

**AWARD NUMBER:**

W81XWH-15-2-0059

**TITLE:**Targeted Alteration of Dietary Omega-3 and Omega-6  
Fatty Acids for the Treatment of Post-Traumatic  
Headaches**PRINCIPAL INVESTIGATOR:**

Kimbra Kenney, M.D.

**CONTRACTING ORGANIZATION:** The Henry M. Jackson Foundation for the Advancement  
of Military Medicine, Inc.**REPORT DATE:**

OCTOBER 2021

**TYPE OF REPORT:**

Annual

**PREPARED FOR:**U.S. Army Medical Research and  
Materiel Command Fort Detrick,  
Maryland 21702-5012**DISTRIBUTION STATEMENT:**

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# REPORT DOCUMENTATION PAGE

*Form Approved*  
*OMB No. 0704-0188*

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<b>1. REPORT DATE</b> OCTOBER 2021			<b>2. REPORT TYPE</b> Annual		<b>3. DATES COVERED</b> 09/30/2020 – 09/29/2021	
<b>4. TITLE AND SUBTITLE</b>  Targeted Alteration of Dietary Omega-3 and Omega-6 Fatty Acids for the Treatment of Post-Traumatic Headaches					<b>5a. CONTRACT NUMBER</b> W81XWH-15-2-0059	
					<b>5b. GRANT NUMBER</b>	
					<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b>  Kimbra Kenney, M.D.  <b>E-Mail:</b> Kimbra.kenney@usuhs.edu					<b>5d. PROJECT NUMBER</b>	
					<b>5e. TASK NUMBER</b>	
					<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>  The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. 6720-A Rockledge Drive Bethesda, MD 20817					<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>  308133-1.00-64802	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b>  U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012					<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
					<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b> SC170244	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b>  Approved for Public Release; Distribution Unlimited						
<b>13. SUPPLEMENTARY NOTES</b>						
<b>14. ABSTRACT</b>  Post-traumatic headache (PTH) is a common problem in military personnel due to their high rate of traumatic brain injury (TBI). From a prior study in migraine we demonstrated that a high Omega-3/low Omega-6 (H3-L6) diet intervention reduced headache pain, altered circulating anti- and pro-nociceptive lipid mediators and their precursor fatty acids, reduced psychological distress and improved quality-of-life in a chronic headache population. We propose to carry out a 2-arm, parallel group, randomized, controlled 12-week dietary intervention trial to evaluate the biochemical effects and therapeutic efficacy of two dietary interventions (one high in Omega-3 and the other high in Omega-6, reflecting the usual US diet) in patients with PTH that are migrainous. We hypothesize that compared to the Control Diet (high Omega-6, low Omega-3), the H3-L6 intervention will produce significant increases in anti-nociceptive n-3 metabolites including 17-hydroxy DHA (Primary Biochemical Aim), and reductions in pro-nociceptive n-6 metabolites. Further, we hypothesize that compared to the Control Diet, the H3-L6 intervention will produce significant improvement in the Headache Impact Test—(a headache-specific quality of life measure-Primary Clinical Outcome), mean total Headache Hours per day, and mean Severe Headache Hours per day.						
<b>15. SUBJECT TERMS</b>  Post-traumatic headache (PTH), traumatic brain injury (TBI), nociceptive neurotransmission, migraine, chronic inflammation, biomarker, Omega-3, Omega-6, Headache Impact Test (HIT), nutritional intervention						
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>	<b>18. NUMBER OF PAGES</b>	<b>19a. NAME OF RESPONSIBLE PERSON</b> USAMRMC	
<b>a. REPORT</b>  Unclassified	<b>b. ABSTRACT</b>  Unclassified	<b>c. THIS PAGE</b>  Unclassified	  Unclassified	  12	<b>19b. TELEPHONE NUMBER</b> (include area code)	

**Standard Form 298 (Rev. 8-98)**  
Prescribed by ANSI Std. Z39.18

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## 1. INTRODUCTION:

Post-traumatic headache (PTH), a common and debilitating secondary headache disorder, is a common problem in military personnel due to their high rate of traumatic brain injury (TBI). Most PTHs have a phenotype indistinguishable from primary headache disorders and have similar responses to therapy. Recent studies indicate that migraine is the most common headache type after trauma, accounting for 50-60% of all PTH, while tension-type headaches account for less than 20%. The mechanisms of PTH are complex and incompletely understood but recent studies emphasize the role of inflammation, cytokine modulation, microglial activation, and abnormalities in neurotransmitter activity in mediating PTH. These observations provide one mechanism underlying the proposed use of dietary interventions designed to reduce chronic inflammation and promote anti-nociceptive neurotransmission, and biomarker data we will obtain will provide direct support for the role of inflammation in PTH. From a prior study in migraine we have preliminary data demonstrate that a high Omega-3/low Omega-6 (H3-L6) diet intervention reduced headache pain, altered circulating anti- and pro-nociceptive lipid mediators and their precursor fatty acids, reduced psychological distress and improved quality-of-life in a chronic headache population. These compelling preliminary data also help establish the feasibility of implementing this dietary intervention in TBI populations with chronic pain. We propose to carry out a 2-arm, parallel group, randomized, controlled 12-week dietary trial to evaluate the biochemical effects and therapeutic efficacy of two dietary interventions (one high in Omega-3 and the other reflecting the usual US diet, high in Omega-6) in patients with PTH with migrainous phenotype. We hypothesize that compared to the Control Diet (high Omega-6, low Omega-3), the H3-L6 intervention will produce significant increases in anti-nociceptive n-3 metabolites including 17-hydroxy DHA (Primary Biochemical Aim), and reductions in pro-nociceptive n-6 metabolites. Further, we hypothesize that compared to the Control Diet, the H3-L6 intervention will produce significant improvement in the Headache Impact Test—a headache-specific quality of life measure- Primary Clinical Outcome); mean total Headache Hours per day; and mean Severe Headache Hours per day.

## 2. KEYWORDS:

Post-traumatic headache (PTH), traumatic brain injury (TBI), nociceptive neurotransmission, migraine, chronic inflammation, biomarker, Omega-3, Omega-6, Headache Impact Test (HIT), nutritional intervention

## 3. ACCOMPLISHMENTS:

**What were the major goals of the project?**

**Task 1:** Planning and Regulatory Review (Months 1-5)

*Subtask 1a.* Complete the detailed protocol, Standard Operating Procedures (SOP) manual, develop Case Report Forms (CRFs), create and beta test Database, create study website. Trial registration in Clinicaltrials.gov. Advertise for and hire study staff.

*Subtask 1b.* Obtain IRB approvals at WRNMMC, USUHS, NIH, UNC-Chapel Hill, and Womack Army Medical Center.

*Subtask 1c.* Training of dietitians and standardize preparation of diets.

*Subtask 1d.* Training of study staff at all sites.

**Task 2.** Start recruitment and enrollment of patients at all sites (Months 6-12)

*Subtask 2a.* Target is that all sites will have enrolled at least 1 participant by the end of Year 1. Target is that all sites combined have enrolled at least 20 participants.

*Subtask 2b.* All sites will have had 1 monitoring visit to ensure adherence to protocol and that all study procedures are being carried out uniformly and efficiently.

*Subtask 2c.* At the end of Year 1, biochemical assays on participants enrolled over the first 6 months will be performed to ensure that sample quality is excellent and that anticipated values are obtained.

**Task 3.** Continue patient recruitment and enrollment (Months 13-24)

*Subtask 3a.* Anticipate that at the end of Year 2, 70 participants will have been enrolled at the three clinical sites.

*Subtask 3b.* Once enrollment is active at each site, monitoring visits q 6 months to ensure adherence to the protocol and that all study procedures are being carried out uniformly and efficiently.

*Subtask 3c.* Complete biochemical assays on participants enrolled in the first half of the study. Prepare first manuscript for publication on the association of baseline PTH characteristics with plasma levels of bioactive lipid mediators.

**Task 4.** Continue patient recruitment and enrollment (Months 25-36)

*Subtask 4a.* Anticipate that at the end of Year 3 110 participants will have been enrolled at the three clinical sites.

*Subtask 4b.* Continue monitoring visits q 6 months to ensure adherence to the protocol and that all study procedures are being carried out uniformly and efficiently.

*Subtask 4c.* Complete biochemical assays on participants enrolled in the first three years of the study. Prepare second manuscript for publication on the association of baseline post-concussive symptoms, mood, affective, and cognitive problems, and plasma levels of bioactive lipids.

**Task 5.** Complete all study procedures (Months 36-40)

*Subtask 5a.* Complete enrollment of 120 participants, including follow up after 12 weeks of dietary intervention.

*Subtask 5b.* Resolve all data queries originating from data monitoring visits.

*Subtask 5c.* Complete biochemical assays for entire study.

**Task 6.** Data analysis and preparation of primary manuscripts. (Months 40 – 48)

*Subtask 6a.* Complete data cleanup and database lock.

*Subtask 6b.* Complete analysis of primary and secondary outcomes.

*Subtask 6c.* Prepare manuscripts for publication for primary and secondary outcomes.

### What was accomplished under these goals?

1. Received full WRNMMC parent/shell multi-site protocol approval 16 FEB 2016
2. First level IRB approval for all site-specific protocols, including WRNMMC, FBCH and WAMC and UNC as the data center was approved by the WRNMMC IRB, with modifications approved 9-23-2017.
3. Second level HRPO approval for all site-specific protocols, including WRNMMC, FBCH, WAMC and UNC approved 25 JUL 2016, 10 JAN 2016, 10 JAN 2017 and 22 DEC 2016,

respectively. HRPO Second Level Approval from: Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US) Date: Jan 10, 2017 Subject: A-18878.d Approval Memorandum (Proposal Log Number PR141560, Award Number W81XWH-15-2-0059).

4. FITBIR and UDEs for study CRFs established.
5. A DSMB with stoppage rules established at UNC and has conducted bi-annual monitoring at each site. The monitor's reports were sent to the DSMB. No safety concerns.
6. Research personnel were hired and trained.
7. The study is enrolling at a steady pace. There was a late start due to lengthy time for IRB approvals partly due to the initiation of IRIS.
8. Registered on ClinicalTrials.org, NCT03272399.
9. Monthly conference calls continue among the 5 campuses lead by Dr. Kenney.
10. Food purchases, storage, and distribution is coordinated and running. Modifications to the protocol allow pick up and direct shipping of food to participants due to COVID-19 pandemic.
11. Blood collection, processing, and storage is on-going per protocol. Modifications due to COVID-19, allowing alternative self-administered finger stick by participants and collection of small blood samples on a droplet card.
12. Web-based randomization and data entry system (RedCap) are working well.
13. A CRADA has been completed between WRNMMC and HJF.
14. An MTA has been executed for transfer of samples from WRNMMC to NIA, NIH for planned study analysis.
15. A newly required (WRNMMC DRP) Data Sharing Agreement DHA has been signed with WRNMMC but is on hold with NIH as the two institutions determine how to proceed. No data is being entered into FITBIR as we wait to learn the outcome of the discussions. No further movement on this issue and were told in 2020 to remove FITBIR sharing data from our consents by WRNMMC DRP.
16. The MOP is continually updated as questions arise on procedures in order to insure uniformity among the institutions. All updates are discussed with the teams and the study monitor.
17. The Continuing Review for 2018, 2019, 2020, and 2021 were approved by the WRNMMC for all sites.
18. Recruitment and enrollment of patients began at all enrolling sites in year 2 and continue into year 5. One hundred and seventy-six participants have signed consents, 117 have been randomized, and 94 have completed the study with 22 withdrawals after randomization, none as a result of AEs. See table below:

***Enrollment by site to Sept. 4, 2021:***

<i>Site</i>	<i>WRNMMC</i>	<i>WAMC</i>	<i>FBCH</i>	<i>TOTAL</i>
<i>Consented</i>	<i>40</i>	<i>74</i>	<i>62</i>	<i>176</i>
<i>Randomized</i>	<i>24</i>	<i>49</i>	<i>44</i>	<i>117</i>
<i>Withdrawn</i>	<i>2</i>	<i>16</i>	<i>4</i>	<i>22</i>
<i>Completed</i>	<i>22</i>	<i>34</i>	<i>38</i>	<i>94</i>

19. We submitted a manuscript of Study Methods to BMJ Open which remains under review currently.
20. Monitoring of the Headache Diary and protocol adherence is done bi-weekly by dieticians and research staff who monitor on-line and by telephone/video conference with participants.
21. The DSMB reviews all available data, aggregate and differential, for safety issues between and within groups. Severity and frequency of the documented AE/UPs are being reviewed at these times. Subsequently, reports are submitted to the DSMB every 6 months to review safety and efficacy data and any other issues raised by the research team.
22. Biochemical assays on participants will be conducted at the end of the study in batch assays for economy of finances and effort. We will run batched lipid analyses of all samples when the study is completed, using LC-MS/MS because it is best to run these assays in one batched analysis, since results can be affected by season, humidity, etc. Dr. Ramsden's lab at NIH has received the majority of the biospecimens, and the final few will be shipped as they are received in the next few months.
23. An NCE was approved in Sept. 2019 for 18 months to allow more time for enrollment and completion of study procedures.
24. The study is enrolling again after COVID restrictions for 6 months during which there were no enrollments and anticipate that we will need additional 5 months to fully enroll the study and analyze the samples. The study requested in March 2021 and was granted an NCE which extended the study to March 31, 2022.
25. Dr. Guerra, PI at FBCH, left and Dr. Chae assumed the position of PI at FBCH. Dr. Chae then left in 2021, and Dr. Christina LaCroix assumed the position of PI. A protocol and grant modification were submitted and approved for the change in PI.
26. Members of the study team presented an invited, virtual 3 hour session, "Using dietary fatty acids in the treatment of chronic pain conditions", to the 11<sup>th</sup> Annual Pain Care Skills Training WRNMMC workshop, 31 AUG to 2 SEP 2021.
27. Continued patient recruitment and enrollment to near complete enrollment currently (94/98 completers and 99/98 enrolled) and anticipate full study completion based on our power analysis.

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

The research dietician at UNC-Chapel Hill, the head dietician for the study, trains the dieticians at each of the sites. The study coordinator trained all study RAs about the protocol and procedures and the monthly conference calls have time for protocol and study procedure instruction by Dr. Kenney and other PIs. The monitor, Dr. Faurot at UNC, also provides input about unique situations and answers questions about AEs and procedures. Members of the study team gave an invited 3 hour session, "Using dietary fatty acids in the treatment of chronic pain conditions", to the 11<sup>th</sup> Annual Pain Care Skills Training WRNMMC workshop, 31 AUG to 2 SEP 2021. Individual lectures included the following: "Molecular mechanisms linking dietary FAs to chronic pain disorders" (Dr. Domenichiello); "Clinical trials of dietary FA interventions to treat chronic, nontraumatic headaches" (Dr. Ramsden); "Clinical Trial of Dietary FA intervention to treat post-traumatic headaches" (Dr. Kenney); "Altering dietary fatty acids as a treatment for chronic headache disorders" (Ms. Beth MacIntosh).

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

As above, presentations made but without study results, as an interim analysis was not scheduled in our study design. A manuscript of study methods has been submitted and is under review. No results to date as study is actively enrolling.

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

Over the next month, recruit and enroll final few study participants, execute the protocol, review, clean and lock the database, analyze the data and blood samples per protocol, and prepare manuscripts of study results.

**4. IMPACT:**

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

Nothing to Report.

**What was the impact on other disciplines?**

Nothing to Report.

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

Nothing to Report.

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

Nothing to Report.

**5. CHANGES/PROBLEMS:**

**Changes in approach and reasons for change**

The sites have instituted broader recruitment tactics, talking with clinic physicians and disseminating new brochures approved by the IRB in order to help boost enrollment numbers. Since the occurrence of COVID-19, the study instituted modified procedures during times when in-person contact is inadvisable or not allowed. The study was placed on institutional hold at the beginning of the pandemic outbreak and became mostly active again at the end of Sept. 2020 with modified procedures, respecting the safety of the patients and staff. COVID continues to be a factor in recruiting participants but the safety measures put in place allowing telehealth visits and blood spot cards for participant blood droplet self-collection and mailing has allowed the study to continue.

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

As noted earlier in this annual report and prior quarterly reports, there was a significant delay in IRB approvals for this study through the multi-site study IRB process since the termination of IRBNet. This delay significantly impacted launching of this study.

The DSMB, investigators, and monitor are closely keeping track of enrollment numbers.

In September 2019 the study received approval for a No Cost Extension for 18 months during which time the study anticipated completion of enrollment and all study procedures.

There was a second unexpected delay/abrupt stop required in enrollment due to COVID 19 from March until September 2020. An NCE was granted until March 31, 2022 during which time the study should be completed as planned.

### **Changes that had a significant impact on expenditures**

Study was on hold for a few months during no in-person contact period of COVID-19.

The study is recruiting and enrolling again but the PI is aware that the situation is fluid and the study could be shut down again if the pandemic situation worsens. COVID continues to impact rate of enrollment. During delays, staff continued to be paid. The study has enough money to complete the study as planned by the end of the NCE.

### **Significant changes in use or care of human subjects**

Nothing to Report.

### **Significant changes in use or care of vertebrate animals**

Nothing to Report.

### **Significant changes in use of biohazards and/or select agents**

Nothing to Report.

## **6. PRODUCTS:**

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

### **Journal publications.**

Nothing to Report. Anticipate 3-4 manuscripts from study.

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

Nothing to Report.

**Other publications, conference papers and presentations.**

1. Cora Davis - oral presentation about the study at the National Capital Region-Medical Quality Symposium - March 26-27, 2019 and Dr. Kenney presented a poster at the MHSRS conference in Kissimmee, FL, Aug. 19-2019. (pre-approvals from the publications dept.)
2. Manuscript: Faurot, K, et al. Targeted Dietary Interventions to Reduce Pain in Persistent Post-traumatic Headache among Service Members: protocol for a randomised, controlled parallel group trial. BMJ Open. (Submitted and under review 3-2021)
3. Drs. Domenichiello, Ramsden, Kenney and MacIntosh gave an invited 3 hour session, "Using dietary fatty acids in the treatment of chronic pain conditions", to the 11th Annual Pain Care Skills Training WRNMMC workshop, 31 AUG to 2 SEP 2021. Individual lectures included the following: "Molecular mechanisms linking dietary FAs to chronic pain disorders" (Dr. Domenichiello); "Clinical trials of dietary FA interventions to treat chronic, nontraumatic headaches" (Dr. Ramsden); "Clinical Trial of Dietary FA intervention to treat post-traumatic headaches" (Dr. Kenney); "Altering dietary fatty acids as a treatment for chronic headache disorders" (Ms. Beth MacIntosh).

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

Nothing to Report.

• **Technologies or techniques**

Nothing to Report.

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

Nothing to Report.

• **Other Products**

Nothing to Report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

*Name:* Kimbra Kenney, M.D.  
*No change*

*Name:* Keturah Faurot PA, Ph.D.  
*No change*

*Name:* Chris Ramsden, M.D.  
*No change*

*Name:* Heechin Chae, M.D.  
*Project Role:* FBCH PI  
*Researcher Identifier:* N/A  
*Nearest person month worked:* 0.5 – left on 06/30/2021  
*Contribution to Project:* Dr. Chae led the study at FBCH.  
*Funding Support:* Federal

*Name:* Christina LaCroix, M.D.  
*Project Role:* FBCH PI  
*Researcher Identifier:* N/A  
*Nearest person month worked:* 0.5  
*Contribution to Project:* Dr. LaCroix leads the study at FBCH.  
*Funding Support:* Federal

*Name:* Beth MacIntosh  
*No change*

*Name:* Carol Moore, MA, CCRC  
*No change*

*Name:* Cora Davis  
*Left study team on 09/30/2021*

*Name:* Margaret Dunlap  
*No change*

*Name:* Wanda Rivera  
*No change*

*Name:* J. Douglass Mann, M.D.  
*No change*

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

PI change at FBCH. Dr. Chae left on 06/30/2021 and Dr. LaCroix took over as PI on June 1, 2020.

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

Nothing to report.

## **8. SPECIAL REPORTING REQUIREMENTS**

**COLLABORATIVE AWARDS:** N/A

**QUAD CHART:** See attached.

**APPENDICES:** See attached.