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TITLE: Strategies to Augment Ketosis (STAK) for Enhanced Readiness and Disease Reversal

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CONTRACTING ORGANIZATION: The Ohio State University, Columbus, OH

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14. ABSTRACT

This project is focused on a unique nutrition-based intervention we refer to as Strategies To Augment Ketosis (STAK) that is designed to broadly address the surging problem of poor metabolic health in many service members and the general population. The STAK program represents the most comprehensive assessment of different methods of achieving physiological levels of ketones (nutritional ketosis) through newly developed ketone esters and well-formulated ketogenic diets. The four proposed research projects encompassing 7 human research studies are being carried out by a highly multidisciplinary team of experts who will provide foundational knowledge on methods of optimizing nutritional ketosis, and the potential role of STAK to improve readiness in response to sleep restriction and improve therapeutic management in individuals with heart failure and polycystic kidney disease. During this first year of the program the primary activities have focused on team communication, research logistics, and ethics and regulatory approvals. We have made significant progress and are now in a position to begin participant recruitment for these studies during Year 2.

15. SUBJECT TERMS
None listed.

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

   This research aims to elucidate Strategies to Augment Ketosis (STAK) that are relevant for the military. Through four major research projects encompassing seven human research studies, we will explore factors related to optimizing STAK interventions that achieve physiological/nutritional ketosis through ingestion of novel ketone esters (KE) or consumption of a well-formulated ketogenic diet (KD). Research projects will examine: 1) military-relevant physical and cognitive performance in response to short-term sleep restriction, 2) physical and cardiac performance in patients with heart failure preserved ejection fraction, and 3) kidney function and clinical, outcomes in patients with polycystic kidney disease (PKD). Our overarching hypothesis is that achieving beneficial levels of ketones improves metabolic health and confers protection from stress. If true, then these ketone-based nutrition interventions could be translated into current military regimens and individualized lifestyle/treatment plans that significantly improve readiness, metabolic health, and disease burden for the military and civilians.

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

   Beta-hydroxybutyrate, cognitive performance, exogenous ketone, heart failure, ketogenic diet, ketone, ketone ester, metabolic health, metabolism, Mediterranean diet, magnetic resonance imaging, obesity, physiology, placebo, polycystic kidney disease, sleep restriction

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

During the first year of this award, our primary goal was to organize the various research teams and finalize details of the research protocols including gaining required ethics and regulatory approvals to put us in a position to begin enrolling participants for all research studies during Year 2. We are on track with this primary goal.

The overall STAK Program involves four major Research Projects and seven independent human Research Studies that each require separate ethics/regulatory approval and unique research expertise as reflected by the highly multidisciplinary and diverse research teams associated with each project.

The major milestones for the seven Research Studies are illustrated in the chart below. In brief, all the required documents have been submitted to the OSU Biomedical IRB for approval, and six of the seven Research Studies were approved. All six of the OSU IRB approved Research Studies have also been submitted and received OHRO approval, as well as being uploaded as required to ClinicalTrial.gov. Participant recruitment/enrollment and data collection is now in process for multiple Research Studies and we will be in full force on these efforts as we enter into Year 2 of the award.

Status of ethics and regulatory activities associated with the seven proposed research studies.

	Independent Research Studies						
	Project 1		**Project 2**		**Project 3**		**Project 4**
	Aim 1	**Aim 2**	**Aim 1**	**Aim 2**	**Aim 1**	**Aim 2**	
OSU IRB Submitted	4/14/22	8/15/22	4/23/22	8/15/22	10/26/22	10/26/22	7/7/23
OSU IRB First Approved	7/26/22	1/13/23	6/24/22	2/28/23	2/13/23	5/19/23	Pending
OSU IRB All Amendments Approved	2/28/23	9/7/23	4/19/23	5/26/23	9/7/23	9/7/23	-
OHRO Submitted	7/27/22	3/12/23	6/24/22	3/12/23	3/13/23	6/12/23	-
OHRO Approved	10/19/22	4/18/23	10/19/22	4/18/23	6/6/23	6/22/23	-
ClinicalTrials.gov Submitted	8/1/22	6/20/23	8/1/22	9/20/23	08/1/23	08/1/23	-
ClinicalTrials.gov Approved	8/12/22	06/30/22	8/12/22	Pending	Pending	Pending	-
Started Recruiting	06/01/23	06/15/23	05/09/23	-	-	-	-
Target Total Enrollment (n)	15	400	60	60	30	60	20
Participants Enrolled (n)	6	7	5	0	0	0	0
Participants Completed (n)	4	6	5	0	0	0	0

On the following pages, we list separately each of the four major Projects (i.e., Project 1, Project 2, Project 3, Project 4) and provide comments for each of the following four Accomplishments Subheadings.

What were the major goals of the project and what was accomplished?
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.

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.

For this section we provide a brief narrative summary and indicate the status of goals as written in our approved SOW (see **Tables 1-4**).

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.

The overall STAK Program serves as a multifaceted platform for both research and educational advancement. Over two dozen people are assigned paid effort on the STAK Program and many more people are providing valuable input as volunteers or in-kind. Three of Dr. Volek's doctoral students (Chris Crabtree, Alex Buga, and Bradley Robinson) have gained advanced research skills, received one-on-one mentorship, and will utilize aspects of the research studies to advance their doctoral dissertations. Two master's students (Drew Decker, a United States Veteran, and Aydan Jordan) have furthered their research expertise, participated in project relevant workshops and seminars, and have integrated the project into their master's theses. Twenty undergraduate volunteers actively assist in research protocols under the Institutional Review Board (IRB) relevant to this funded research portfolio. Six undergraduate volunteers (Justen Stoner, Lucas Arce, Quinlin Scherl, Katlyn Kramer, Xavier El-Shazly, Corban Trick) are undergoing research distinction and training through this project. This comprehensive engagement provides valuable research experience and professional development opportunities directly relevant to Department of Defense end-user health and performance application, enhancing the skills and knowledge of all participants while contributing to the project's success.

Cathy Saenz, PhD, RD was hired as an Assistant Professor in Kinesiology. She will be assisting with the dietetic demands of the STAK program. For Project 3, Alyssa Marie Castillo was hired and trained to serve as an additional research coordinator, gaining experience in a new role. Chris Crabtree (Graduate Student) conducted a volunteer study on healthy patients to pilot acute imaging protocols immediately following supplementation and a talk was given on this subject at a conference (SCMR) in 2022. Research scientist Dr. Katie Binzel is working on MR elastography protocols (a new imaging modality for her) and will be helping with MRI acquisition and analysis. Graduate Research Fellow Neeraja Mahalingam is working closely with Dr. Simonetti (her mentor) on automated methods to quantify abdominal and epicardial fat in the MR images.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

There is nothing to report on research findings for any of the projects.

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

For this section we provide a brief narrative of future goals and indicate planned activities in blue text (see **Tables 1-4**).

PROJECT 1: OPTIMIZATION OF KETONE DELIVERY STRATEGIES

Project Lead: Brianna Stubbs, DPhil

What were the major goals of the project and what was accomplished?

Exogenous ketones are compounds which, when ingested, can rapidly increase blood ketone concentrations without other dietary changes. Over the last five years, the number of exogenous ketones that are commercially available has increased. However, there are no studies that compare the metabolic and physiologic dose-dependent effects of these compounds.

Project 1, Aim 1 will provide first-of-its-kind comparative data that will inform selection of exogenous ketone compounds for optimizing end-user application with different user needs. In order to provide maximal resolution of the attributes of the compounds under study, the research population will be as homogenous as possible and closely matched to the military end-user phenotype. This research project also addresses the lack of understanding of what drives changes in exogenous ketone metabolism (e.g., phenotypic differences between individuals).

Project 1, Aim 2 will recruit a large and highly diverse cohort of subjects and perform an 'oral ketone tolerance test' to allow statistical modeling of the drivers of changes in ketone kinetics. Together, the data from Aims 1 & 2 will facilitate the use of different exogenous ketone compounds and guide individualized dosing of individuals to optimize end-user application.

Project 1 is a collaboration between OSU and the Buck Institute. A subaward agreement has been finalized from OSU to the Buck Institute. Harmonization has been achieved to ensure standardized testing protocols between the OSU and Buck sites for Aim 2.

In brief, we have completed all Project 1 Major Tasks and Subtasks planned for Year 1. This included developing regular meeting schedules to facilitate communication among Team 1 team members, preparing all research protocols, securing all exogenous ketone testing materials, developing blood ketone assessment methodology, completing all required IRB and OHRO documents, securing IND exemption, and finalizing agreements with various entities to provide materials for the projects. Subject recruitment began in June 2023, and are on track with expected enrollment goals. We have completed n=4 for Aim 1 and n=5 at OSU for Aim 2.

Table 1 is a **s**ummary of major goals for the project and progress accomplished under these goals as detailed in the SOW. Plans for the next reporting period are indicated in blue text. The status of subtasks, along with completion dates are also provided.

Table 1. Project 1 major goals and accomplishments.

Project 1: Optimization of Ketone Delivery Strategies					
Aims 1 and 2: (1) Characterize responses to ingestion of three different KEs in a homogenous cohort (compound effects); (2) Characterize responses to ingestion of a single KE in a cohort across a range of ages and metabolic health (phenotype effects)	**Timeline**				
	Proposed Months	Location/Involved		Status	Date
Major Task 1: Prepare research protocols and agreements (Aims 1 & 2)					
Subtask 1: Refine research and nutrition protocols and prepare regulatory documents	1-6	BS	JV/OSU Core	Completed	7/27/23
If applicable, coordinate with Sites for Cooperative Research and Development Agreements (CRADA), Memoranda of Understanding (MOU), Memoranda of Agreement (MOA), and/or Data Sharing Agreements (DSA) submission	1-3	BS	JV/OSU Core	Completed	01/13/23
If applicable, coordinate with Sites for material transfer agreements (MTAs) or clinical trial agreements (CTSs) submission	1-3	BS	JV/OSU Core	Completed	01/13/23

If applicable, coordinate with Sites for nondisclosure agreements (NDAs)	1-3	BS	JV/OSU Core	Completed	12/15/22
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	BS	JV/OSU Core	Completed	07/27/22
Develop supplementation protocol	1-3	BS	JV/OSU Core	Completed	07/27/22
Develop standardized meals for 24hrs prior to test days and on test day	1-3		JV/TB	Completed	07/27/22
Finalize consent form & human subjects protocol	1-3	BS	JV/OSU Core	Completed	07/27/22
Coordinate with Sites for IRB protocol submission	1-6	BS	JV/OSU Core	Completed	07/27/22
Coordinate with Sites for OSU IRB review	1-6	BS	JV/OSU Core	Completed	07/27/22
Coordinate with Sites for USAMRDC review (ORP/HRPO)	1-6	BS	JV/OSU Core	Completed	04/18/23
Clinicaltrial.gov registration	6	BS	JV	Completed	06/23/23
Major Task 2: LC-MS assay development and measurement (Aims 1 & 2)					
Subtask 1: Develop and measure ketones (BHB, AcAc, and acetone) in plasma	1-45		JV/CM	Completed	05/30/2023
Method development for different ketone assays	1-6		JV/CM	Completed	05/30/2023
Batched sample measurement	Every 6-months		JV/CM	Delayed. See Sec. 5.	
Milestone Achieved: Successfully developed methodology for measuring ketones in plasma	6		JV/CM	Completed	06/05/2023
Major Task 3: Coordinate Study Staff for Clinical Trial (Aims 1 & 2)					
Subtask 1: Hiring and training of study staff	1-48	BS	JV/MK/TB	Ongoing	
Onboard dietitian	5-7		JV/TB	N/A	01/03/2023
Onboard graduate and undergraduate volunteers **(will be involved with projects 1-3)**	4-7	BS	JV/MK/TB	Completed	01/03/2023
Train all appropriate staff/volunteers at OSU and Buck	5-7	BS	JV/MK/TB	Completed	01/03/2023
Milestone Achieved: Research staff trained	7	BS	JV/MK/TB	Completed	01/03/2023
Subtask 2: Facilitate and coordinate with sites for hiring, training, supervision and fidelity checks as needed for attrition	7-48	BS	JV/MK/TB	Ongoing	
Milestone Achieved: Maintained trained and available research staff for clinical trials	7-48	BS	JV/MK/TB	Ongoing	
Major Task 4: Participant Recruitment, Enrollment, and Intervention					
Subtask 1: Recruit, screen, and consent participants for Aim 1	12-21	BS	JV/MK/TB	Y2	
Coordinate with ROTC leaders on recruiting cadets	4-10	BS	JV/MK/TB	Y2	
Screen, consent, and enroll potential participants	12-21	BS	JV/MK/TB	Y2	
Milestone Achieved: 1st participant consented, screened and enrolled	12-14	BS	JV/MK/TB	Complete	06/05/2023
Milestone Achieved: Aim 1 begins	12-14	BS	JV/MK/TB	Complete	06/05/2023
Subtask 2: Familiarize participants with testing protocol	12-21	BS	JV/MK/TB	Y2	
Review testing protocol	12-21	BS	JV/MK/TB	Y2	
Schedule all nine testing visits (tentatively)	12-21	BS	JV/MK/TB	Y2	
Milestone Achieved: all 15 participants familiarized and scheduled	15	BS	JV/MK/TB	Y2	
Subtask 3: Recruit, screen, and consent participants for Aim 2	9-39	BS	JV/MK/TB	Ongoing	

Create ResearchMatch and Study Search accounts for recruitment	6-9	BS	JV/MK/TB	Complete	09/12/2023
Screen, consent, and enroll potential participants	16-39	BS	JV/MK/TB	Ongoing	
Milestone Achieved: 1st participant consented, screened and enrolled	16-17	BS	JV/MK/TB	Complete	06/10/2023
Milestone Achieved: Aim 2 begins	16-17	BS	JV/MK/TB	Complete	06/15/2023
Subtask 4: Familiarize participants with testing protocol for Aim 2	16-39	BS	JV/MK/TB	Ongoing	
Participants complete familiarization and KE responsive testing	16-39	BS	JV/MK/TB	Ongoing	
Major Task 5: Controlled Clinical Trial (Aims 1 & 2)					
Subtask 1: Conduct a randomized, placebo-controlled study for Aim 1	12-24	BS	JV/MK/TB	Y2	
Run participants through all 9 testing visits and collect all appropriate data	12-24	BS	JV/MK/TB	Y2	
Milestone Achieved: all 15 participants complete all 9 intervention days	24	BS	JV/MK/TB	Y2	
Subtask 2: Conduct a large, diverse cohort study for Aim 2	16-39	BS	JV/MK/TB	Ongoing	
Run participants through KE responsiveness testing days	16-39	BS	JV/MK/TB	Ongoing	
Milestone Achieved: all 400 participants completed the study (100 at Buck and 300 at OSU-PAES)	39	BS	JV/MK/TB	Ongoing	
Major Task 6: Data Analysis (Aims 1 & 2)					
Subtask 1: Coordinate with sites & data core for monitoring data collection rates and data quality	15-45	BS/JN/DF	JV/OSU Core	Ongoing	
Perform all analyses according to specifications, share output and finding with all investigators	15-45	BS/JN/DF	JV/OSU Core	Ongoing	
Work with data core and dissemination of findings (abstracts, presentations, publications, DOD)	15-45	BS/JN/DF	JV/OSU Core	Ongoing	
Milestone Achieved: Report results from data analyses	15-48	BS/JN/DF	JV/OSU Core	Ongoing	

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

Now that the research protocols have been finalized and approved, our focus during Year 2 is on achieving a steady pace of enrollment for both Project 1 Aims 1 and 2. OSU is already enrolling participants for Aim 2 and the Buck site will start enrolling later this year. By the end of Year 2 (Sept 30, 2024), we expect to have enrolled all 15 subjects for Aim 1 and ~150 subjects for Aim 2 (including enrollment from both OSU and Buck sites).

Project 1 target enrollment (n) per quarter.

	Year 1				Year 2				Year 3				Year 4				Total
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
OSU - Aim 1	-	-	-	5	5	5	0	0	0	0	0	0	0	0	0	0	15
OSU - Aim 2	-	-	-	-	-	37	37	37	39	39	37	37	37	0	0	0	300
Buck - Aim 2	-	-	-	-	-	10	10	15	15	15	15	10	10	0	0	0	100

PROJECT 2: KETONE CONFERRED RESILIENCY AGAINST SLEEP RESTRICTION

Project Lead: William Kraemer, PhD

What were the major goals of the project and what was accomplished?

Suboptimal sleep is a major problem in military populations, as well as the general population. Some major consequences of sleep loss are poor metabolic health, inability to concentrate, poor work efficiency, and increase in errors during daily tasks. There is preliminary evidence that ketone ester supplements and a ketogenic diet that achieve nutritional ketosis may lessen the adverse effects of sleep restriction.

Project 2, Aim 1 will examine if ingesting a ketone ester supplement, twice daily, can improve military relevant cognitive and physical performance and shooting performance during short-term sleep restriction (50% of habitual sleep) for 4 nights.

Project 2, Aim 2 will involve a similar short-term sleep restriction protocol and battery of tests as Aim 1, but explore whether sustained nutritional ketosis over 6-weeks achieved through either a ketogenic diet or ketone esters further influences sleep outcomes, cognitive performance, shooting aptitudes, neuromuscular monitoring, body composition and blood parameters.

In brief, we have completed all Project 2 Major Tasks and Subtasks planned for Year 1. This included developing regular meeting schedules to facilitate communication among Project 2 team members, preparing all research protocols, completing all required IRB and OHRO documents, securing IND exemption, developing database management protocols, finalizing dietetic protocols for ketogenic and mixed diets, performing validation testing of our shooting aptitude protocol, and completing agreements with various entities to provide materials for the projects (e.g., Abbott's continuous glucose and ketone monitoring systems, Oura rings, KetoMojo finger stick glucose and ketone monitoring, Polar heart rate monitoring devices, etc.). Subject recruitment began in May 2023, and we are on track with expected enrollment goals. We have completed n=5 for Aim 1.

Table 2 is a summary of major goals for the project and progress accomplished under these goals as detailed in the SOW. Plans for the next reporting period are indicated in blue text. The status of subtasks, along with completion dates are also provided.

Table 2. Project 2 major goals and accomplishments.

Project 2: *Strategies to Augment Ketosis: Ketone Conferred Resiliency Against Sleep Restriction*				
Aims (1) Determine the degree to which short-term use of KEs protects against fatigue from moderate sleep restriction and exercise; (2) Examine whether adaptation to nutritional ketosis over several weeks confers additional protection from the sleep restriction and exercise fatigue; (3) Explore body composition responses and whether specific biomarkers and subject characteristics are predictive of positive effects of ketosis on performance.	Proposed Months	Location/Involved	Status	Date
Major Task 1: Prepare Research Protocols				
Subtask 1: Refine research, testing, and nutrition protocols prepare regulatory documents	1-6	JV/WK/OSU Core	Completed	6/24/22
If applicable, coordinate with Site for CRADA, MOU, MOA, and/or DSA submission	1-3	JV/WK/OSU Core	Completed	6/24/22
If applicable, coordinate with Site for MTAs or clinical trial CTSs submission	1-3	JV/WK/OSU Core	Completed	6/24/22
If applicable, coordinate with Site for NDAs	1-3	JV/WK/OSU Core	Completed	6/24/22
Submit Investigator initiated study (IIS) application to Abbott	1-3	JV/WK/OSU Core	Completed	6/24/22
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	JV/WK/OSU Core	Completed	6/24/22

Develop supplementation protocol	1-3	JV/WK/OSU Core	Completed	6/24/22
Develop dietary protocols	1-3	JV/TB/OSU Core	Completed	6/24/22
Refine neuropsychological assessment protocol	1-3	JV/WK/SH	Completed	6/24/22
Refine sleep-restriction protocol	1-3	JV/WK/UM	Completed	6/24/22
Finalize consent form & human subjects protocol	1-3	JV/WK/OSU Core	Completed	6/24/22
Coordinate with Sites for IRB protocol submission	1-3	JV/WK/OSU Core	Completed	6/24/22
Coordinate with Sites for OSU IRB review	1-6	JV/WK/OSU Core	Completed	6/24/22
Coordinate with Sites for USAMRDC review (ORP/HRPO)	1-6	JV/WK/OSU Core	Completed	10/10/22
Clinicaltrial.gov registration	*6*	*JV/WK/OSU Core*	*Pending (Project 2 Aim 2 Only)*	---
Milestone Achieved: Protocols finalized, and necessary regulatory documents approved	3	JV/WK/OSU Core	Completed	10/7/22
Milestone Achieved: IRB approval through OSU and HRPO approval for all protocols	6	JV/WK/OSU Core	Completed	6/24/22
Major Task 2: Coordinate Study Staff for Clinical Trial				
Subtask 1: Hiring and training of study staff	1-48	JV/WK/MK/AB/TB	Completed	3/27/2023
Onboard dietitian	5-7	JV/TB	Completed	1/03/2023
Onboard graduate and undergraduate volunteers **(will be involved with projects 1-3)**	4-7	JV/WK/MK/AB	Completed	3/27/2023
Train all appropriate staff/volunteers at OSU	5-7	JV/WK/MK/AB	Completed	3/27/2023
Milestone Achieved: Research staff trained	7	JV/WK/MK/AB	Completed	3/27/2023
Subtask 2: Facilitate and coordinate with sites for hiring, training, supervision and fidelity checks as needed for attrition	7-48	JV/WK/MK/AB	Completed	5/20/23
Milestone Achieved: Maintained trained and available research staff for clinical trials	7-48	JV/WK/MK/AB	Completed	5/1/23
Major Task 3: Participant Recruitment, Enrollment, and Intervention				
Subtask 1: Recruit, screen, and consent participants for Aim 1	*7-23*	*JV/MK/AB*	*In-Progress*	
Coordinate with ROTC leaders on recruiting cadets	4-22	JV/MK/AB	Completed	5/22/23
Screen, consent, and enroll potential participants	*7-23*	*JV/MK/AB*	*Ongoing*	
Milestone Achieved: 1st participant consented, screened and enrolled	7-9	JV/MK/AB	Completed	5/22/23
Milestone Achieved: Aim 1 begins	*7-9*	*JV/MK/AB*	*Completed*	*5/22/23*
Subtask 2: Familiarize participants with performance testing panel for Aim 1	*7-24*	*JV/SH/UM/WK/MK/AB*	*Ongoing*	
Review neuropsychological assessment and military-relevant performance assessment	7-24	JV/SH/MK/AB	Completed	5/03/23
Review sleep restriction and exercise protocol	7-24	JV/UM/MK/AB	Completed	5/03/23
Major Task 4: Controlled Clinical Trial (Aims 1 & 2)				
Subtask 1: Conduct a double-blind, placebo-controlled, 2-period cross-over study for Aim 1	*7-24*	*JV/WK/UM/SH/ OSU Core*	*Ongoing*	
Pre-testing, sleep restriction, exercise protocol, post-testing followed by 2-week washout and replication of 5-day protocol with opposite treatment	*7-24*	*JV/WK/UM/SH/ OSU Core*	*Ongoing*	

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

Now that the research protocols have been finalized and approved, our focus during Year 2 is on achieving a steady pace of enrollment for both Project 2 Aims 1 and 2. By the end of Year 2 (Sept 30, 2024), we expect to have enrolled 40 subjects for Aim 1 and 30 subjects for Aim 2.

Project 2 target enrollment (n) per quarter.

	Year 1				Year 2				Year 3				Year 4				Total
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	
OSU - Aim 1	-	-	-	5	5	10	10	10	10	10	0	0	0	0	0	0	60
OSU - Aim 2	-	-	-	-	-		10	10	10	10	10	10	0	0	0	0	60

PROJECT 3: KETONE THERAPY TO IMPROVE EXERCISE TOLERANCE IN HEART FAILURE

Project Lead: Yuchi Han, MD and Lon Simonetti, PhD

What were the major goals of the project and what was accomplished?

Heart failure (HF) is a major clinical diagnosis affecting 5 million Americans with 550,000 new diagnoses being made annually. Defined as a clinical syndrome, HF is generally characterized by dyspnea and intolerance to exercise caused by impaired ventricular filling and/or ventricular ejection of blood. Although most subjects experience these symptoms in the setting of a reduced left ventricular function, HF can occur in the presence of preserved ejection fraction (HFpEF), defined as having heart failure symptoms with an ejection fraction (EF) of ≥ 50%. Unlike the treatment of systolic heart failure, HFpEF does not have a large body of evidenced-based therapy to guide management. There is strong evidence that the ketogenic diet can improve comorbidities such as obesity and type 2 diabetes, and preliminary evidence that ketone ester supplements can improve cardiac function acutely. Project 3 will represent the first trial to study sustained use of ketone esters and a ketogenic diet intervention to improve clinical outcomes in patients with HFpEF.

Project 3, Aim 1 will evaluate cardiac function and exercise capacity after acute ingestion of KE and sustained use (6-weeks) on cardiac and exercise performance in patients with HFpEF.

Project 3, Aim 2 will examine the effects of a KD compared to mixed diet on cardiac function and exercise tolerance after 6-weeks (food provided) and 6-months (free-living) in patients with HFpEF.

In brief, we have completed all Project 3 Major Tasks and Subtasks planned for Year 1. This included developing regular meeting schedules to facilitate communication among Project 3 team members, preparing all research and imaging protocols, hiring study staff, completing all required IRB and OHRO documents, securing IND exemption, developing database management protocols, finalizing dietetic protocols for ketogenic and mixed diets, refining the imaging approach, and completing agreements with various entities to provide materials for the projects (e.g., Abbott's continuous glucose and ketone monitoring systems, Oura rings, KetoMojo finger stick glucose and ketone monitoring, Polar heart rate monitoring devices, etc.). A pilot study was performed in healthy subjects which contributed to our knowledge of the supplement's effects in the absence of heart failure while at the same time helping to inform our study design for implementation in patient populations. Additionally, the pilot testing led to collaboration with the MRI clinical technicians and physicians and has built a level of familiarity and enthusiasm for the project, design, and science before enrollment has officially begun.

Table 3 is a **s**ummary of major goals for the project and progress accomplished under these goals as detailed in the SOW. Plans for the next reporting period are indicated in blue text. The status of subtasks, along with completion dates are also provided.

Table 3. Project 3 major goals and accomplishments.

Project 3: Ketone Therapy to Improve Exercise tolerance in Heart Failure				
Aims 1 and 2: (1a) Evaluate cardiac function and exercise capacity after acute ingestion of KE; (1b) Determine the effect of sustained use of KE on cardiac performance; (2) Examine the effects of a KD compared to mixed diet on cardiac function and exercise tolerance after 6-weeks (food provided) and 6-months (remote care monitoring) in patients with T2D and HFpEF				
	Proposed Months	Location/Involved	Status	Date
Major Task 1: Prepare Research Protocols (Aims 1 & 2)				

Subtask 1: Refine research, testing, nutrition protocols	1-9	JV/OSU Core	OS/YH/ CC/DS	Completed	12/07/22
If applicable, coordinate with Sites for CRADA, MOU, MOA, and/or DSA submission	1-3	JV/OSU Core	OS/YH/ CC/DS	N/A	
If applicable, coordinate with Sites for MTAs or clinical trial CTSs submission	1-3	JV/OSU Core	OS/YH/ CC/DS	N/A	
If applicable, coordinate with Sites for NDAs	1-3	JV/OSU Core	OS/YH/ CC/DS	N/A	
Submit Investigator initiated study (IIS) application to Abbott	1-3	JV/OSU Core		Completed	05/31/23
Refine eligibility criteria, exclusion criteria, screening protocol	1-6	JV/OSU Core	OS/CC/ DS	Completed	12/07/22
Develop supplementation protocol	1-6	JV/OSU Core	OS/CC/ DS	Completed	12/07/22
Develop dietary protocols	1-6	JV/TB/O SU Core		Completed	12/07/22
Develop GMCB protocols (group mediated cognitive behavioral)	*7-12*	*OSU Core*	*OS/CC/DS*	*Completed*	*08/01/23*
Refine cardiopulmonary exercise protocol	1-6	JV	OS/YH	Completed	12/07/22
Refine CPET-CMR protocol	1-6	JV	OS/YH	Completed	12/07/22
Finalize consent form & human subjects protocol	1-6	JV/OSU Core	OS/CC/ DS	Completed	12/07/22
Coordinate with Sites for IRB protocol submission	1-6	JV	CC/DS	Completed	12/07/22
Coordinate with Sites for OSU IRB review	*1-12*	*JV*	*CC/DS*	*Completed*	*08/01/23*
Coordinate with Sites for USAMRDC review (ORP/HRPO)	*1-12*	*JV*	*CC/DS*	*Completed*	*08/01/23*
Clinicaltrial.gov registration	*12*	*JV*	*DS*	*Completed*	*08/01/23*
Milestone Achieved: Protocols finalized, and necessary regulatory documents approved	6	JV/OSU Core	CC/DS	Completed	12/07/22
Milestone Achieved: IRB approval through OSU and HRPO approval for all protocols	*12*	*JV/OSU Core*	*CC/DS*	*Completed*	*08/01/23*
Major Task 2: Coordinate Study Staff for Clinical Trial (1 & 2)					
Subtask 1: Hiring and training of study staff	1-48	JV/TB	CC/DS	Completed	---
Onboard dietitian	5-7	JV/TB		Completed	5/1/23
Onboard behavioral counselor	7-12	JV/TB/M K		Completed	5/1/23
Onboard graduate and undergraduate volunteers (**will be involved with projects 1-4)**	4-7	JV/TB/C C/DS	CC/DS	Completed	1/03/2023
Train all appropriate staff/volunteers at OSU	5-7	OSU Core/TB/MK/DS		Completed	5/1/23
Review protocol and onboard behavioral health coach designated to take over CRCM after the first 6 weeks	12-19	OSU Core/TB/MK/DS		Completed	5/1/23
Milestone Achieved: Research staff trained	7	OSU Core/TB/MK/DS		Completed	5/1/23
Subtask 2: Facilitate and coordinate with sites for hiring, training, supervision and fidelity checks as needed for attrition	7-48	OSU Core/TB/MK/DS		Completed	5/1/23

Milestone Achieved: Maintained trained and available research staff for clinical trials	7-48	OSU Core/TB/MK/DS		Completed	5/1/23

Major Task 3: Participant Recruitment, Enrollment, and Intervention					
Subtask 1: Recruit, screen, and consent participants for Aim 1	*7-37*	*OSU Core*		*Ongoing*	
Coordinate with physicians at Ross Heart Hospital and OSU	*4-16*	*OSU Core*	*DS/YH*	*Ongoing*	
Screen, consent, and enroll potential participants	*7-16*	*OSU Core*	*DS/YH*	*Ongoing*	
Milestone Achieved: 1st participant consented, screened and enrolled	*7-9*	*OSU Core*	*DS/YH*	*In progress*	
Milestone Achieved: Aim 1 begins	*7-9*	*OSU Core*	*DS/YH*	*In progress*	
Subtask 2: Familiarize participants with testing protocol for Aim 1	*7-16*	*OSU Core*		*In progress*	
Review CPET-CMR protocol	*7-16*	*OSU Core*		*Ongoing*	
Review KE supplementation protocol	*7-16*	*OSU Core*		*Ongoing*	
Review ketone/glucose and CKM protocol	*7-16*	*OSU Core*		*Ongoing*	
Subtask 3: Recruit, screen, and consent participants for Aim 2	*19-36*	*OSU Core*		*In progress*	
Coordinate with physicians at Ross Heart Hospital	*19-36*	*OSU Core*		*Ongoing*	
Screen, consent, and enroll potential participants	*19-36*	*OSU Core*		*Ongoing*	
Milestone Achieved: 1st participant consented, screened and enrolled	*19-21*	*OSU Core*		*In progress*	
Milestone Achieved: Aim 2 begins	*19-21*	*OSU Core*		*In progress*	
Subtask 4: Familiarize participants diet and testing protocol for Aim 2	*19-36*	*OSU Core*		*In progress*	
Review appropriate diet protocol with randomized participants	*19-36*	*OSU Core*		*Ongoing*	
Review CPET-CMR protocol	*19-36*	*OSU Core*		*Ongoing*	

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

Now that the research protocols have been finalized and approved, our focus during Year 2 is on achieving a steady pace of enrollment for both Project 3 Aims 1 and 2. By the end of Year 2 (Sept 30, 2024), we expect to have enrolled 24 subjects for Aim 1 and 30 subjects for Aim 2.

Project 3 target enrollment (n) per quarter.

	Year 1				**Year 2**				**Year 3**				**Year 4**				**Total**
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	
OSU - Aim 1	-	-	-	-	6	6	6	6	6	0	0	0	0	0	0	0	30
OSU - Aim 2	-	-	-	-	-	10	10	10	10	10	10	0	0	0	0	0	60

PROJECT 4: FEASIBILITY AND EFFICACY OF A KETOGENIC DIET IN THE MANAGEMENT OF CHRONIC KIDNEY DISEASE

Project Lead: Rima Kang, MD

What were the major goals of the project and what was accomplished?

Polycystic kidney disease (PKD) is a condition known to result in end-stage kidney disease or the need for dialysis. While lifestyle modifications like proper hydration have been explored to mitigate disease progression, it inevitably culminates in end-stage kidney disease. There is potential for lifestyle interventions, such as the ketogenic diet, which has shown promise in animal models, but comprehensive long-term studies in humans are lacking. If a ketogenic dietary intervention can slow the deterioration of kidney function and hinder kidney growth, it would represent a novel and translatable treatment approach for this form of chronic kidney disease.

Project 4, Aim 1 will assess kidney structure and function over 6-months in a group of patients with heart failure preserved ejection fraction (HFpEF) randomized to either a ketogenic or mixed diet (Note, kidney-related measures will be assessed from the subject cohort in Project 3, Aim 2).

Project 4, Aim 2 will determine the safety, feasibility and efficacy of a 1-year pilot ketogenic diet intervention in patients with polycystic kidney disease (PKD).

The major activity for Project 4 has been to identify a research team at OSU in nephrology, including a new Project Lead, and formulate a new research design. Rima Kang, MD is now the Project 4 Lead and we have had several meetings to plan out the research protocols to be carried out in Aims 1 and 2.

Table 4 is a **s**ummary of major goals for the project and progress accomplished under these goals as detailed in the SOW. Given the delayed start for Project 4, all Major Tasks and Subtasks are "In Progress" as indicated in blue text.

Table 4. Project 4 major goals and accomplishments.

Project 4: Feasibility and Efficacy of a Ketogenic Diet in the Management of Chronic Kidney Disease						
Aims 1 and 2: (1) Assess kidney structure and function in a group of patients with heart failure preserved ejection fraction (HFpEF) and glucose intolerance randomized to either a ketogenic or mixed diet; (2) Perform a pilot trial to determine the feasibility and efficacy of a ketogenic diet in patients with polycystic kidney disease (PKD)						
	Proposed Months	Location/Involved			Status	Date
Major Task 1: Prepare Research Protocols						
Subtask 1: Refine research, testing, nutrition protocols	6-12	JV	OS/YH	RK, BR, AK	In Progress	
If applicable, coordinate with Sites for CRADA, MOU, MOA, and/or DSA submission	6-12	JV	OS/YH	RK, BR, AK	NA	
If applicable, coordinate with Sites for MTAs or clinical trial CTSs submission	6-12	JV	OS/YH	RK, BR, AK	NA	
If applicable, coordinate with Sites for NDAs	6-12	JV	OS/YH	RK, BR, AK	NA	
Refine eligibility criteria, exclusion criteria, screening protocol for Aim 2	6-12	JV	OS/YH	RK, BR, AK	In Progress	

Coordinate with Sites for USAMRDC review (ORP/HRPO)	6-12	JV	OS/YH	RK, BR, AK	In Progress	
Clinicaltrial.gov registration	12	JV	OS/YH	RK, BR, AK	In Progress	
Milestone Achieved: Protocols finalized, and necessary regulatory documents approved	12	JV	OS/Y	RK, BR, AK	In Progress	
Milestone Achieved: IRB approval through OSU and HRPO approval for all protocols	12	JV	OS/YH	RK, BR, AK	In Progress	
Major Task 2: Coordinate Study Staff for Clinical Trial (Aims 1 & 2)						
Subtask 1: Training of study staff	6-12	JV/TB	CC/DS	RK, BR, AK	In Progress	
Onboard graduate and undergraduate volunteers (**will be involved with projects 1-4)**	6-12	JV/TB/MK	CC/DS	RK, BR, AK	In Progress	
Onboard clinical staff	6-12	JV/TB/MK	CC/DS	RK, BR, AK	In Progress	
Train all appropriate staff/volunteers at OSU	6-12	JV/TB/MK	CC/DS	RK, BR, AK	In Progress	

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

The required documents for Project 4 Aim 2 were submitted to the OSU Biomedical IRB in July 2023 and the status is currently pending. We expect to obtain IRB approval in October 2023, followed by submission to OHRO. We expect all these ethics/regulatory approvals to be in place no later than Dec 2023. This would put us in a position to start recruitment in Q1 2024 after the Christmas and New Year Holidays. By the end of Year 2 (Sept 30, 2024), we expect to have enrolled 24 subjects for Aim 1 and 10 subjects for Aim 2.

Project 4 target enrollment (n) per quarter.

	Year 1				**Year 2**				**Year 3**				**Year 4**				**Total**
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	
OSU - Aim 1 (see Project 3 Aim 2)	-	-	-	-	-	10	10	10	10	10	10	0	0	0	0	0	60
OSU - Aim 2	-	-	-	-	-	-	5	5	5	5	0	0	0	0	0	0	20

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

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

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

Nothing to report – no publications in year 1

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 – no publications in year 1

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 – no publications or patents in year 1

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

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

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.

There have been two major modifications from the original design. Both have been formerly brought to the attention of the IRB, OHRO, and DoD and were officially approved.

1. Project 4 Modification: We were required to redesign Project 4 based on OSU's Office of Compliance interpretation of Ohio Ethics law that there may be a conflict for Dr. Volek based on his stock options in Virta Health. As a result, the planned subaward to Virta Health and their involvement in the STAK Program was removed. A new Project 4 Team and research study was proposed. The appropriate modification documents (e.g., revised budget and budget justification, updated SOW, Technical Abstract, Research Plan, and bios/other support documents) were all formerly submitted to DoD and approved in August 2023 with no change to the overall budget.

2. Ketone Ester Reformulation: The manufacturer of the ketone ester used in Projects 1, 2 and 3 made a change to the product formulation, which led to a slight delay in gaining IRB and OHRO approvals as we had to submit amendments and justification for IND status and wait for manufacturing facilities to revamp production for both the ketone ester and placebo. This was only a minor delay, and we now have both ketone ester and placebo study materials stored in refrigerators on site at OSU in our newly constructed research kitchen. The reformulation has the major benefit of dramatically improving the palatability of the ketone ester while maintaining near identical biokinetics. We deem this a major breakthrough that will have a positive impact on participant perceived taste and therefore retention given the improved tolerance.

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.

Project 1. Analysis: In order to increase future workflow and data reliability, Dr. McElroy moved affiliations from OSU to InfinixBio. Slight delays are anticipated to establish appropriate agreements between OSU and InfinixBio. First batch samples will be analyzed 10/2023

Project 2. We anticipate enrollment may be slow. To address this potential problem, we have developed strong relationships with the military leadership at OSU including ROTC cadets and the Veteran associations to increase veteran status and other military-affiliated recruitment efforts. We have also developed relationships with the Columbus and OSU Police and other civil servants who are interested in utilizing our virtual shooting lab. We expect they may be interested and eligible participants in both Aim 1 and 2 research studies.

Project 3. We anticipate enrollment may be slow. We have established procedures for automatic query of the clinical information warehouse at Ohio State, which has enabled us to screen over 1,200 potentially eligible subjects to date. Initial screenings indicated that Inclusion/Exclusion criteria needed to be relaxed in order to hit recruitment targets. These criteria have been adjusted through IRB amendments and we expect this will address the potential problem of slow enrollment.

Project 4. Because Project 4 required the design of a completely new research study and team (see "Changes in approach and reasons for change" above), we are slightly behind schedule in obtaining IRB and OHRO approvals. However, we do not expect any problems securing ethics and regulatory approvals and carrying out the work during the performance period of this award.

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.

Nothing to report

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

Nothing to report

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Nothing to report

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).*

Nothing to report

  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).*

Nothing to report

  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.*

Nothing to report

- **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.

Nothing to report

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

None

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

  None

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

  Nothing to report

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".

The following personnel assigned to the Core Group are described below.

Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Jeff Volek, PhD, RD* *Principal Investigator* *0000-0001-8702-0351* *1* *Team Lead; responsible for writing, proposing, and securing the project grant funding.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Madison Kackley, PhD* *Research Scientist, Project Coordination* *0000-0001-5527-9529* *1* *Dr. Kackley has extensive experience coordinating human clinical trials and controlled feeding studies related to ketogenic diets and exogenous ketones. She manages IRB submission, clinicaltrials.gov, participant testing and continuing reviews.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Teryn Bedell, MS, RD* *Research Dietitian, Project Coordination 0000-0002-5950-2318* *1* *Ms. Bedell provides administrative oversight coordinating team meetings and other logistical plans to facilitate regular communication, budget management, and managing the nutrition protocol.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Alex Buga, MS* *Graduate Student Research Assistant* *0000-0001-8509-4330* *1* *Project lead responsible for recruiting participants, collecting data, and ensuring project progress for Project 2*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Qing Wu, PhD* *Statistician* *0000-0003-4679-8903* *0.3* *Dr. Wu is replacing Dr. Brock to provide biostatical support for data interpretation, results generation, and data collection form design.*

Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Andrew]Koutnik, PhD* *Co- Investigator, Consultant* *0000-0002-5491-3919* *0.3* *Dr. Koutnik has extensive expertise related to clinical studies of exogenous ketone drinks in military settings. He is responsible for contributing to the successful execution of the project and provides relevant knowledge on direct military and operational translation.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Audra Hanners* *Co-Investigator* *0000-0003-4714-6237* *0.1* *Ms. Hanners Certified Ketogenic Nutrition Specialist (CKNS) and works closely with Teryn to support the dietetic and clinical demands for all Projects.*

The following personnel assigned to Project 1 are described below.

Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Brianna Stubbs, DPhil* *Principal Investigator* *0000-0001-9566-9134* *0.6* *Dr. Stubbs has extensive expertise related to clinical studies of exogenous ketone drinks. She oversees all protocol development, oversees all ketone supplement interventions, and conducts bi-weekly project meetings.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Craig McElroy,* *PhD Co-* *Investigator* *0000-0001-5950-0120* *0.3* *Dr. McElroy has extensive expertise in analytical chemistry and metabolic profiling, including collaborative work with Dr. Volek to develop a novel enantiomer-specific method of quantifying S-BHB. He provides analytical support for quantification of ketones (BHB, acetoacetate, acetone) in plasma samples using ultra-performance liquid chromatography-mass spectrometry.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Aydan Jordan* *Graduate Student* *----* *0.5* *Student lead for Project 1 Aim 2. Responsible for ensuring project progress, data collection, and data analysis*

The following personnel assigned to Project 2 are described below.

Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*William Kraemer, PhD* *Co-Principal Investigator 0000-0002-6907-0264* *0.6* *Co-Investigator; responsible for guiding and overseeing all physiological and metabolic aspects of project 2 data collection.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Ulysses Magalang, PhD* *Co-Principal Investigator 0000-0002-5052-2494* *0.06* *Co-Investigator; responsible for designing, implementing, and overseeing the sleep deprivation protocols.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Scott Hayes, PhD* *Co-Principal Investigator 0000-0002-1185-5149* *1* *Co-Investigator; responsible for designing, implementing, and overseeing the cognitive test batteries.*

The following personnel assigned to Project 3 are described below.

Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Yuchi Han, MD* *Principal Investigator 0000-0001-7582-1848* *1* *Team Lead; responsible for clinical coordination and study design regarding patient population and safety.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Orlando Simonetti, PhD* *Co-Principal Investigator 0000-0002-8994-0095* *1* *Co-Investigator; responsible for designing, implementing, and overseeing imaging protocol and analysis.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Christopher Crabtree, MS* *Graduate Student Research Assistant 0000-0001-7284-3048* *1* *Student lead responsible for ensuring project progress, data collection, and data analysis*

Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Debbie Scandling, BS* *Imaging Specialist and Research Coordinator* *0000-0002-3799-8703* *1* *Overall study coordinator, management of imaging schedule, appointments, and recruitment.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Ayesha Hasan, MD* *Imaging Specialist and Research Coordinator* *0000-0002-3176-384X* *1* *Responsible for overseeing clinical care, specifically respective of cardiometabolic concerns.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Joshua Joseph, MD* *Clinical Physician* *0000-0001-9169-8261* *1* *Management and oversight of clinical care.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Jenny Shrodes, RD, LD* *Dietician* *1* *Assists Teryn Bedell with dietary guidance for participant.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Alyssa Castillo, BS* *Research Coordinator. Responsible for ensuring project scheduling, progress, data collection, and data analysis*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Cathy Saenz, PhD, RD* *Research Dietitian,* *0000-0002-7072-2039* *1* *Dr. Saenz provides oversight and expertise on the the nutrition protocol.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Katie Binzel, PhD* *Research Scientist* *0000-0001-9439-33671* *0.6* *Responsible for assisting Dr. Simonetti in designing, implementing, and overseeing imaging protocol and analysis.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Neeraia Mahalingham, MS* *Research Fellow* *0.6* *Responsible for assisting Dr. Simonetti in ensuring project scheduling, progress, data collection, and data analysis*

Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Zachary Chaplow, PhD* *Behavioral Interventionalist* *0.3* *Responsible for behavioral interventions in Project 3.*

The following personnel assigned to Project 4 are described below.

Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Rima Kang, MD* *Principal Investigator* *0000-0002-6515-3580* *1* *Team Lead; responsible for clinical coordination and study design regarding patient population and safety.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Orlando Simonetti, PhD* *Co-Principal* *Investigator 0000-0002-* *8994-0095* *.1* *Co-Investigator; responsible for designing, implementing, and overseeing imaging protocol and analysis.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Arunark Kolipaka, PhD* *Co-Principal* *Investigator 0000-0001-* *7940-5059* *.1* *Co-Investigator; responsible for designing, implementing, and overseeing imaging protocol and analysis.*
Name: ***Project Role:*** ***Researcher Identifier (ORCID):*** ***Nearest person month worked:*** ***Contribution to Project:***	*Brad Rovin* *Key Personnel* *0000-0001-5639-0210* *.1* *Key Personnel, responsible for providing expertise on Polycystic Kidney Disease and clinical advise on protocol.*

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. Volek received an award from the National Institute on Aging (1R01AG081226-01). This award does not affect his effort on this project.

Dr Simonetti received effort from Pfizer/Myovant AWD-115127. This award does not affect his effort on this project.

Dr Stubbs received an award from the National Institute on Aging (K01AG078125). This award does not affect her effort on this project.

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

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

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

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

BHB Therapeutics Ltd (Ireland) – Providing ketone ester and placebo for Projects 1, 2 and 3.

Disruptive Nutrition (USA) – Providing ketone ester study product for Project 1, Aim 1.

Genomatica (USA) – Providing butanediol study product for Project 1, Aim1.

Abbott Biowearables (USA) – Providing continuous glucose and ketone monitoring devices for all projects.

Polar (USA) – Providing heart rate and heart rate variability monitoring for projects.

Oura (Finland) – Providing rings for assessment of sleep, activity, temperature, and heart rate variability.

Keto-Mojo (USA) – Providing fingerstick capillary blood glucose and ketone monitoring devices for all research studies.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

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

None

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

None