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TITLE: Long-Term Vascular-Related Cognitive Decline after Traumatic Brain Injury

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CONTRACTING ORGANIZATION: University of Pennsylvania, Philadelphia, PA

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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 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.					
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1. INTRODUCTION:

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:

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

3. ACCOMPLISHMENTS:

○ What were the major goals of the project?

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
<u>Major Task 1:</u> Study start-up phase and regulatory processes.	Month 6	100% Complete
<u>Major Task 2:</u> 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	75% Complete
<u>Major Task 3:</u> Develop and validate inverse probability of attrition weighting and multiple imputation using chained equations methods to account for study attrition	Month 16	100% Complete
<u>Major Task 4:</u> Develop and validate methods to model longitudinal cognitive trajectories (using generalized estimating equations and mixed effects models).	Month 16	Not Yet Started
<u>Major Task 5:</u> 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
<u>Major Task 6:</u> 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	Not Yet Started

<p>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.</p>		
<p><u>Major Task 7:</u> 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.</p>	<p>Month 25</p>	<p>Not Yet Started</p>
<p><u>Major Task 8:</u> Perform glucose and lipid profile assays, securely transfer data to TRACK-TBI Study Biostatistics Core, and clean and quality check data.</p>	<p>Month 12</p>	<p>25% Complete</p>
<p><u>Major Task 9:</u> 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.</p>	<p>Month 26</p>	<p>Not Yet Started</p>
<p><u>Major Task 10:</u> 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.</p>	<p>Month 34</p>	<p>Not Yet Started</p>
<p><u>Major Task 11:</u> 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 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</p>	<p>Month 34</p>	<p>Not Yet Started</p>

impairment), compared to individuals with comparable TBI but no or less severe vascular risk factors and to controls.		
<u>Major Task 12</u> : Study completion phase.	Month 36	Not Yet Started

○ **What was accomplished under these goals?**

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.
- Post-doctoral fellow, Katherine Hunzinger PhD, was hired and started on 3/1/2022. Dr. Hunzinger 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 approximately 75% complete.

- This task is slightly behind the schedule outlined in the original SOW due to the death Dr. Levin, who was the neuropsychology consultant originally on the grant helping with this task.
- Lindsey Nelson PhD (Associate Professor at University of Wisconsin) has joined the team to help move this task forward. She is a neuropsychologist and has been a TRACK-TBI Study investigator for over 5 years. She has published on the factor structure of neuropsychology tests in the past.
- Dr. Nelson and her team, in collaboration with Drs. Schneider, Hunzinger, and Gardner, have performed the confirmatory factor analyses for the creation of global and domain-specific cognitive factor scores within the TRACK-TBI cohort. We are currently evaluating the factor analyses and determining if the domain-specific factor scores are valid; we may need to focus on the global factor scores (and not domain-specific factor scores) for the subsequent longitudinal analyses.
- Dr. Nelson will send Dr. Jain and her team the derived cognitive factor scores to use in subsequent analyses once quality checking is complete (expected by 11/2022).

Major Task 3 – Methods to Account for Study Attrition and Missing Data: This task is 100% complete ahead of schedule.

- With Dr. Jain's team, we have 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. These variables will be used to create the inverse probability of attrition weights used in subsequent analyses to account for study attrition/missing data.

Major Task 4 – Longitudinal Data Analysis Methods: This task has not yet started but will start once Major Task 2 is complete (expected start 11/2022).

Major Task 5 – Define Vascular Risk Factor Variables: This task is 100% complete ahead of schedule.

- 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.
- The prevalence of hypertension was 17.1%, the prevalence of diabetes was 8.4%, the prevalence of hyperlipidemia was 6.3%, and the prevalence of smoking was 27.7% among individuals with TBI.
- An overall risk score variable (0-4) was also created and binned into 0, 1, or 2+ risk factors.
- Among individuals with TBI, 54.0% had 0 vascular risk factors, 34.8% had 1 vascular risk factor, and 11.2% have 2+ vascular risk factors.

Major Task 6 – Associations of Vascular Risk Factors with 1-Year Cognitive Change: This task has not yet started.

Major Task 7 - Associations of Vascular Risk Factors with 5-Year Cognitive Change: This task has not yet started.

Major Task 8 – Glucose and Lipid Profile Assays: This task is 25% complete.

- This task is behind the originally proposed schedule in the SOW, but assays will be completed in time to keep on track with the proposed analyses in Year 3.
- In collaboration with Drs. Jain and Diaz-Arrastia, participant serum samples to be assayed have been identified at the TRACK-TBI Study biorepository at the University of Pittsburgh.
- Planning to have samples shipped to the University of Pennsylvania to have glucose and lipid profile assays performed within the next 3-6 months (by 2/2023) to keep subsequent analyses on schedule for Year 3 of the award.

Major Task 9 – Define Vascular Risk Factor Severity Variables: This task has not yet started.

Major Task 10 – Associations of Vascular Risk Factor Severity with 1-Year Cognitive Change: This task has not yet started.

Major Task 11 – Associations of Vascular Risk Factor Severity with 5-Year Cognitive Change: This task has not yet started.

Major Task 12 – Study Completion: This task has not yet started

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

Post-doctoral fellow, Katherine Hunzinger PhD, was hired and started on 3/1/2022. Dr. Hunzinger received her PhD in Biomechanics from the University of Delaware, studying rugby-related concussion. Dr. Hunzinger has completed onboarding at the University of Pennsylvania and is now actively working on the project. Her post-doctoral fellowship training is focused on Epidemiology and Biostatistics methods. Specifically, Dr. Hunzinger's training is 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 recently awarded a slot on the Brain Injury Training Grant T32 (PI: Douglas Smith) and will also take formal Epidemiology and Biostatistics classes over the coming year.

○ **How were the results disseminated to communities of interest?**

- Dr. Schneider gave a presentation at the annual University of Pennsylvania “Mind Your Brain” Conference in March 2022. This conference is attended by 150+ TBI patients and caregivers. This presentation focused on cognitive decline after TBI and was designed to educate TBI survivors and caregivers on dementia risk and overall brain health after a TBI. The presentation also was designed to educate about the value of information that can be gained through research studies.

- Dr. Schneider was an invited speaker at the Grand Rounds of the Johns Hopkins University Department of Neurology in September 2021, at the 11th Annual Traumatic Brain Injury Conference (Arrowhead Publishers Conferences) in October 2021, at the International Initiative for Traumatic Brain Injury Research (InTBIR) meeting in July 2022 in Berlin, Germany. 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?**

- We expect to complete Major Task 2 by 11/2022 (Dr. Nelson will send Dr. Jain and her team the derived cognitive factor scores to use in subsequent analyses once quality checking is complete).

- We expect to perform the analyses investigating associations of vascular risk factors with 1-year and 5-year cognitive trajectories and have an accompanying manuscript drafted (Major Tasks 6 & 7)

- We expect to complete Major Task 8 by 2/2023 (glucose and lipid profile assays)

4. **IMPACT:**

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

Nothing to report at this time.

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?**

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 including the dementia field.

- **What was the impact on technology transfer?**

Nothing to report.

- **What was the impact on society beyond science and technology?**

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:**

- **Changes in approach and reasons for change.**

There have been no significant changes of objectives or scope.

- **Actual or anticipated problems or delays and actions or plans to resolve them.**

- Major Task 2 is slightly behind the schedule outlined in the original SOW, partly due to the death Dr. Levin, who was the neuropsychology consultant originally on the grant helping with this task. Lindsey Nelson PhD (Associate Professor at University of Wisconsin) has joined the team to help move this task forward. She is a neuropsychologist and has been a TRACK-TBI Study investigator for over 5 years. Dr. Nelson and her team have performed the confirmatory factor analyses for the creation of global and domain-specific cognitive factor scores within the TRACK-TBI cohort. We are currently evaluating the factor analyses and determining if the domain-specific factor scores are valid; we may need to focus on the global factor scores (and not domain-specific factor scores) for the subsequent analyses. Dr. Nelson will send Dr. Jain and her team the derived cognitive factor scores to use in subsequent longitudinal analyses once quality checking is complete (expected by 11/2022).

- Major Task 8 is behind the originally proposed schedule in the SOW. Participant serum samples to be assayed have been identified at the TRACK-TBI Study biorepository at the University of Pittsburgh. We are planning to have samples shipped to the University of Pennsylvania to have glucose and lipid profile assays performed within the next 3-6 months (by 2/2023) to keep subsequent analyses on schedule for Year 3 of the award.

- Major Tasks 3 and 5 have been completed ahead of schedule.

- **Changes that had a significant impact on expenditures.**

Dr. Schneider was awarded a K23 award (75% salary support effective 5/1/2022) so decreased salary support from this grant from 15% to 5%. Dr. Schneider's scientific effort on this grant remains at 15% (i.e., no scientific effort reduction).

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), which will cover 100% of her salary for 1-2 years.

Funds are being re-budgeted to hire a biostatistician to work directly with my research team. This position has been posted, but not yet filled. The total of this re-budgeting is within 10% of total cost. CDMRP has been notified of the plans for re-budgeting.

Consulting funds previously budgeted for Dr. Levin (now deceased) are now budgeted for Dr. Nelson.

Dr. Gardner has moved from UCSF to Sheba Medical Center in Israel effective 9/1/2022. The Year 2 UCSF Subcontract will transition to Sheba Medical Center. CDMRP has been notified of this change in institution.

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

6. **PRODUCTS:**

- **Publications, conference papers, and presentations.**
- **Journal publications.**

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.

Acknowledgement of Federal Support: YES

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

None.

- **Other publications, conference papers, and presentations.**
- **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: 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 1, Dr. Schneider collaborated closely with co-investigators at the University of Pennsylvania, the University of California San Diego, and the University of California San Francisco to achieve study milestones. Dr. Schneider submitted and received IRB and HRPO approval for the project and hired post-doctoral fellow, Dr. Hunzinger. She has worked with Dr. Diaz-Arrastia to start coordination of blood samples (stored at University of Pittsburgh) for glucose and lipid profile assays. She led regular meetings with the core analytic team consisting of Dr. Jain, Dr. Gardner, Dr. Nelson, and Dr. Hunzinger.

Funding Support: Dr. Schneider's scientific effort on this grant is 15% (Starting 5/1/2022, her salary support from this grant decreased from 15% to 5%. The other 10% of funding 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 has completed all onboarding requirements and has been reviewing the literature in the topic area of TBI, vascular risk factors, cognitive decline, dementia risk. She has been actively involved in the regular core analytic team meetings and is 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 (effect 7/1/2022) which currently 100% funds her post-doctoral fellowship position.

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 1. She has been actively involved in the regular core analytic team meetings.

Name: Raquel Gardner MD (UCSF through 8/31/2022, Sheba Medical Center effect 9/1/2022)

Project Role: Subcontract PI

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?**

Dr. Schneider was awarded a K23 award (75% salary support effective 5/1/2022) so decreased salary support from this grant from 15% to 5%. Dr. Schneider's scientific effort on this grant remains at 15% (i.e., no scientific effort reduction).

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), which will cover 100% of her salary for 1-2 years.

Funds are being re-budgeted to hire a biostatistician to work directly with my research team. This position has been posted, but not yet filled. The total of this re-budgeting is within 10% of total cost. CDMRP has been notified of the plans for re-budgeting.

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Dr. Gardner has moved from UCSF to Sheba Medical Center in Israel effective 9/1/2022. The Year 2 UCSF Subcontract will transition to Sheba Medical Center. CDMRP has been notified of this change in institution.

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

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.

Organization Name: University of California San Francisco (UCSF)

Location of Organization: San Francisco, California, USA

Partner's Contribution to the Project: Collaboration. Co-I Dr. Gardner is located at UCSF and she has provided expertise in the cognitive factor score analyses and in the design of longitudinal models of cognition. Dr. Gardner has moved from UCSF to Sheba Medical Center in Israel effective 9/1/2022. The Year 2 UCSF Subcontract will transition to Sheba Medical Center. CDMRP has been notified of this change in institution.

8. SPECIAL REPORTING REQUIREMENTS

○ **COLLABORATIVE AWARDS:**

Not Applicable.

○ **QUAD CHARTS:**

Not Applicable.

9. APPENDICES:

None.