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TITLE: Biomarkers in the Brain Oxygen Optimization in Severe TBI Trial (Bio-BOOST)

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CONTRACTING ORGANIZATION: University of Pennsylvania, Philadelphia, PA

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14. ABSTRACT

Traumatic brain injury (TBI) remains a major cause of death and disability, with an estimated cost of $45 billion/year in the United States alone. Of the 300,000 hospital admissions for TBI annually, approximately 40% are classified as severe TBI, and there are currently limited objective tools for personalization of TBI treatment and for monitoring response to novel therapies. Blood and cerebrospinal fluid (CSF) levels of structural proteins components of brain cells that are released in the aftermath of brain injury may be a promising adjunct for detecting and monitoring secondary brain injury. The recently launched BOOST-3 (Brain Oxygen Optimization in Severe TBI Phase 3) trial offers a unique opportunity to study and validate biomarkers and therefore accelerate our understanding of the pathophysiology of severe TBI, and promote the development of effective interventions. BOOST-3 will enroll 1094 participants with severe TBI from 2018 – 2023 representing a federal investment. Capitalizing on the infrastructure of BOOST-3, we propose conducting an ancillary biomarker study, Bio-BOOST. Our primary objective is to quantify the effect of total brain tissue hypoxia exposure on brain injury using biofluid-based biomarkers of brain injury. We hypothesize that total brain tissue hypoxia exposure within 48 hours of randomization is independently associated with higher peak levels of biomarkers of astrocytic (GFAP) and axonal (UCH-L1, Total Tau and NFL) injury, after adjusting for age, gender, and time between injury and randomization.

15. SUBJECT TERMS Brain tissue hypoxia; Intracranial hypertension; Neurofilament light chain; Glial fibrillary acidic protein; Ubiquitin C-terminal hydrolase; Tau;

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1. INTRODUCTION:

Traumatic brain injury (TBI) remains a major cause of death and disability, with an estimated cost of $45 billion/year in the United States alone. Of the 300,000 hospital admissions for TBI annually, approximately 40% are classified as severe TBI, and these patients require admission to an intensive care unit (ICU) for supportive care and interventions aimed at limiting secondary brain injury. Less than 20% of patients with severe TBI make a good recovery, and most are left with life-long disabilities, representing a large unmet medical need. There are currently limited objective tools for personalization of TBI treatment and for monitoring response to novel therapies. Blood and cerebrospinal fluid (CSF) levels of structural proteins components of brain cells that are released in the aftermath of brain injury may be a promising adjunct for detecting and monitoring secondary brain injury. Serial measurements of these biomarkers especially in CSF may be useful for monitoring ongoing secondary. The recently launched BOOST-3 (Brain Oxygen Optimization in Severe TBI Phase 3) trial offers a unique opportunity to study and validate biomarkers and therefore accelerate our understanding of the pathophysiology of severe TBI, and promote the development of effective interventions. BOOST-3 will enroll 1094 participants with severe TBI from 2018 – 2023, across 45 clinical sites in the US, and represents a $32.5 M federal investment. The primary hypothesis of BOOST-3 is that a treatment based on brain tissue oxygen (PbtO2) and intracranial pressure (ICP) monitoring improves neurologic outcome measured by the Glasgow Outcome Scale-Extended (GOS-E) 6 months after injury compared to treatment based on ICP monitoring only. Capitalizing on the infrastructure and the rich study population for BOOST-3, we propose conducting an ancillary biomarker study, Bio-BOOST.

2. KEYWORDS:

Brain tissue hypoxia; Intracranial hypertension; Neurofilament light chain; Glial fibrillary acidic protein; Ubiquitin C-terminal hydrolase; Tau;

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Our primary objective is to quantify the effect of total brain tissue hypoxia exposure on brain injury using biofluid-based biomarkers of brain injury. We hypothesize that total brain tissue hypoxia exposure within 48 hours of randomization (defined as the depth and duration of PbtO2<20 mmHg during the first 48 hours of injury, quantified using the AUC methodology) is independently associated with higher peak levels of biomarkers of astrocytic (GFAP) and axonal (UCH-L1, Total Tau and NFL) injury, after adjusting for age, gender, and time between injury and randomization. Our secondary objectives are:

1. Determine the effect of total cerebral hypoperfusion exposure on peak biomarker levels.
2. Determine whether a prescribed treatment protocol based on $PbtO_2$ monitoring results in a decrease in blood and CSF levels of TBI biomarkers.
3. Determine whether in severe TBI patients, the initial CSF and blood levels of brain injury TBI biomarkers are associated with unfavorable functional outcome as measured by the Glasgow Outcome Scale Extended (GOSE) 6 months after injury.
4. Determine whether the rate of increase in brain injury biomarker levels during the first 24 hours after randomization are associated with unfavorable functional outcome.
5. Determine the time-point at which biomarker levels provide the best discriminative ability
6. Create a biorepository at the University of Pittsburgh TBI Biorepository of longitudinal serum, plasma, CSF, mRNA and DNA samples of severe TBI patients for validating novel brain injury biomarkers.

What was accomplished under these goals?

Major Task 1: During the first year of this project, we have completed most of the Major task 1:
(1). Bio-BOOST study was registered in FITBIR. Bio-BOOST investigators completed the FITBIR orientation training session. We have finalized the procedures between the BOOST Data Coordinating Center at MUSC and the NINDS FITBIR for uploading Bio-BOOST data into FITBIR.
(2). We have completed site interest and qualification surveys among all BOOST sites.
We have completed the Bio-BOOST Protocol, Manual of Operations, and Informed Consent Form.
(3). The SIREN Data Safety and Monitoring Board have approved the Bio-BOOST protocol and ICF, after our responses to minor stipulations. We obtained Central IRB approval (Advarra) for the Bio-BOOST study.
(4). We have selected the 10 of the 15 sites that will participate in Bio-BOOST. Most have completed the IRB ceding to Advarra, which will serve as the central IRB for this project. The remaining 5 clinical sites will be chosen when sufficient sites have demonstrated efficient enrollment in the parent BOOST-3 protocol
(5). We have conducted site training and site initiation visits for Bio-BOOST related activities at 5 clinical sites, which will be ready to open for enrollment as soon as HRPO approval is finalized.
(6). We have registered the study in ClincalTrials.gov
(7). We have conducted site initiation phone calls with 6 of the selected Bio-BOOST sites.
(8). Subcontract between Univ. of Pennsylvania, MUSC, University of Michigan, and Univ. of Pittsburg have been finalized.
(9). University of Michigan is working on subcontracts with the 8 clinical sites that do not already have subcontracts.
(10). We have worked diligently with HRPO to obtain final second-level clearance for launching this study at the clinical sites. So far final HRPO approval has been obtained at 3 sites.
(9). We have worked with HRPO to finalize the second level regulatory approvals. Approval have been finalized for 3 Bio-BOOST clinical sites, and approval for the remaining sites is expected soon.
(10). One site (University of Pittsburgh) is open for enrollment in Bio-BOOST
Major Task 2: All tasks related to Major Task 2 have been completed by the end of the first year
(1). We have completed the Bio-BOOST Case Report Forms (CRFs) for documenting biospecimen collection .
(2). Database programmers at MUSC finished programming Bio-BOOST specific Database fields. They have finalized the Case Report Forms for biospecimen tracking to the Bio-BOOST repository at the University of Pittsburgh.
(3). The Manual of Operations has been completed and posted on the Bio-BOOST website.

What opportunities for training and professional development has the project provided?

None to date. Several junior investigators at Bio-BOOST sites have expressed interest in using Bio-BOOST resources, when they are available, for use in investigator-initiated research projects.

How were the results disseminated to communities of interest?

Dr. Diaz-Arrastia has given a presentation to the TBI Patient Support Group at the University of Pennsylvania on ongoing research at the Penn TBI Center, which included extensive discussion on BOOST and Bio-BOOST. This presentation was designed to educate and gauge enthusiasm for TBI survivors and caregivers about participation in these studies, and to educate them on the value of the information that can be obtained through such research..

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

We expect to obtain HRPO approval for launching the clinical activities of this project within the first quarter of 2021. Since we have completed staff recruitment and training, we expect that enrollment will proceed efficiently at all the clinical sites.
We will carefully (1). Monitor CRF completion, to insure that complete and clean data is being entered into the Bio-BOOST database. When appropriate, data queries will be sent to the clinical sites, to insure accuracy. (2). Monitor the transfer and quality of blood speciments (serum, plasma, DNA, PAXGene) collected as part of this project and sent to the Bio-BOOST Biospecimen Repository at the University of Pittsburgh.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report. This project is in its early stages.

What was the impact on other disciplines?

Nothing to report. This project is in its early stages.

What was the impact on technology transfer?

Nothing to report. This project is in its early stages.

What was the impact on society beyond science and technology?

Nothing to report. This project is in its early stages.

5. CHANGES/PROBLEMS:

Nothing to Report.
It is possible that, given delays due to HRPO approval and the effect of COVID-19 restrictions on enrollment in the parent BOOST-3 trial, that re-budgeting will be necessary during Year 2 of this project. We will obtain written approval from CDMRP before any rebudgeting is done.

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

(1). Enrollment in the parent BOOST-3 study has been slower than anticipated. This is likely due to multiple reasons.

(a). The approval of EFIC activities by the Advarra Central IRB has been slower than anticipated. As a consequence, the launch of BOOST-3 at the 45 targeted clinical sites has been slowed, and is only now nearing completion.

(b). COVID-19 restrictions led to most BOOST-3 sites being closed for enrollment for over 6 months (several still are). We are anticipating that these will be lifted by the end of the 2nd quarter of 2021.

(2). Staff turnover in the Penn Department of Neurology Business Office have delayed the subcontracting with all the clinical sites. New leadership and staff has been hired and trained at the Business Office, and the importance of this project has been given priority.

Changes that had a significant impact on expenditures

Due to the factors outlined above, our expenditures are lower than anticipated by this point in the project. We have been diligent in not spending money unless absolutely necessary, and sufficient funds are available to complete the study. We expect that most of the carry-forward funds will be spent over the next 12 months, with the need for minor rebudgeting.

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

Significant changes in use or care of human subjects

No significant changes.

Significant changes in use or care of vertebrate animals

Not applicable. This project does not utilize vertebrate animals.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS:

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

Journal publications.

Diaz-Arrastia R, Shahim P, Sandsmark DK. Molecular biomarkers in the neurological ICU: is there a role? *Curr Opin Crit Care.* 2020 Apr;26(2):103-108. PubMed PMID: 32004197. Acknowledgement of federal support: YES

Books or other non-periodical, one-time publications.

None.

Other publications, conference papers and presentations.

None.

- **Website(s) or other Internet site(s)**

None.

- **Technologies or techniques**

None.

- **Inventions, patent applications, and/or licenses**

None.

- **Other Products**

None.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Ramon Diaz-Arrastia, MD, PhD (University of Pennsylvania)
Project Role: Principal Investigator
Months worked: 1
Contribution to Project: Dr. Diaz-Arrastia has supervised the work of Ms. Dabrowski in preparing the Bio-BOOST MOP, ICF, in revising the protocol based on comments from the Penn IRB. Dr. Diaz-Arrastia has also coordinated with Drs. Korley and Yeatts and the Bio-BOOST Executive Committee regarding integrataion of Bio-BOOST with the parent BOOST-3 study, and identification of appropriate sites for clinical recruitment. Finally, Dr. Diaz-Arrastia has worked with UMichigan and MUSC Staff for developing the BioBOOSTspecific CRFs and database fields. With colleagues at UMichigan and MUSC, he participated in the FITBIR orientation start-up call for this project.

Name: Cian Dabroswki, MA (University of Pennsylvania
Project Role: Project Manager, Bio-BOOST
Months worked: 3
Contribution to Project: Ms. Dabrowski has worked under Dr. Diaz-Arrastia's direction in completing the Protocol, Manual of Operations, Informed Consent Form, and Case Report Forms. She completed the IRB submission and approval process at the University of Pennsylvania IRB, and has managed the HRPO submission process. She has also interphased with UCSF staff exploiting the built-in synergies between the TRACK-TBI EPI project and the ongoing TRACK-TBI LONG.

Name: Fred Korley, MD, PhD (University of Michigan)
Project Role: co-PI, Bio-BOOST
Months worked: 1
Contribution to Project: Dr. Korley has interacted closely with the BOOST-3 leadership and staff at SIREN, and has supervised the work of SIREN staff launching the Bio-BOOST study. He has worked closely with Dr. Diaz-Arrastia and Ms. Dabrowski. The Protocol, MOP, ICF forms have all been completed as part of this effort. Dr. Korley has also coordinated the IRB ceding process at the clinical sites, which have ceded to the Advarra IRB (which will function as the central IRB for this project).

Name: Ava Puccio, RN, PhD (University of Pittsburgh)
Project Role: Director, Bio-BOOST Biorepository
Months worked: 1
Contribution to Project: Dr. Puccio is the Director of the University of Pittsburgh TBI Biorepositoryand leads biospecimen-related operations for Bio-BOOST. She completed the sample collection, processing, and shipping aspects of the Bio-BOOST Protocol and MOP, and developed training materials to train staff at the clinical sites. She has overseen training sessions and site initiation visits, in close coordination with Drs. Diaz-Arrastia and Korley.

Name: Erin Bengelink (University of Michigan)
Project Role: Project Manager, BOOST-3, Bio-BOOST and SIREN
Months worked: 1
Contribution to Project: Ms. Bengelink is the Project Manager for BOOST-3 and Bio-BOOST, and has extensive experience working with the NETT and now the SIREN Network. She has been primarily involved in dealing the Advarra and coordinated integration of the Bio-BOOST study with the parent BOOST-3 study.

Name: Kavita Patel (Medical University of South Carolina)
Project Role: Database specialist
Months worked: 1
Contribution to Project: Ms. Patel is a database specialist at the SIREN Data Coordination Center. She has worked to develop the Bio-BOOST Research Database and Case Report Forms, and coordinated with programmers at MUSC to create the electronic database for this project.

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

Nothing to report.

What other organizations were involved as partners?

Organization Name: University of Michigan
Location of Organization: Ann Arbor, Michigan
Partner's contribution to the project: Collaboration. The University of Michigan is the Clinical Coordinating Center for the SIREN Network, which runs the parent BOOST-3 study. Investigators at UMichigan (Drs. Korley, Ms. Bengeling, and other SIREN collaborators) have played key roles in finalizing the Bio-BOOST Protocol, MOP, and have managed interactions with the Advarra central IRB.

Organization Name: University of Pittsburgh Medical Center
Location of Organization: Pittsburgh, Pennsylvania
Partner's contribution to the project: Collaboration. The University of Pittsburgh houses the Bio-BOOST Biorepository. Investigators at Pitt (Dr. Puccio) has adapted the TRACK-TBI Biorepository procedures to accept samples from the Bio-BOOST project, have developed training materials, and conducted training sessions with the clinical sites.

Organization Name: Medical University of South Carolina
Location of Organization: Charleston, California
Partner's contribution to the project: Collaboration. MUSC houses the Data Coordination Center for the SIREN Network, which runs the parent BOOST-3 study. Investigators at MUSC have been instrumental in finalizing the Case Report Forms, Database, and MOP, working closely with Drs. Diaz-Arrastia, Korley, Puccio, and the rest of the Bio-BOOST team.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

(1). Bio-BOOST Protocol

(2). Bio-BOOST Manual of Operations

(3). Bio-BOOST Case Report Forms