AWARD NUMBER: W81XWH-16-2-0023

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

PRINCIPAL INVESTIGATOR: Theresa Pape, DrPH

CONTRACTING ORGANIZATION:
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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)

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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 #2 Advancing Clinically Reported TBI Outcomes using Modern Psychometrics

Major Goal 1: Development and testing of meaningful change anchors (Months 1-6)
Milestones: Valid hierarchy of anchor descriptors

Accomplishments: We interviewed 21 clinicians and transcribed 19 of these interviews and wrote summaries for the remaining two. We have conducted thematic analysis of the transcripts and from these analyses have written 21 vignettes which will serve as the basis of the anchor descriptions. We have applied for and received IRB approval to cognitively test these descriptors. We have conducted 11 cognitive interviews with two additional cognitive interviews scheduled for May 16th. From our cognitive interviews we have identified key ingredients needed for clinical decision-making. Prior to our next round of data collection, we are analyzing the vignettes with Labov's checklist. This checklist ensures that our vignettes include the key ingredients for writing a narrative. We have identified the 18 vignettes we plan to test using paired comparisons. We have also identified the survey layout and recruitment strategy.

Major Goal 2: Create patient video cases and collection of linking data (Months 6-12)
Milestones: Complete standardize case videos;
Collect data on these videos;

Accomplishments: Although challenged in recruiting participants we have made concerted effort to identify and make contact with alternative recruitment sources to create patient video cases. We have continued to reach out to our new contacts to build capacity for this goal. JW and TM have established a collaboration with a physician hospitalist at GW Hospital who treats patients in DoC. TM is in the process of becoming certified at GW Hospital and JW became certified at GW Hospital, which will enable them to recruit participants to be in these training videos. We anticipate completing the videos by the end of the year.

Major Goal 3: Examine basic psychometrics for each assessment (Months 13-18)
Milestones: Complete rating scale, item, and person analyses;

Accomplishments: We have completed the primary analyses of the psychometric properties for the Coma Near Coma Scale and established preliminary alignment between the CNC and DOCS-25. Two manuscripts have been developed. The manuscript of the primary findings has been revised based on reviewer feedback and was resubmitted to Brain Injury in July 2019. A key output from this work was the development of a nomogram for use by clinicians to rapidly score and interpret the clinical meaningfulness of results. Data from the clinical trial will be validated against these initial calibrations. A second manuscript reporting on indices of responsiveness for

the CNC will be submitted in October 2019. The psychometrics of the CRS-R have proved more challenging than initially anticipated. However, we have found another data source, FITBIR, and are actively working on signing the Data Use Agreement at GWU. The Data Use Agreement was submitted to GWU in June 2019. TM and JW have been following up with GW to ensure the process is moving forward.

Work on the CNC and DOCS-25 has demonstrated to us that stimulus-level data rather than item-level data would be most informative for evaluating the CRS-R because the ordering of the stimuli within CRS-R items (from least to most challenging) does not comport with what we have learned from our studies of the CNC and DOCS. In addition, the hierarchical ordering of the CRS-R stimuli has never been empirically validated. If we were to only analyze of item level stimuli and find that rating scale steps or items were disordered, we would not know how to proceed to rectify the problem. To ensure we have sufficiently precise and robust findings from this clinical trial, we have developed and pilot tested a stimulus-level data collection form for the CRS-R, which we will shortly begin implementing with study participants, as well as with other individuals with DoC from a newly established collaborative relationship with TIRR Memorial Hermann Hospital in Houston Texas. We are in the process of arranging an Institutional Authorization Agreement with TIRR. Finally, we have significantly improved our methodology for examining assessment psychometrics based on the Rasch Model and have used our experience as a springboard to initiate a separate but related effort by establishing and leading an ACRM Measurement Task Force focused on Rasch Analysis. This task force is a collaborative effort of 9 researchers from 8 institutions nationally. The results of this task force, which will be presented at the ACRM Annual conference in 2019 and IOMC 2019 (a pre-conference to ACRM), will provide the most rigorous guidance to date for authors publishing articles using Rasch Analysis.

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;

Accomplishments: We have completed extensive analyses using existing DOCS-25 data to define the methodology to conduct rater severity/leniency analyses and to quantify when rater differences produce a meaningful impact on patient measures. A manuscript describing this preparatory work is in development. We will implement these analyses when more trial data are available.

Major Goal 7: Dissemination activities (Months 33-36)

Accomplishments: The CNC psychometric paper has been submitted to a journal and is under review. We are revising the manuscript for the CNC indices of responsiveness. We have upcoming presentations at ACRM and IOMC conferences in November 2019.

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. This data will supplement the data collected from patients in the clinical trial and allow us to move these methods forward as recruitment for the parent clinical trial continues. 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 revise our clinician vignettes based on Labov's checklist. Once our vignettes are finalized, we will generate and conduct a paired comparison survey after securing all necessary regulatory approvals.

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

5. **CHANGES/PROBLEMS:**

a. Rational for Changes in Approach: This grant was awarded to further support subject enrollment and performance of the currently parent grant and to add two projects to enhance the clinical and scientific impact of the same. While the delay of enrollment in said RCT impacted these projects, the Principal Investigator, Dr. Theresa Pape and her staff have found alternative solutions enabling them to work on each study aim. Dr. Pape and her team are working diligently to recruit and enroll in the parent RCT, which has been an unanticipated lengthy process. They were not able to officially begin enrolling patients until June and August of 2016 due to several requested IRB/HRPO modifications.

b. Rational & Resolutions for Problems/Delays:
SCREENING AND ENROLLMENT PATTERNS AS INDICES OF BARRIERS TO ENROLLMENT

- Strict Eligibility Criteria: The reasons for ineligibility:
  - Most common reason continues to be that patients are admitted to standard acute rehabilitation first and then referred to the study. During acute rehabilitation, many of the patients emerge from the minimally conscious state (i.e., are classified as conscious). Thus, at time of acute rehabilitation discharge, they are no longer eligible for study enrollment.
  - The next most common reason for ineligibility is that the patient remains in a state of disordered consciousness but is referred to us after the 2-year cut-off.
  - The third most common reason is that the patient is on an anti-epileptic medication and cannot be titrated off of this medication safely.
- Considering the Randomization Protocol: When an enrolled participant is randomized to group, we follow the double-blinded randomization protocol. According to this protocol, all participants randomized to the placebo rTMS group have the opportunity to continue with study participation and transition to the active rTMS group. This study design, based on the risk-benefit ratio, also facilitates subject recruitment.
  - To date, two participants have been randomly assigned to the placebo group, one of the two completes the placebo arm on July 10, 2019 and will then re-enroll in the active arm at that time.

- Alternatives/Solutions Relative to Advantages/Disadvantages: With the first EWOF of the parent study, we extended the time post TBI from 1 year to 2 years. While we could further

extend the post injury timeline, the goal is to recruit and study an acute and sub-acute sample. With a smaller sample, a covariate for time post -TBI may not account for between subject variability that would be needed to draw a clear conclusion about effect during acute/sub-acute recovery stage. However, if we see an effect for the chronic population, then this certainly holds promise for use earlier after injury. Dr. Pape has seen effects in chronic patients in a different study, which is in manuscript preparation stage. If the restriction regarding time post TBI is eliminated then the research question we are addressing is: IS there a therapeutic effect of rTMS for persons in states of disordered consciousness across all recovery trajectories (acute, sub-acute and chronic)?

RE-EVALUATION OF RECRUTIMENT STRATEGIES AND REFERRAL SYSTEMS

Direct Patient Referrals from Specialty Hospitals/Units:

- Direct referrals of civilians from physicians at emerging consciousness programs at the Shirley Ryan Ability Lab and the Texas Institute for Rehabilitation Research have been the most successful strategy to date with the majority of our enrolled patients coming from these referrals
    - While direct referrals continue to be made by study physicians for screening prior to acute rehabilitation admission, families continue largely to choose admission to standard rehabilitation prior to enrolling in an experimental trial.
- The paucity of VA PRC referrals was discussed between the PI, Dr. Pape, and Dr. Joel Scholten, the VA Central Office PM&R and Polytrauma Medical Director. During his monthly leadership meetings with the PRC Chiefs (medical directors of the emerging consciousness programs at each PRC), he emphasizes importance of referrals to the study. To date, however, there have been no PRC referrals. Thus, we continue to receive lists from the VA CO emerging consciousness program database as the method for identifying study candidates from PRC admissions.

DART/VINCI**:**

- Veterans diagnosed with severe TBI and admitted to a VA hospital or medical center with the primary reason for admission being severe TBI, were identified using the national inpatient files available at VA Informatics and Computing Infrastructure (VINCI). We accessed these data files on VINCI using the Data Access Request Tracker (DART) system and then searched the database according to the ICD9CM and ICD10CM codes that allowed us to search by three eligibility criteria. Records from 9/30/2016 to date, were searched (i.e., approximately past 3 years).
    - This national search yielded a list of 33,398 unique Veterans,
    - After filtering outpatient files, the sample was reduced to 4,546 unique Veterans
    - After filtering for only station 578 (Hines VA), the sample was further reduced to 98 unique Veterans
    - After filtering for deaths and bad addresses, the final group of Veterans to be screened was 80
    - We have screened 10 of the 80 to date and these 10 were not eligible (i.e., they are accounted for in Table 1 above). We are actively screening the remaining 70 Veterans on the list.
    - After screening the Hines VA Veterans records, we will then identify duty stations within the radius of the donated air ambulance service and screen these

records from the filtered list.

Study Flyer Distributions and Inservice's:

- Since October of 2017 study flyers at Landstuhl Regional Medical Center (LRMC) have been distributed by Dr. Kendra Jorgensen, Defense and Veterans Brain Injury Centers (DVBIC) Director for Landstuhl. To date, no families have contacted the study team.
- Dr. Saafan Z. Malik, Director, Research Division, DVBIC distributed via email the study information to the 16 DVBIC military treatment facilities.
- Dr. Maheen Adamson, Disordered Consciousness point of contact for DVBIC, presented this research opportunity during their routine meetings
- My study team continues to send email reminders to specialty providers and continues to provide in -services at Level I trauma centers throughout the Chicago-land area as well as extended care facilities
- Study flyers have also been posted on salient web sites locally and nationally

New Recruitment Strategy Implemented 6.25.19

- **We recently hired the services of PatientWing, which provides an online interface for** potential participant families searching for clinical trials and provides contact information for the study team (https://www.patientwing.com). All trials from clinicaltrials.gov are uploaded and synchronized daily with the PatientWing site. Participants and families can search for clinical trials based on conditions and geography. Each trial has a "landing page" which provides trial specific information, such as inclusion criteria, as well as a contact form. The page will also hold "pre-screener" questions to collect further information about participant eligibility. These questions will not require families to provide any PHI. When a potential participant's family enters contact information and answers the pre-screener questions, an email notification is sent to the study contact listed on the site. PatientWing fully complies with patient privacy (HIPAA and GDPR) and FDA (21 CFR Part 11) regulations to ensure patient information is secure and handled properly. In addition, all patient communication on the portal and any associated marketing follows the appropriate Institutional Review Board approved materials. **Northwestern's IRB approved use of this recruitment tool on 6.24.2019 and the landing page for our trial is website on 6.25.19. Hines VA IRB will approve this.**

Table 2 Projected Screening and Enrollment (15 months) with EWOF and New End Date of 9.30.2020

	07/1/19 - 09/30/19	10/01/19 - 12/31/19	01/01/20 - 03/31/20	04/01/20 - 06/30/20	07/01/20 - 09/30/20	Total
Screens Expected						
Hines VAH	30	30	35	40	45	180
Northwestern	8	10	10	10	10	48
						228
Enrollment Expected						
Hines VAH	3	3	3	3	3	15
Northwestern	3	3	3	3	3	15
						30

c. Significant Impact on Expenditures: Expenditures related to subject enrollment is minimal due to delay in patient recruitment.
d. Regulatory Processes to date (IRB, HRPO): The parent project did officially begin enrolling patients until June and August of 2016 due to several requested IRB/HRPO modifications. This had a direct impact on the progress of said subprojects. There are no regulatory issues to report for subproject.

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: 6.21
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, ran in 2016, yielded 8,612 and the title and abstract review

phases are 100% complete. The full text review process is 40% complete and she plans to re-run the search strategy in September 2019 to update the search. The results from the systematic review effort will allow JW and TM to finalize 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 is actively working on writing up the results for publication. We estimate that this publication will be under review by December 2019. She 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 conducted and we are in the writing stages. We intend to submit this manuscript in October of 2019. She is also actively working to create collaborations with local institutions and has become a certified GWU Hospital observer. She has created Data Use Agreements and Institutional Authorization Agreements with collaborative partners to work on collecting additional CRSR data. She also actively works with Ms. Ann Guernon on co-calibrating the DOCS and CNC, this is currently in the analysis stage. We intend to complete the analyses by December 2019.

Name: Trudy Mallinson, PhD
Project Role: PI of Supplemental Project # 2
Nearest person months worked: 2.23
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 was involved in the data analysis of the transcribed interviews and is also contributing to the manuscript. She led JW in the analyses for the CNC—both the psychometric properties and indices of responsiveness. She is also working on the rater severity/leniency analyses plan and overseeing Ms. Jen Weaver and Ms. Ann Guernon on the DOCS and CNC co-calibration 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

American Institute for Research (Co-PI Mallinson) 06/01/2018-12/31/2019
1.5 Calendar Months

"No One Listens to Me"
This proposal'sperformance period is 06/01/2018-12/31/2019. The goal of this project is to explore meaningful change for patient's recovery of consciousness following a brain injury from the caregiver's perspective. From the caregiver's descriptions, we will create vignettes, conduct a paired comparison to develop a hierarchy and then pilot test this hierarchy with caregivers and clinicians.

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.

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Subproject: “miRNA as Biomarkers for Severe TBI and rTMS Mediated Gains in Neurobehavioral Activity”

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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 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 approved

Accomplishments: 100% completed.

Major Goal 2: Coordinate Study Staff and Logistics for Study (Months 1-36)
Milestones: Milestone Achieved: Study staff hired and trained
Accomplishments: 100% completed.

Major Goal 3: Validation of sample collection, shipment, processing and storage
Milestones: Validation and standardization of sample collection, shipping, processing and storage;
Accomplishments: 100% completed.

Major Goal 4: Validation of miRNA in severe TBI patients
Milestones: Validation of target miRNA to follow in TBI patients;

Accomplishments: 18.8% completed- We have 9 out of the 48 patients complete.

Major Goal 5: Assessment of miRNA in entire study population
Milestones: All study participants recruited and completion of research participation;

Accomplishments: 44.1% completed- We have obtained samples for 10 TBI patients and have the miRNA isolated and sequenced for 7 of the patients. We have all healthy control samples collected, miRNA isolated and sequenced. The blood samples from the 8th patient is in the queue to be isolated and sequenced and we should have the data soon. Blood from the 9th patient has been drawn and blood from the 10th patient is currently being drawn. The RNA from both of these patients will be isolated within the next month and the process for miRNA sequencing following the RNA isolation.

Major Goal 6: Data Analysis (Months 37-48)

Accomplishments: **12.1% completed** - MicroRNAs (miRNAs) are small regulatory RNAs that post-transcriptionally regulate the expression of thousands of genes and play key roles in a number of essential cellular and developmental processes, in both normal physiologic and disease contexts. The miRNA expression profile can provide insights about up and down regulated genes and pathways, that when combined with clinical data, can help to explain the

efficacy of treatments and further inform targeting of therapeutics. The miRNA from **7 TBI patients** have been completely isolated, sequenced and analyzed.

Methods: Blood samples of the severe TBI patients enrolled in the ongoing clinical trial examining efficacy and safety of transcranial magnetic stimulation (TMS) were collected. Samples were collected at different time points during active/sham TMS treatment and after stopping active/sham TMS treatment. Each sample was surveyed through miRNA sequencing on the Illumina MiSeq bench-top sequencer. Bioinformatic analysis was conducted using CutAdapt v2.3 tool to remove adapter sequences and Bowtie2 v2.3.5 to align the sequences to the Genome Reference Consortium Human Build 38 (GRCH38). The miRNAs that aligned to the reference genome were counted with HTSeq v0.3.7 tool. The count files were then used to analyze the miRNA expression with the tool DESeq2 v3.9 in R v3.5.1 software, using a fold-change of 2.0 and p-value <0.05 as cutoffs.

Analyses': To date, we have conducted three analyses. First, all 7 patients were examined as one group as this allows us to maintain blinding. We first compared the patients to their age and gender matched healthy controls. We conducted a second analysis by examining the changes in miRNA during active/sham TMS treatment provision for this group. To provide additional insights on TMS treatment responsiveness, we conducted a third analyses where we compared clinical gains for a patient optimally responding to TMS versus a sub-optimal clinical responder (both of whom were in active group).

Results: For the first group analysis (n=7, 7 time-points), we found 27 up-regulated and 15 down-regulated miRNAs in patients vs. age and gender matched healthy controls. Approximately half are consistently found across timepoints. Also, miR-151b is significantly elevated in our severe TBI patients compared to the healthy controls. There were also *significant differences with miR-9-3p, miR20a.* Each of these miRNA have been previously reported to correlate with TBI severity. Increased circulating serum levels of these miRNAs have been shown to correlate with more neurocognitive impairment. Lower expression of miR-9-3p is also associated with better synaptic plasticity and working memory.

During and after active/sham TMS treatment we found 5 up-regulated and 19 down-regulated miRNAs. We also found miR-9 family members consistently down-regulated. miR-9-3p is significantly decreased following active/sham TMS treatment 4.27-fold from baseline following 2 treatments, 3.47- fold after 9 TMS treatments, 2.98-fold after16 TMS treatments, and 4-fold after 23 TMS treatments. miR20a is also decreased 1.5-fold after 9 treatments.

When comparing the optimal versus sub-optimal clinical responders to active TMS, miR-20a and let-7i, miRNAs known to decrease/inhibit the release of BDNF, were significantly down-regulated. MiR-27a was also consistently down-regulated and it is associated with neuron apoptosis and DNA damage response.

Conclusions: Overall, findings indicate that miRNA expression is likely useful as a biomarker of TBI severity. For a population with many challenges for demonstrating treatment efficacy, findings also indicate that changes in miRNA expression advance understanding of TMS treatment efficacy. Our findings also indicate that miRNA expression will likely be helpful in understanding differences in treatment responsiveness and identifying potential therapeutic targets (e.g. let-7i). We found several regulated miRNAs of interest and particularly the miR-9 family, which is associated with neuron differentiation and brain development. The let-7 family been reported to be related to cortical plasticity. miR-9-3p, miR20a, and miR151 have all been previously reported to correlate with severity of injury after mild and severe TBI. Increased circulating serum levels of these miRNAs have also been shown to correlate with more

neurocognitive impairment, and two of them are significantly down-regulated in our study. These miRNAs may lead to novel biomarkers for response to treatment and efficacy.

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

How were the results disseminated to communities of interest? Although no dissemination has occurred, preparation of the first manuscript has begun to describe the miRNA data obtained between healthy controls and patients with severe TBI. A second manuscripts is also in preparation describing the changes in miRNA induced by TMS in severe TBI patients over time.

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

We repeated the first group analysis described above, but we eliminated the one placebo from this group. That is, the PI has since the time of the first analysis been unblinded (per protocol) and is able to group patients while maintaining blinding of the geneticists conducting analyses. Our next step for that group analysis of active TMS participants is to conduct pathway analyses to understand how the above miRNA changes affect different physiological pathways. We are also conducting these same pathway analyses with all 7 patients (active and sham), but the patients are stratified by two levels of behavioral responsiveness according to five different behavioral measures.

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 will continue to analyze the data that we will obtain for the first 7 TBI participants. We anticipate that the 8th patient samples will be run on the miSeq. We will finish the collection of the 10th patient and isolation of the RNA from both the 9th and 10th patients along with the sequencing of the miRNA. We also plan to continue obtaining new patient samples and process them as all previous samples

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

5. **CHANGES/PROBLEMS:**

a. Rational for Changes in Approach: This grant was awarded to further support subject enrollment and performance of the currently parent grant and to add two projects to enhance the clinical and scientific impact of the same. The delay of enrollment in said RCT has had a direct impact these projects. The Principal Investigator, Dr. Theresa Pape and her staff have found alternative solutions enabling them to work on each study aim. The team is working diligently to recruit and enroll in the parent RCT, which has been an unanticipated lengthy process. They were not able to officially begin enrolling patients until June and August of 2016 due to several requested IRB/HRPO modifications.

b. Rational & Resolutions for Problems/Delays:
SCREENING AND ENROLLMENT PATTERNS AS INDICES OF BARRIERS TO ENROLLMENT

- <u>Strict Eligibility Criteria:</u> The reasons for ineligibility:

- Most common reason continues to be that patients are admitted to standard acute rehabilitation first and then referred to the study. During acute rehabilitation, many of the patients emerge from the minimally conscious state (i.e., are classified as conscious). Thus, at time of acute rehabilitation discharge, they are no longer eligible for study enrollment.
- The next most common reason for ineligibility is that the patient remains in a state of disordered consciousness but is referred to us after the 2-year cut-off.
- The third most common reason is that the patient is on an anti-epileptic medication and cannot be titrated off of this medication safely.

- Considering the Randomization Protocol: When an enrolled participant is randomized to group, we follow the double-blinded randomization protocol. According to this protocol, all participants randomized to the placebo rTMS group have the opportunity to continue with study participation and transition to the active rTMS group. This study design, based on the risk-benefit ratio, also facilitates subject recruitment.
  - To date, two participants have been randomly assigned to the placebo group, one of the two completes the placebo arm on July 10, 2019 and will then re-enroll in the active arm at that time.

- Alternatives/Solutions Relative to Advantages/Disadvantages: With the first EWOF of the parent study, we extended the time post TBI from 1 year to 2 years. While we could further extend the post injury timeline, the goal is to recruit and study an acute and sub-acute sample. With a smaller sample, a covariate for time post -TBI may not account for between subject variability that would be needed to draw a clear conclusion about effect during acute/sub-acute recovery stage. However, if we see an effect for the chronic population, then this certainly holds promise for use earlier after injury. Dr. Pape has seen effects in chronic patients in a different study, which is in manuscript preparation stage. If the restriction regarding time post TBI is eliminated then the research question we are addressing is: IS there a therapeutic effect of rTMS for persons in states of disordered consciousness across all recovery trajectories (acute, sub-acute and chronic)?

RE-EVALUATION OF RECRUTIMENT STRATEGIES AND REFERRAL SYSTEMS

Direct Patient Referrals from Specialty Hospitals/Units:

- Direct referrals of civilians from physicians at emerging consciousness programs at the Shirley Ryan Ability Lab and the Texas Institute for Rehabilitation Research have been the most successful strategy to date with the majority of our enrolled patients coming from these referrals
  - While direct referrals continue to be made by study physicians for screening prior to acute rehabilitation admission, families continue largely to choose admission to standard rehabilitation prior to enrolling in an experimental trial.
- The paucity of VA PRC referrals was discussed between the PI, Dr. Pape, and Dr. Joel Scholten, the VA Central Office PM&R and Polytrauma Medical Director. During his monthly leadership meetings with the PRC Chiefs (medical directors of the emerging consciousness programs at each PRC), he emphasizes importance of referrals to the study. To date, however, there have been no PRC referrals. Thus, we continue to receive lists from the VA CO emerging consciousness program database as the method for identifying study candidates from PRC admissions.

DART/VINCI**:**

- Veterans diagnosed with severe TBI and admitted to a VA hospital or medical center with the primary reason for admission being severe TBI, were identified using the national inpatient files available at VA Informatics and Computing Infrastructure (VINCI). We accessed these data files on VINCI using the Data Access Request Tracker (DART) system and then searched the database according to the ICD9CM and ICD10CM codes that allowed us to search by three eligibility criteria. Records from 9/30/2016 to date, were searched (i.e., approximately past 3 years).
    - This national search yielded a list of 33,398 unique Veterans,
    - After filtering outpatient files, the sample was reduced to 4,546 unique Veterans
    - After filtering for only station 578 (Hines VA), the sample was further reduced to 98 unique Veterans
    - After filtering for deaths and bad addresses, the final group of Veterans to be screened was 80
    - We have screened 10 of the 80 to date and these 10 were not eligible (i.e., they are accounted for in Table 1 above). We are actively screening the remaining 70 Veterans on the list.
    - After screening the Hines VA Veterans records, we will then identify duty stations within the radius of the donated air ambulance service and screen these records from the filtered list.

Study Flyer Distributions and Inservice's:

- Since October of 2017 study flyers at Landstuhl Regional Medical Center (LRMC) have been distributed by Dr. Kendra Jorgensen, Defense and Veterans Brain Injury Centers (DVBIC) Director for Landstuhl. To date, no families have contacted the study team.
- Dr. Saafan Z. Malik, Director, Research Division, DVBIC distributed via email the study information to the 16 DVBIC military treatment facilities.
- Dr. Maheen Adamson, Disordered Consciousness point of contact for DVBIC, presented this research opportunity during their routine meetings
- My study team continues to send email reminders to specialty providers and continues to provide in -services at Level I trauma centers throughout the Chicago-land area as well as extended care facilities
- Study flyers have also been posted on salient web sites locally and nationally

New Recruitment Strategy Implemented 6.25.19

- **We recently hired the services of PatientWing, which provides an online interface for** potential participant families searching for clinical trials and provides contact information for the study team (https://www.patientwing.com). All trials from clinicaltrials.gov are uploaded and synchronized daily with the PatientWing site. Participants and families can search for clinical trials based on conditions and geography. Each trial has a "landing page" which provides trial specific information, such as inclusion criteria, as well as a contact form. The page will also hold "pre-screener" questions to collect further information about participant eligibility. These questions will not require families to provide any PHI. When a potential participant's family enters contact information and answers the pre-screener questions, an email notification is sent to the study contact listed on the site. PatientWing fully complies with patient privacy (HIPAA and GDPR) and FDA (21 CFR Part 11) regulations to ensure patient information is secure and handled properly. In addition, all patient communication on the portal and

any associated marketing follows the appropriate Institutional Review Board approved materials. **Northwestern's IRB approved use of this recruitment tool on 6.24.2019 and the landing page for our trial is website on 6.25.19. Hines VA IRB will approve this.**

Table 2 Projected Screening and Enrollment (15 months) with EWOF and New End Date of 9.30.2020						
	07/1/19 - 09/30/19	10/01/19 - 12/31/19	01/01/20 - 03/31/20	04/01/20 - 06/30/20	07/01/20 - 09/30/20	Total
Screens Expected						
Hines VAH	30	30	35	40	45	180
Northwestern	8	10	10	10	10	48
						228
Enrollment Expected						
Hines VAH	3	3	3	3	3	15
Northwestern	3	3	3	3	3	15
						30

c. Significant Impact on Expenditures: Expenditures related to subject enrollment is minimal due to delay in patient recruitment.

d. Regulatory Processes to date (IRB, HRPO): The parent project did officially begin enrolling patients until June and August of 2016 due to several requested IRB/HRPO modifications. This had a direct impact on the progress of said subprojects. There are no regulatory issues to report for subproject.

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 **(STUDY SITE CLOSED)**
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:

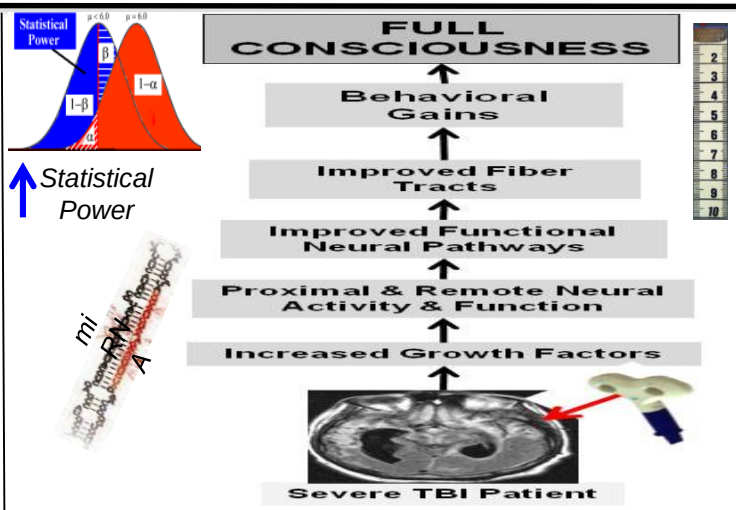
1. Determine the extent to which the five TBI outcome assessments do or do not measure the same trait(s).
2. Increase accuracy of TBI outcome measures by neutralizing influence of rater severity and leniency
3. Develop meaningful indices of change (Effect Sizes, Minimally Detectable Change, & Minimally 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: $199,648
Expenditures to Date: $1,881,701
Comments/Challenges/Issues/Concerns: Nothing to report

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