to report.

5. **CHANGES/PROBLEMS:** Nothing to report.

6. **PRODUCTS:** Nothing to Report

7. **PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:**

**What individuals have worked on the project?**

*Name: Theresa Pape. Dr. PH*
*Project Role: Principal Investigator*
*Nearest person months worked: 1*
*Contribution to project: Dr. Pape has overseen protocol development, staffing at each site, and overall project flow.*

*Name: Lisel Kwartnik*
*Project Role: Project Manager*
*Nearest person months worked: 2*
*Contribution to project: Ms. Kwartnik is responsible for the development and monitoring of study budgets and ensuring all financial allocations and expenditures are in accordance with the grant and VA requirements for the currently funded research clinical trial and the three supplemental projects. She provides daily operational assistance to project staff. No Change.*

*Name: Ann Guernon, MS*
*Project Role: Clinical Research Manager*
*Nearest person months worked: 1*
*Contributions to project: Ms. Guernon is responsible for the oversight of regulatory submissions and clinical data collection. She works closely with Dr. Walsh, Mallinson and Pape to insure the quality of the data collected in these projects. No change.*

*Name: Elyse Walsh, DPT*
*Project Role: Research Therapist*
*Nearest person months worked: 1*
*Contributions to project: Dr. Walsh managed the specific IRB submission for the Clinician Language Protocol at all three submission sites. She also manages screening*

*of potential participants for both protocols and schedule of research procedures. No change.*

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

There have been no changes since the last reporting period.

**What other organizations were involved as partners?**

Organization Name: Northwestern University
Location of Organization: Chicago, IL, USA
Partner's Contribution to the Project: Collaboration

Organization Name: Santa Clara Valley Medical Center
Location of Organization: San Jose, CA, USA
Partner's Contribution to the Project: Collaboration

Organization Name: Loyola Genomics Facility
Location of Organization: Maywood, IL, USA
Partner's Contribution to the Project: Quality control testing of blood cell RNA

8. **SPECIAL REPORTING REQUIREMENTS:** None.

9. **APPENDICES:** Quad Chart.

# Advancing Clinical Outcomes, Biomarkers, & Treatments for Severe TBI

**Study PI:** Theresa L.-B. Pape, Dr.PH, [Chicago Association for Research & Education in Science (CARES)] & Hines VA
**P2 Project PI:** Trudy Mallinson, PhD, (The George Washington University);
**P3 Project PIs:** Karen Saban, RN, PhD (CARES/Hines VA); Eileen Foecking, PhD (CARES/Hines VA);

**Currently Funded Double-Blind RCT**

Purpose: Address the need for treatments that safely induce and modulate neural activity and improve functional recovery for *severe Traumatic Brain Injury (TBI)*.

Summarized Study Aims are to:

1. Determine if repetitive Transcranial Magnetic Stimulation (rTMS) is related to safe improvement of neurobehavioral functioning and sustainment of neurobehavioral gains.
2. Determine whether rTMS associated changes in neural activation and white fiber tracts correspond with neurobehavioral changes.

**Project #1: Supplement to Currently Funded RCT**

Purpose: To optimize subject enrollment by supporting additional bed days per subject for the currently funded RCT.

**Project #2: Supplement to Currently Funded RCT**

Purpose**:** Advance clinical assessments for severe TBI research by leveraging the unique data collected for the RCT. Study Aims are to:

1. Determine the extent to which the five TBI outcome assessments do or do not measure the same trait(s).
2. Increase accuracy of TBI outcome measures by neutralizing influence of rater severity and leniency
3. Develop meaningful indices of change (Effect Sizes, Minimally Detectable Change, & Minimally Clinically Important Differences) for each of the five TBI outcome assessments.

**Project #3: Supplement to Currently Funded RCT**

Purpose**:** Identify specific miRNA associated with severe TBI, rTMS and severe TBI, untreated and rTMS induced recovery from severe TBI. Study Aims are to:

1. Identify miRNAs associated with severe TBI and rTMS.
2. Determine the extent to which the severe TBI-associated miRNA are altered by rTMS.
3. Determine the extent to which changes in miRNA levels are associated with non-rTMS-treatment related change in neurobehavioral functioning.

| Estimated Timeline and Estimated Costs | | | |
|---|---|---|---|
| **Projects** | **Year 1** | **Year 2** | **Year 3** |
| Project #1 | | | |
| Project #2 | | | |
| Project #3 | | | |
| **Estimated Budget $3,014,629** | **1,499,354** | **781,907** | **733,368** |


**Goals/Milestones Project #2**

☑ Develop/test meaningful change anchors
☑ Create patient video cases and collection of linking data
☑ Examine basic psychometrics for each assessment
☐ Conduct the Rater Severity/Leniency analyses
☑ Conduct Minimally Detectable Change, Minimally Clinically Important Difference, & Effect Size analyses
☐ Complete deliverables including conversion tables, crosswalks, and change indices tables
☐ Dissemination activities

**Goals/Milestones Project #3**

☑ Regulatory requirements
☑ Coordinate study staff and logistics for study
☑ Validation of sample collection, shipment, processing and storage
☐ Validation of miRNA in severe TBI patients
☐ Assessment of miRNA in entire study population
☐ Data analysis

**Quarter Expenditure:** $197,971
**Expenditures to Date:** $1,278,844
Comments/Challenges/Issues/Concerns: Nothing to report

**Goals and milestones for currently funded project and Project #1 reported in parent grant.**