AWARD NUMBER: W81XWH-19-1-0829

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

PRINCIPAL INVESTIGATOR: Ramon Diaz-Arrastia, MD, PhD

CONTRACTING ORGANIZATION: University of Pennsylvania

REPORT DATE: October 2022

TYPE OF REPORT: Annual Report

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
OCTOBER 2022	Annual	30 Sep 2021 – 29 Sep 2022

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-19-1-0829

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

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 $32.5 M 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

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	14	**19b. TELEPHONE NUMBER** *(include area code)*

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

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:** *Provide a brief list of keywords (limit to 20 words).*

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

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

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?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major Task 1: Preparing sites for study enrollment. Conducting site qualification surveys, collecting regulatory documents from sites, obtaining regulatory approval from individual IRBs, conducting site training for biospecimen collection, processing, and shipping, and conducting site initiation phone calls.

COMPLETED. We have launched the study at 11 clinical sites (Table below), and all have enrolled at least one participant in Bio-BOOST.

The original budget and plan was to have 15 sites launched. However, due to slow enrollment in the parent BOOST study, only 12 sites have been sufficiently active in enrolling to warrant launching Bio-BOOST at those sites. We are currently in late stages of negotiations to launch an additional 3 sites (Ohio State, Detroit Receiving/Wayne State Univ, and University of North Carolina), which will represent most of the sites that are currently successfully enrolling subjects in the parent BOOST study and have the capacity for collecting and processing blood samples.

(a). HRPO approval has been obtained for Ohio State, and Detroit Receiving.
(b). HRPO approval is pending for University of North Carolina and Regions Hospital.
(c). Site interest negotiations under way with additional 4 sites (of which one of more may be invited to participate in the study based on their success in enrolling participants in the parent study)

Major Task 2—Prepare study database: All tasks related to Major Task 2 have been completed by the end of the first year. No additional work on this task was necessary during Year 2.

Major Task 3--Collect Biospecimens: This task is underway.

IN PROGRESS: Specimens have been collected on 91 subjects. This represents an additional 13 subjects over the past 3 months, and an increase of 55 participants over the past 12 months. Table 1 summarizes those details:

Site	Number of participants enrolled
Ben Taub General Hospital/Baylor College of Medicine	26
Maine Medical Center	7
Oregon Health and Sciences University Hospital	17
Penn Presbyterian Medical Center	5
Strong Memorial Hospital	7
University of California, Davis	5
University of Florida Shands Hospital	3
University of Pittsburgh Medical Center	12
University of Chicago Medical Center	5
University of Cincinnati Medical Center	3
University of Utah Healthcare	1
TOTAL	91

Over the past 4 months approximately 50% of subjects enrolled in the parent BOOST3 study have been co-enrolled in BioBOOST, reflecting our choice to launch the BioBOOST study at sites that have demonstrated a good track record of recruitment for the parent study.

While enrollment in the parent BOOST3 study is behind schedule (for reasons outlined in section 5 below), the enrollment rate over the past 6 months has increased substantially, and we are now on track to complete enrollment in the parent BOOST3 study by the 4th Quarter of 2025. At the current rate of enrollment in BioBOOST, we anticipate completing enrollment in BioBOOST by the 1st Quarter of 2025. We expect that by adding additional sites, BioBOOST will be fully enrolled at some time prior to that, likely sometime in 2023.

Major Task 4--Measure biomarkers: This task has not yet started.

Major Task 5--Analyze data: This task has not yet started.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Dr. Diaz-Arrastia gave a platform presentation at the American Neurological Association Annual Meeting in Chicago, IL, titled "Long-term prognosis after TBI: Novel Biomarker Insights," during the NeuroCritical Care and TBI Workshop. Bio-BOOST was prominently discussed during this presentation. This workshop was attended by over 100 neurologists interested in neurocritical care and TBI.
Dr. Diaz-Arrastia was an invited speaker at Grand Rounds of the Department of Neurosurgery at the University of Utah, on the topic of "Endophenotypes of TBI." The BioBOOST study was discussed to emphasize the importance of the data to be obtained.
Dr. Diaz-Arrastia also gave a presentation at the Arrowhead TBI Conference in June, 2022, to over 150 TBI researchers, which included a discussion of the importance of blood biomarkers to assist in management of acute TBI in the ICU.

If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We expect to obtain HRPO approval for launching the clinical activities at an additional 4 sites by the end of Q1, 2023. Training at the additional 4 sites will also be completed. We anticipate that the new sites will enroll as efficiently as the 11 sites that have already been launched. 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:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

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

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

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

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

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

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

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

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

There have been no changes in the project goals or direction.
It is likely, given the delays in the enrollment in the parent BOOST3 study as well as delays in launching BioBOOST, that re-budgeting will be necessary during Year 3 of this project, and that a no-cost extension will be needed beyond Year 4. We will obtain written approval from CDMRP before any rebudgeting is done.

Not applicable.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Enrollment has been slower than anticipated. There are several reasons for this.
(1). There was substantial turnover of research staff at Penn and other sites, due to COVID-19 restrictions and other unforeseen circumstances. There were also delay in recruiting staff, in part due to COVID-19 restrictions.
(2). Enrollment in the parent BOOST3 study has also been behind projections, for the same reasons outlined above, and a lower than expected incidence of severe TBI during the pandemic. However, the enrollment rate has picked up over the past 6 months, and current enrollment stands at 417. Over the past 6 months, approximately half of BOOST3 enrollments have also co-enrolled in Bio-BOOST, and if that pace keeps up, we anticipate fully enrolling the Bio-BOOST study (target n=300) approximately one year prior to completing enrollment in the BOOST3 trial.
(3). Several sites that were expected to be excellent recruitment sites bowed out of the parent BOOST3 study as well as BioBOOST, due to staffing shortages and excessive COVID-related burdens in their intensive care units.

Staffing at Penn, in the Penn Neurology Business Office as well as the TBI research staff, is now stable and new staff have efficiently been managing the study. The same is the case at most of the clinical sites.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

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 only minor rebudgeting.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

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: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

- 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.
- Lippa SM, Werner JK, Miller MC, Gill JM, Diaz-Arrastia R, Kenney K. Recent Advances in Blood-Based Biomarkers of Remote Combat-Related Traumatic Brain Injury. *Curr Neurol Neurosci Rep.* 2020 Sep 28;20(12):54. doi: 10.1007/s11910-020-01076-w. PMID: 32984931

Acknowledgement of federal support: YES for all.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

None.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

None.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

None.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

None.

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

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

None.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

None.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*

Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Ramon Diaz-Arrastia, MD, PhD
Project Role: Principal Investigator
Months worked: 0.22
Contribution to Project: Dr. Diaz-Arrastia has worked closely with Drs. Fred Korley at Univ. of Michigan. Ava Puccio at Univ. of Pittsburgh, Sharon Yeatts at MUSC and supervised the work of Ms. Dabrowski at Penn in finalizing the Bio-BOOST MOP, ICF, in revising the protocol based on comments from the SIREN DSMB. Finally, Dr. Diaz-Arrastia has worked with SIREN CCC and DCC Staff in completing the Bio-BOOST-specific CRFs and database fields. With colleagues at Michigan, MUSC, and Pittsburgh, he participated in the FITBIR orientation start-up call for this project.

Name: Fred Korley, MD, PhD
Project Role: co-Principal Investigator
Months worked: 0.22
Contribution to Project: Dr. Korley has worked closely with Dr. Diaz-Arrastia, Dr. Ava Puccio at Univ. of Pittsburgh, Sharon Yeatts at MUSC in finalizing the Bio-BOOST MOP, ICF, in revising the protocol based on comments from the SIREN DSMB. Finally, Dr. Korley has worked with SIREN CCC and DCC Staff for finalizing the Bio-BOOST-specific CRFs and database fields. With colleagues at Penn, MUSC, and Pittsburgh, he participated in the FITBIR orientation start-up call for this project.

Name: Ava Puccio, RN, PhD
Project Role: Investigator
Months worked: 0.22
Contribution to Project: Dr. Puccio leads the Bio-BOOST sample repository. She was primarily responsible for completing the laboratory and specimen-handling aspects of the Bio-BOOST MOP.

Name: Nathan Smyk, MA
Project Role: Project Manager, Univ. of Pennsylvania
Months worked: 2
Contribution to Project: Mr. Smyk has worked under Dr. Diaz-Arrastia's direction as the project manager for this study at Penn. He has been primarily responsible for maintaining IRB documentation and for communications with HRPO. He has also worked in optimizing the MOP, particularly as it relates to shipments of samples to the Biorespository at the University of Pittsburgh.

Name: Jodie Riley
Project Role: Data Manager
Months worked: 1
Contribution to Project: Ms. Riliey worked with Dr. Yeatts and Korley in finalizing the Bio-BOOST Case Report Forms and instructed the Database Programmers.

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.

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

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: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

None applicable