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CONTRACTING ORGANIZATION: University of Pennsylvania

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14. ABSTRACT

The overall objective of this project is to use rigorously developed sophisticated biostatistical and epidemiological methods that account for study attrition to model cognitive trajectories assessed at multiple time-points over 5 years of follow-up and to determine if individuals with TBI and vascular risk factors have less cognitive recovery in the first year post-TBI and have greater cognitive decline over years1-5 post-TBI compared to individuals with comparable TBI without vascular risk factors and to controls.The overarching hypothesis of this project is that individuals with TBI and vascular risk factors will have less cognitive recovery over the first year post-TBI and greater cognitive decline over years 1-5 post-TBI than individuals with comparable TBI without vascular risk factors and controls. Further, we hypothesize that individuals with TBI and greater severity of vascular risk factors will have less cognitive recovery over the first year post-TBI and greater cognitive decline over years 1-5 post-TBI compared to individuals with comparable TBI and lower severity of vascular risk factors or no vascular risk factors and controls. This project has the potential to generate the following innovative deliverables: 1.) identifying vascular risk factor reduction as a high-priority target for dementia prevention strategies and clinical trials in TBI populations, and 2.) developing biostatistical and epidemiological methods to model cognitive trajectories post-TBI that account for study attrition that can be shared with other i nvestigators and translated both within and across studies with the goal of collaboratively advancing research on post-TBI cognitive decline and dementia.

15. SUBJECT TERMS

Traumatic Brain Injury (TBI), Cognitive Decline, Vascular Risk Factors, Hypertension, Diabetes, Smoking, Hyperlipidemia

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

The overall objective of this project is to use rigorously developed sophisticated biostatistical and epidemiological methods that account for study attrition to model cognitive trajectories assessed at multiple time-points over 5 years of follow-up and to determine if individuals with TBI and vascular risk factors have less cognitive recovery in the first year post-TBI and have greater cognitive decline over years 1-5 post-TBI compared to individuals with comparable TBI without vascular risk factors and to controls. The overarching hypothesis of this project is that individuals with TBI and vascular risk factors will have less cognitive recovery over the first year post-TBI and greater cognitive decline over years 1-5 post-TBI than individuals with comparable TBI without vascular risk factors and controls. Further, we hypothesize that individuals with TBI and greater severity of vascular risk factors will have less cognitive recovery over the first year post-TBI and greater cognitive decline over years 1-5 post-TBI compared to individuals with comparable TBI and lower severity of vascular risk factors or no vascular risk factors and controls. *This project has the potential to generate the following innovative deliverables: 1.) identifying vascular risk factor reduction as a high-priority target for dementia prevention strategies and clinical trials in TBI populations, and 2.) developing biostatistical and epidemiological methods to model cognitive trajectories post-TBI that account for study attrition that can be shared with other investigators and translated both within and across studies with the goal of collaboratively advancing research on post-TBI cognitive decline and dementia.*

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

Traumatic Brain Injury (TBI), Cognitive Decline, Vascular Risk Factors, Hypertension, Diabetes, Smoking, Hyperlipidemia

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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.*

Using data from one of the largest, most comprehensively phenotyped, ongoing longitudinal TBI cohort studies, the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Study, and its follow-up continuation study, the TRACK-TBI Longitudinal (TRACK-TBI LONG) Study, we proposed the following specific aims:

Specific Aim 1. To collaboratively use cutting-edge, rigorous, biostatistical and epidemiological methods to generate 5-years of analysis-ready cognitive trajectory models that account for study attrition. The methods developed will be readily translatable and able to be shared both among TRACK-TBI study investigators and across studies to facilitate advancing research on post-TBI cognitive decline.

Hypothesis 1. Inverse probability of attrition weighting and multiple imputation using chained equations will be valid methods to account for missing data due to study attrition in the TRACK-TBI Study and when combined with generalized estimating equations and mixed models, these methods will result in less biased estimates of longitudinal cognitive change than complete case analyses.

Specific Aim 2. To investigate if vascular risk factors are associated with unfavorable cognitive outcomes after TBI. Specifically, we will examine the impact of the vascular risk factors of diabetes, hypertension, hyperlipidemia, smoking, and obesity on early (1-year post-TBI) and late (5-years post-TBI) cognitive trajectories.

Hypothesis 2a. TBI patients with comorbid vascular risk factors (diabetes, hypertension, hyperlipidemia, smoking, and obesity) will have a lower slope of cognitive recovery in the first year post-TBI (i.e., early cognitive impairment), compared to individuals with comparable TBI but no vascular risk factors and to controls.

Hypothesis 2b. TBI patients with comorbid vascular risk factors (diabetes, hypertension, hyperlipidemia, smoking, and obesity) will have greater cognitive decline over years 1-5 post-TBI (i.e., late cognitive impairment), compared to individuals with comparable TBI but no vascular risk factors and to controls.

Specific Aim 3. To evaluate if markers of modifiable vascular risk severity are associated with unfavorable cognitive outcomes after TBI. Specifically, we will examine the impact of the markers of modifiable vascular risk severity of glucose, systolic and diastolic blood pressure, lipid profile, pack-years of smoking, and body-mass index on early (1-year post-TBI) and late (5-years post-TBI) cognitive trajectories. As an important step in achieving this aim, we propose to measure the glucose and lipid profiles of participants using stored biospecimens from the 2-week post-TBI in-person visit (time of the first cognitive assessment).

Hypothesis 3a. TBI patients with greater vascular risk factor severity (assessed using glucose, systolic and diastolic blood pressure, lipid profile, pack-years of smoking, and body-mass index) will have a lower slope of cognitive recovery in the first year post-TBI (i.e., early cognitive impairment), compared to individuals with comparable TBI but no or less severe vascular risk factors and to controls.

Hypothesis 3b. TBI patients with greater vascular risk factor severity (assessed using hemoglobin A1c, systolic and diastolic blood pressure, lipid profile, pack-years of smoking, and body-mass index) will have greater cognitive decline over years 1-5 post-TBI (i.e., late cognitive impairment), compared to individuals with comparable TBI but no or less severe vascular risk factors and to controls.

The project contains the following 12 Major Tasks:

	Target Completion Date	Current Status
Major Task 1: Study start-up phase and regulatory processes.	Month 6	100% Complete
Major Task 2: Using the TRACK-TBI dataset, perform confirmatory factor analyses to create global and domain-specific cognitive factor scores (using data combined from tests administered via phone and in-person) for use in analyses with vascular risk factors and vascular risk factor severity.	Month 9	100% Complete
Major Task 3: Develop and validate inverse probability of attrition weighting and multiple imputation using chained equations methods to account for study attrition	Month 16	100% Complete
Major Task 4: Develop and validate methods to model longitudinal cognitive trajectories (using generalized estimating equations and mixed effects models).	Month 16	75% Complete
Major Task 5: Using participant data existing in the ongoing TRACK-TBI study, code for the presence or absence of individual vascular risk factors (diabetes, hypertension, hyperlipidemia, smoking, obesity), creating an overall risk score (0-5) that will be binned into 0, 1, or 2+ risk factors.	Month 17	100% Complete
Major Task 6: Using the vascular risk factor coding from MT5 and existing post-TBI cognitive test data from TRACK-TBI (from MT2), analyze (using methods developed in MT3 and MT4) the individual and	Month 25	50% Complete

cumulative contributions of presence of vascular risk factors (n~1,300 with 1+ vascular risk factors) with cognitive recovery in the first year post-TBI compared to individuals with 1) comparable TBI but no risk factors (n~1,350) and 2) healthy controls (n~600). We hypothesize that TBI patients with comorbid vascular risk factors will have a lower slope of cognitive recovery in the first year post-TBI (i.e., early cognitive impairment), compared to individuals with comparable TBI but no vascular risk factors and to controls.		
Major Task 7: Using the vascular risk factor coding from MT5 and existing post-TBI cognitive test data from TRACK-TBI (from MT2), analyze (using methods developed in MT3 and MT4) the individual and cumulative contributions of presence of vascular risk factors (n~1,300 with 1+ vascular risk factors) on cognitive recovery in the years 1-5 post-TBI compared to individuals with 1) comparable TBI but no risk factors (n~1,350) and 2) healthy controls (n~600). We hypothesize that TBI patients with comorbid vascular risk factors will have greater cognitive decline over years 1-5 post-TBI (i.e., late cognitive impairment), compared to individuals with comparable TBI but no vascular risk factors and to controls.	Month 25	50% Complete
Major Task 8: Perform glucose and lipid profile assays, securely transfer data to TRACK-TBI Study Biostatistics Core, and clean and quality check data.	Month 12	N/A – See Below for Changes in Approach
Major Task 9: Categorize and code the severity of the following risk factors: diabetes (glucose), hypertension (systolic and diastolic blood pressure), hyperlipidemia (lipids), smoking (pack-years), and obesity (body mass index) using the newly-generated glucose and lipid profile assays from TRACK-TBI samples in MT8 and patient records, creating an overall severity risk score categorized as 0 vascular risk factors, only less severe vascular risk factors, 1+ more severe vascular risk factors.	Month 26	75% Complete
Major Task 10: Using the vascular risk factor severity coding from MT9 and existing post-TBI cognitive test data from TRACK-TBI (from MT2), determine (using methods developed in MT3 and MT4) if TBI patients with greater vascular risk factor severity (n~700) have a lower slope of cognitive recovery in the first year post-TBI (i.e., early cognitive impairment), compared to individuals with 1) comparable TBI but no (n~1,350), 2) lower severity vascular risk factors (n~600), and 3) healthy controls (n~600). We hypothesize that TBI patients with greater vascular risk factor severity will have a lower slope of cognitive recovery in the first year post-TBI (i.e., early cognitive impairment), compared to individuals with comparable TBI but no or less severe vascular risk factors and to controls.	Month 34	25% Complete
Major Task 11: Using the vascular risk factor severity coding from MT9 and existing post-TBI cognitive test data from TRACK-TBI (from MT2), determine (using methods developed in MT3 and MT4) if TBI patients with greater vascular risk factor severity (n~700) have greater cognitive decline over years 1-5 post-TBI (i.e., late cognitive impairment) compared to individuals with 1) comparable TBI but no (n~1,350), 2) lower severity	Month 34	25% Complete

vascular risk factors (n~600), and 3) healthy controls (n~600). We hypothesize that TBI patients with greater vascular risk factor severity will have greater cognitive decline over years 1-5 post-TBI (i.e., late cognitive impairment), compared to individuals with comparable TBI but no or less severe vascular risk factors and to controls.		
Major Task 12: Study completion phase.	Month 36	Not Yet Started

- **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 – Study Start-up: All subtasks related to Major Task 1 have been completed as scheduled and the following milestones have been achieved:
- The study has received University of Pennsylvania Institutional Review Board (IRB) and DoD Human Research Protection Office (HRPO) approval.
- Katherine Hunzinger PhD completed her post-doctoral fellowship at the University of Pennsylvania from 3/1/2022 through 6/30/2023. As of 7/1/2023, she is now an Assistant Professor of Exercise Science at Thomas Jefferson University. She remains actively involved in the drafting of manuscripts related to this project.
- Data Analyst, Connor Law BS was hired on 12/1/2022. He has completed onboarding and is now actively working on the project.
- All TRACK-TBI data to be used for the analyses in this project has been cleaned and quality checked.

Major Task 2 – Confirmatory Factor Analyses to Create Cognitive Factor Scores: This task is now 100% complete.
- After the death of Dr. Levin (neuropsychology consultant originally on the grant helping with this task), Lindsay Nelson PhD (Associate Professor at the Medical College of Wisconsin) joined the team and has helped to move this task forward. She is a neuropsychologist and has been a TRACK-TBI Study investigator for over 5 years and has previously published on the factor structure of neuropsychology tests.
- Dr. Nelson and her team, in collaboration with Drs. Schneider, Hunzinger, Gardner, and Mr. Law have performed the confirmatory factor analyses for the creation of global and domain-specific cognitive factor scores within the TRACK-TBI cohort.
- We have created a global cognitive factor model to evaluate cognition within the first year after TBI (at 2 weeks, 6 months, and 12 months post injury) comprised of the RAVLT Trial 1–5 total score, RAVLT Delayed recall score, Trail making test (TMT) parts A and B, and the WAIS-IV processing speed index.
- To evaluate cognition from 6 months to 5 years post-injury (assessments at 6 months and then yearly), we have created global and domain specific (episodic memory and executive functioning) factor scores using the Brief Test of Adult Cognition by Telephone (BTACT), in accordance with methods described in Dr. Nelson's prior publication (Nelson et al. *Journal of Neurotrauma*. 2021).
- The derived cognitive factor scores have been sent by Dr. Nelson to Dr. Jain and her team for use in subsequent analyses.

Major Task 3 – Methods to Account for Study Attrition and Missing Data: This task is 100% complete.
- With Dr. Jain's team, we have carefully evaluated patterns of missing cognitive data in the TRACK-TBI cohort.
- Given the substantial amount of missing data (~50%) at later time-points, with Dr. Boscardin's input, we have decided to use inverse probability of attrition weighting to account for study attrition/missing data as

opposed to a multiple imputation using chained equations approach (which is less robust to large amounts of missing data).
- We have identified variables which predict death and dropout in the TRACK-TBI cohort which are used to create the inverse probability of attrition weights for subsequent analyses to account for study attrition/missing data.

Major Task 4 – Longitudinal Data Analysis Methods: This task is 75% complete.
- Working with Dr. Jain's team (as well as Drs. Boscardin, Gardner, Hunzinger, and Mr. Law), we have evaluated both linear mixed effects models and generalized estimating equations models to model change in our cognitive factor scores over the first-year post-injury and between 6 months and 5 years post injury.
- We are continuing to evaluate our models, incorporating inverse probability of attrition weighting methods to account for study attrition over time and are making progress to determine which will be our final models.

Major Task 5 – Define Vascular Risk Factor Variables: This task is 100% complete.
- With Dr. Jain's team, we have derived vascular risk factor variables, including hypertension, diabetes, hyperlipidemia, smoking, and obesity.
- Obesity data was collected only among a subset of participants (only those who were admitted to the hospital), so the subsequent analyses will focus on hypertension, diabetes, hyperlipidemia, and smoking.
- An overall risk score variable (0-4) was also created and binned into 0, 1, or 2+ risk factors.

Major Task 6 – Associations of Vascular Risk Factors with 1-Year Cognitive Change: This task is 50% complete.
- The work for this analysis is ongoing (this Major Task incorporates features from the above Major Tasks, including inverse probability of attrition weighting, longitudinal modeling, defining vascular risk factor variables, and the creation of cognitive factor scores).
- We plan to have one resultant manuscript describing the associations of vascular risk factors with 1-year cognitive change (Major Task 6) and one resultant one resultant manuscript describing the associations of vascular risk factors with cognitive change between 6-months and 5-years post-injury (Major Task 7).
- We aim to submit the work from this analysis as an abstract over the coming months and plan to submit the associated manuscript within the next 6-12 months.

Major Task 7 - Associations of Vascular Risk Factors with 5-Year Cognitive Change: This task is 50% complete.
- The work for this analysis is ongoing (this Major Task incorporates features from the above Major Tasks, including inverse probability of attrition weighting, longitudinal modeling, defining vascular risk factor variables, and the creation of cognitive factor scores).- We plan to have one resultant manuscript describing the associations of vascular risk factors with 1-year cognitive change (Major Task 6) and one resultant one resultant manuscript describing the associations of vascular risk factors with cognitive change between 6-months and 5-years post-injury (Major Task 7).
- We aim to submit the work from this analysis as an abstract over the coming months and plan to submit the associated manuscript within the next 6-12 months.

Major Task 8 – Glucose and Lipid Profile Assays: This task is likely to change after discussions with Dr. Diaz-Arrastia and TRACK-TBI Study leadership regarding prioritization of assays for which stored samples will be used (see below for a detailed description for the changes in approach). Briefly, it is likely that other emerging novel vascular-related biomarkers will be prioritized over the initially proposed lipid and glucose assays (from the 2-week timepoint). As an alternate approach, we can classify hyperlipidemia severity by the presence or absence of medication use. The TRACK-TBI Study does have a measure of emergency department/presentation glucose that we will be able to use to classify diabetes severity. Importantly, emergency department/presentation glucose was identified as an important

predictor of poor 1-year cognitive outcome in our prior work in this cohort (Schneider et al. *Neurology*. 2022).

Major Task 9 – Define Vascular Risk Factor Severity Variables: This task is 75% complete.
- With Dr. Jain's team, we are currently working to derive vascular risk factor severity variables.
- We have defined severity of hypertension using measured systolic and diastolic blood pressure, smoking using pack-years, as described in the grant proposal.
- Resulting from the likely changes in Major Task 8, we have created definitions of diabetes and hyperlipidemia severity that are different from those initially included in the grant proposal. We define diabetes severity using the emergency department/presentation glucose and hyperlipidemia severity by the presence or absence of medication use.
- An overall severity risk score variable (0-3) was also created and categorized as 0 vascular risk factors, only less severe vascular risk factors, 1+ more severe vascular risk factors.

Major Task 10 – Associations of Vascular Risk Factor Severity with 1-Year Cognitive Change: This task is 25% complete.
- The work for this analysis is ongoing (this Major Task incorporates features from the above Major Tasks, including inverse probability of attrition weighting, longitudinal modeling, defining vascular risk factor severity variables, and the creation of cognitive factor scores).
- At this time, we are not sure if the associations of vascular risk factor severity with 1-year cognitive change will be a separate manuscript or a part of the manuscript outlined in Major Task 6. Irrespective if it will be one or two separate manuscripts, we plan to have an abstract and manuscript incorporating the analyses outlined in Major Task 10 within in the next 6-12 months.

Major Task 11 – Associations of Vascular Risk Factor Severity with 5-Year Cognitive Change: This task is 25% complete.
- The work for this analysis is ongoing (this Major Task incorporates features from the above Major Tasks, including inverse probability of attrition weighting, longitudinal modeling, defining vascular risk factor severity variables, and the creation of cognitive factor scores).
- At this time, we are not sure if the associations of vascular risk factor severity with cognitive change from 6-months to 5 years will be a separate manuscript or a part of the manuscript outlined in Major Task 7. Irrespective if it will be one or two separate manuscripts, we plan to have an abstract and manuscript incorporating the analyses outlined in Major Task 11 within in the next 6-12 months.

Major Task 12 – Study Completion: This task has not yet started. If the likely changes to the Major Task 8 occur (where the prioritization of assays for which TRACK-TBI stored blood specimens will be used may change from those proposed herein), there will not be any new data obtained as part of this grant and nothing will need to be uploaded into FITBIR.

- **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.*

Katherine Hunzinger PhD completed her post-doctoral fellowship at the University of Pennsylvania from 3/1/2022 through 6/30/2023. Dr. Hunzinger received her PhD in Biomechanics from the University of Delaware, studying rugby-related concussion. Her post-doctoral fellowship training was focused on Epidemiology and Biostatistics methods. Specifically, Dr. Hunzinger's training was focused on one-on-

one work with Dr. Schneider, learning about confirmatory factor analyses, longitudinal data analyses, and methods to account for study attrition/missing data. She was funded in part by the Brain Injury Training Grant T32 (PI: Douglas Smith) and took formal Epidemiology and Biostatistics classes during her post-doctoral fellowship. As of 7/1/2023, she is an Assistant Professor of Exercise Science at Thomas Jefferson University. She remains actively involved in the drafting of manuscripts related to this project.

A new post-doctoral fellow, Bernadette D'Alonzo will be starting with Dr. Schneider in early 2024 and will collaborate on this project. Ms. D'Alonzo is currently an Epidemiology PhD student at the University of Pennsylvania and will defend in late 2023/early 2024. Since Ms. D'Alonzo and Dr. Schneider are already at the same institution, Ms. D'Alonzo will be able to start getting involved in the project over the coming months.

Data Analyst, Connor Law BS was hired on 12/1/2022. He has completed onboarding and is now actively collaborating on the project. Mr. Law has been working closely with Dr. Schneider to learn about confirmatory factor analyses, longitudinal data analyses, and methods to account for study attrition/missing data.

- **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. Schneider was part of the "Research Panel" at the University of Pennsylvania "Mind Your Brain" Conference in March 2023. This conference is attended by 150+ TBI patients and caregivers. This panel discussion is designed to educate TBI survivors and caregivers on overall brain health after a TBI and to educate about the valuable information that can be gained through research studies.
- Dr. Schneider was an invited plenary speaker at the National Capital Area Traumatic Brain Injury Symposium in March 2023, an invited speaker at the Zucker School of Medicine at Hofstra/Northwell Department of Neurology Grand Rounds in September 2022 and at the Boston University School of Medicine Clinical Neuroscience Grand Rounds in November 2022. She additionally was an invited speaker in the Department of Medical Psychology Seminar at the Johns Hopkins University School of Medicine in November 2022, at the University of Pennsylvania Department of Biostatistics, Epidemiology, and Informatics Research Day in March 2023, and at the University of Pennsylvania Neuroscience Graduate Group (NGG) - Clinical Neuroscience Training Program (CNST) Seminar in April 2023. In addition, Dr. Schneider was a plenary speaker at the American Neurological Association Annual Meeting in September 2023 in the setting of being awarded the Derek Denny-Brown Young Neurological Scholar Award. These presentations were given to neurologists, neurosurgeons, and other TBI researchers and included a discussion on the importance of epidemiology in TBI-related cognition research.

- **What do you plan to do during the next reporting period to accomplish the goals?** *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 have submitted abstract(s) and drafted/submitted manuscript(s) related to the analyses investigating associations of vascular risk factors (Major Tasks 6 and 7) and vascular risk factor severity (Major Tasks 10 and 11).

4. **IMPACT:** *Describe 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).

Investigators within TRACK-TBI are actively considering the use of inverse probability of attrition weighting and other longitudinal data analysis methods in analyses of the TRACK-TBI LONG data.

By study completion, we will have rigorously developed biostatistical and epidemiological methods to model cognitive trajectories post-TBI that account for study attrition which will be able to be shared with other investigators and translated both within and across studies with the goal of collaboratively advancing research on post-TBI cognitive decline and dementia.

- **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 at this time. By study completion, the rigorously developed biostatistical and epidemiological methods to model cognitive trajectories post-TBI that account for study attrition will be able to be translated to other disciplines.

- **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. Not applicable.

- **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 at this time.

By study completion, this body of work will improve public knowledge about associations of TBI with cognition.

5. **CHANGES/PROBLEMS:** *The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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:*

- **Changes in approach and reasons for change.** *Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.*

Although there are no significant changes of objectives or scope of the project, there is a potential change for Major Task 8 (Glucose and Lipid Profile Assays). After discussions with Dr. Diaz-Arrastia and TRACK-TBI Study leadership regarding prioritization of assays for which stored samples will be used, it

is possible that there will not be enough specimen from the 2-week timepoint remaining to perform lipid and glucose assays. Other emerging novel vascular-related biomarkers are likely to be prioritized over the initially proposed lipids and glucose. As an alternate approach, we can classify hyperlipidemia severity by the presence or absence of medication use. The TRACK-TBI Study does have a measure of emergency department/presentation glucose that we will be able to use to classify diabetes severity. Importantly, emergency department/presentation glucose was identified as an important predictor of poor 1-year cognitive outcome in our prior work in this cohort (Schneider et al. *Neurology*. 2022).

- **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.*

- See above discussion regarding potential changes to Major Task 8.

- **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.*

Dr. Gardner has moved from UCSF to Sheba Medical Center in Israel effective 9/1/2022. The original Year 2 and 3 UCSF subcontract will be changed to yearly consultant fees.

Katherine Hunzinger PhD, was funded by this grant at 50% from 3/1/2022 to 6/30/2022 when she was funded 100% by a T32 award (7/1/2022 through 6/30/2023). She is no longer financially supported by this project. A new post-doctoral fellow, Dr. Bernadette D'Alonzo will be supported by this grant starting in early 2024.

Mr. Connor Law BS is a biostatistician/data analyst who was hired 12/1/2022 and is supported by this grant using funds that were re-budgeted from the post-doctoral fellow salary. The total of this re-budgeting is within 10% of total cost and was previously reported to CDMRP and in the prior technical report.

The potential change Major Task 8 (Glucose and Lipid Profile Assays) may result in ~$25,000 that would need to be re-budgeted (would make sense to re-budget for biostatistician/data analyst and post-doctoral fellow effort).

- **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 (this project does not use any biohazards or select agents).

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).*

1. **Schneider ALC**, Huie JR, Boscardin WJ, Nelson L, Barber JK, Yaffe K, Diaz-Arrastia R, Ferguson AR, Kramer J, Jain S, Temkin N, Yuh E, Manley GT, Gardner RC; TRACK-TBI Investigators. Cognitive Outcome 1 Year After Mild Traumatic Brain Injury: Results From the TRACK-TBI Study. Neurology. 2022 Mar 22;98(12):e1248-e1261. doi: 10.1212/WNL.0000000000200041. Epub 2022 Feb 16. PMID: 35173018.
2. **Schneider ALC**, Barber J, Temkin N, Gardner RC, Manley G, Diaz-Arrastia R, Sandsmark D. Associations of Preexisting Vascular Risk Factors With Outcomes After Traumatic Brain Injury: A TRACK-TBI Study. J Head Trauma Rehabil. 2022 Jun 9. doi: 10.1097/HTR.0000000000000798. Online ahead of print. PMID: 35687893.
3. **Schneider ALC**, Gottesman RF, Mosley TH, Shrestha S, Rowan NR, Sharrett AR, Chen H, Kamath V. Associations of Prior Head Injury With Olfaction in Older Adults: Results From the Atherosclerosis Risk in Communities (ARIC) Study. JAMA Otolaryngol Head Neck Surg. 2022 Jul 21:e221920. doi: 10.1001/jamaoto.2022.1920. Online ahead of print. PMID: 35862067.
4. Tai K, Leland EM, Seal SM, **Schneider ALC**, Rowan NR, Kamath V. Olfactory Dysfunction Following Moderate to Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Neuropsychol Rev. 2022 Sep 7. doi: 10.1007/s11065-022-09563-2. Online ahead of print. PMID: 36070126.
5. **Schneider ALC**, Peltz CB, Li Y, Bahorik A, Gardner RC, Yaffe K. Traumatic Brain Injury and Long-Term Risk of Stroke Among U.S. Military Veterans. *Stroke*. 2023 Aug;54(8):2059-2068. doi: 10.1161/STROKEAHA.123.042360. Epub 2023 Jun 19. PMID: 37334708.

Acknowledgement of Federal Support: Yes.

- **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.*

1. Abstract Oral Presentation*: **Schneider ALC**, Peltz C, Li Y, Bahorik A, Gardner R, Boscardin WJ, Yaffe K. Traumatic Brain Injury and Long-term Risk of Stroke Among U.S. Military Veterans. *American Heart Association: Epidemiology, Prevention, Lifestyle and Cardiometabolic Health 2022 Scientific Sessions*. Chicago, Illinois, March 1-4, 2022.

2. Abstract Oral Presentation*: **Schneider ALC**, Gottesman RF, Mosley TH, Shrestha S, Rowan NRR, Sharrett AR, Chen H. Kamath V. Associations of Prior Head Injury with Olfaction: Results from the Atherosclerosis Risk in Communities (ARIC) Study. *15th International Neurotrauma Symposium*. Berlin, Germany, July 17-20, 2022.

- **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. In addition to a description of the technologies or techniques, describe how they will be shared.*

None.

- **Inventions, patent applications, and/or licenses**. *Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. 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; biospecimen 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."*

Name: Andrea Schneider MD PhD (University of Pennsylvania)
Project Role: PI
Research Identifier: ORCID 0000-0003-0026-5052
Person-Months Worked: 2
Contribution to Project: Dr. Schneider has primary responsibility for designing and overseeing the conduct of the study. She is responsible for and oversees all administrative, budgetary, regulatory, and scientific aspects of the project. Over the course of Year 2, Dr. Schneider collaborated closely with co-investigators at the University of Pennsylvania, the University of California San Diego and consultants Drs. Boscardin, Gardner, and Nelson to achieve study milestones. She led regular meetings with the core analytic team consisting of Dr. Jain, Dr. Gardner, Dr. Nelson, Dr. Hunzinger, and Mr. Law. She is currently overseeing the analysis and will start working on abstract and manuscript preparation.

Funding Support: Dr. Schneider's scientific effort on this grant is 5% (Starting 5/1/2022, her salary support for this project comes from her complementary, but non-overlapping K23 award).

Name: Katherine Hunzinger PhD (University of Pennsylvania)
Project Role: Post-Doctoral Fellow
Research Identifier: ORCID 0000-0002-4599-8543
Person-Months Worked: 6
Contribution to Project: Dr. Hunzinger was hired as Dr. Schneider's post-doctoral fellow and started at the University of Pennsylvania on 3/1/2022. She completed her post-doctoral fellowship at the University of Pennsylvania on 6/30/2023. As of 7/1/2023, she is now an Assistant Professor of Exercise Science at Thomas Jefferson University. She remains actively involved in the drafting of manuscripts related to this project and has been involved in the regular core analytic team meetings, taking an active role in the interpretation of analyses.
Funding Support: Dr. Hunzinger was supported by this grant from 3/1/2022 to 6/30/2022. She was awarded a NIH/NINDS T32 award (from 7/1/2022 to 6/30/2023) which funded 100% of her post-doctoral fellowship position.

Name: Connor Law BS (University of Pennsylvania)
Project Role: Biostatistician/Data Analyst
Research Identifier: N/A
Person-Months Worked: 6
Contribution to Project: Mr. Law was hired as Dr. Schneider's data analyst/biostatistician and started at the University of Pennsylvania on 12/1/2022. He has completed all onboarding requirements and has been reviewing the literature on confirmatory factor analyses, longitudinal data analyses, and methods to account for study attrition/missing data. He has been involved in the regular core analytic team meetings, taking an active role in the interpretation of analyses.
Funding Support: Mr. Law has been supported by this grant since 12/1/2022.

Name: Sonia Jain PhD (UCSD)
Project Role: Subcontract PI
Research Identifier: ORCID 0000-0001-8408-1247
Person-Months Worked: 1
Contribution to Project: Dr. Jain is co-director of the TRACK-TBI Study Biostatistics Core. She has supervised all statistical analyses performed during Year 2. She has been actively involved in the regular core analytic team meetings.

Name: Lindsay Nelson PhD (Medical College of Wisconsin)
Project Role: Consultant
Research Identifier: N/A
Person-Months Worked: 1
Contribution to Project: Dr. Nelson has been actively involved in the regular core analytic team meetings and in the interpretation of analyses. Her team helped to derive the cognitive factor score variables.

Name: Raquel Gardner MD (UCSF through 8/31/2022, Sheba Medical Center effective 9/1/2022)
Project Role: Subcontract PI through 8/31/2022, Consultant effective 9/1/2022
Research Identifier: ORCID 0000-0003-4028-440X
Person-Months Worked: 1
Contribution to Project: Dr. Gardner has been actively involved in the regular core analytic team meetings and in the interpretation of analyses. She has provided expertise in the cognitive factor score analyses and in the design of longitudinal models of cognition.

- **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.

Dr. Schneider has been awarded a new DoD TBIPH grant (HT9425-23-1-0981), titled, “Trajectories of Neuroimaging and Blood-based Biomarkers after Remote Traumatic Brain Injury and Associations with Dementia Risk” which started on 9/1/2023. This grant is complementary but not overlapping with her existing grants. There are no changes to her effort on this project as a result of this new grant.

Katherine Hunzinger PhD, the post-doctoral fellow who was funded at 50% salary support by this grant starting 3/1/2022, was awarded a T32 award (effective 7/1/2022 through 6/30/2023), which covered 100% of her salary. She finished her post-doctoral fellowship on 6/30/2023 and became an Assistant Professor of Exercise Science at Thomas Jefferson University. Ms. Bernadette D’Alonzo will start as a post-doctoral fellow in early 2024 and will be supported by this grant.

Dr. Gardner has moved from UCSF to Sheba Medical Center in Israel effective 9/1/2022. The Years 2 and 3 UCSF Subcontract will transition to a consultant fee.

- **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.*

Organization Name: University of California San Diego (UCSD)
Location of Organization: La Jolla, California, USA
Partner’s Contribution to the Project: Collaboration. UCSD is the location of the Biostatistics Core for the TRACK-TBI Study), led by Dr. Jain. Dr. Jain and her team are primarily responsible for the data analysis for this project.

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:** *For collaborative awards, independent reports are required from **BOTH** the Initiating 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://ebrap.org for each unique award.*

Not Applicable.

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

Not Applicable.

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. Reminder: Pages shall be consecutively numbered throughout the report. **DO NOT RENUMBER PAGES IN THE APPENDICES.***

None.