PROTOCOL TITLE: Feasibility Trial Assessing Adherence and Response to a Ketogenic Dietary Intervention for Individuals at High Risk for Alzheimer's Disease

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	10/28/19	Removal of fMRI Procedures	Y
2	2/4/20	Addition of follow-up assessment & clarify some procedures in Consent	Y
3	3/27/20	Adaptation of contingency plan in response to recent COVID-19 restrictions	Y

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1.0 Study Summary

Study Title	Feasibility Trial Assessing Adherence and Response to a Ketogenic Dietary Intervention for Individuals at High Risk for Alzheimer's Disease
Study Design	Intervention with pre- and post-assessments
Primary Objective	Assess ways to promote adherence & acceptability of ketogenic diet for individuals at high risk for Alzheimer's
Secondary Objective(s)	Assess neuropsychological, health, and functional outcomes in response to a 6-week ketogenic diet.
Research Intervention(s)	6-week group diet intervention
Study Population	Older adults aged, 60-75 (approximately)
Sample Size	N=10
Study Duration for individual participants	6-week intervention, and a maximum of 2 pre-intervention assessment meetings, 2 follow-up intervention assessments, and 1-month follow-up assessment.
Study Specific Abbreviations/ Definitions	EEG = electroencephalogram; APOE = apolipoprotien E; MNCD = Mild Neurocognitive Disorder; AD = Alzheimer's Disease

2.0 Objectives*

There is significant and growing evidence that adherence to a ketogenic diet may be an effective behavioral intervention for AD. While previous studies have identified the basic mechanisms and interactions of a ketogenic diet with ApoE and lipid and glucose metabolism, feasibility testing in diverse human samples remains in the earliest phases of translational science. The current project will translate these findings into a new behavioral intervention to prevent AD using the *NIH ORBIT model* for early phase translational behavioral studies. This model includes Phase 1a: Define the Intervention, Phase 1b: Refine the Intervention, Phase 2a: Proof of Concept, and Phase 2b: Pilot Study.[22] Phase 1a of this model (Defining the intervention) is underway. We have already recruited over 500 participants for the initial phase to identify a sample meeting our study criteria. Additionally, we have teamed with a community nurse practitioner to modify an existing ketogenic group intervention for application in research with older individuals. **The current study builds on both the basic science and existing feasibility trials to implement an intervention that would take into account genetics, neurophysiological correlates, and other psychosocial factors in a diverse, high risk older adult population. Especially important to the current application is the inclusion of neurophysiological assessment to identify neural correlates and improve assessment of intervention effects.**

Measurement of Intervention effect and Identification of Neural Correlates

The existing literature suggests a link between the ApoE genotype and risk for AD—and further implicates a ketogenic diet in ameliorating this risk. One of the primary goals of the current study is to extend this work to neural measures linked to both ApoE genotype and ad in a diverse population. To this end, the current proposal involves the use of neuropsychological testing, electroencephalogram (EEG) to assess neurophysiological risk for ad and potential changes in neural measures post-intervention.

Aim 1: Refine. Use a team science approach to optimize and develop a protocol to promote adherence to a 6-week ketogenic diet intervention in high risk older adults. We expect that the use of a team science and patient-driven approach will enhance adherence (80%) and retention (100%) in the Proof of Concept stage.

Aim 2: Proof of Concept. Assess the feasibility, acceptability, and preliminary effects of implementing a ketogenic dietary intervention for older adults at high risk for AD. Participants, aged 60-75 (N=50), will complete in-person neuropsychological assessments to assess for MNCD status, and saliva samples will be collected to assess for ApoE genotype. We will recruit 10 participants (5/10 ApoE €4+) who meet criteria for MNCD to complete a feasibility study assessing adherence to a ketogenic diet. **Hypothesis 1: We expect that interdisciplinary collaboration and a patient-centered approach will increase acceptability to a ketogenic diet, as evidenced by an 80% dietary adherence rate. Hypothesis 2: We expect preliminary evidence that adherence to the ketogenic diet will improve cognitive performance on memory tasks, and the diet may have a greater impact on cognitive scores for ApoE €4+ participants.**

Aim 3: Examine the intervention effect on neural correlates of AD and ApoE €4. Participants selected for the intervention (N=10) will complete pre- and post-

intervention EEG assessments to identify treatment effects. **Hypothesis 1: Ketogenic Diet will reduce P300 latency and increase P300 amplitude Hypothesis 2: The impact of the ketogenic diet on P300 latency and amplitude will be larger among ApoE €4+ carriers.**

COVID-19 Update: Pre- intervention assessments have mostly been completed. Post-intervention EEG assessments have been suspended; however, if COVID-19 restrictions are lifted in time, post-intervention EEG, vitals, and blood-draw assessments will be completed according to original protocol. For the 1 participant who did not complete the pre-assessments, we will collect cognitive data over the phone and will not include EEG data.

Aim 4: We will examine whether variability in the p300 relates to cognitive measures, and if it better differentiates ApoE genotype and the impact of a ketogenic diet than cognitive measures. In conjunction with the in-person neuropsychological assessments and genotyping (n=50), we are proposing to add an EEG assessment at this phase to assess neural risk factors for ad. For this portion, we are interested in adding an additional 25 low-risk participants to the sample as a comparison group in order to identify and confirm neural correlates of MNCD and ApoE €4 status. **Hypothesis 1: MNCD will have increased latency and reduced amplitude p300 relative to healthy controls. Hypothesis 2: among MNCD, ApoE €4 genotype will be associated with increased latency and reduced amplitude p300.**

COVID-19 Update: All phase 2 in-person and EEG assessments were completed prior to recent restrictions and are not subject to change.

1.0 Background*

AD is the sixth leading cause of death in the United States,[1] **and minority older adults are disproportionately affected by such neurocognitive disorders**.[2] For example, the Alzheimer's Association[3] reports that African Americans are twice as likely to develop AD, while Hispanic Americans are approximately one and a half times more likely compared to Caucasians. Existing research demonstrates that genetic risks such as the apolipoprotein E (ApoE) €4 allele may be a significant contributor to this discrepancy, due to higher rates in certain minority groups.[4] In addition to increased genetic risk, minority individuals may also be more likely to experience sociocultural risk factors, such as reduced access and poorer quality of health care,[5] lower quality of education,[6] and increased chronic environmental and psychosocial stressors.[7] Combined, the literature demonstrates that aging African Americans and other minority groups may be at the greatest risk for being diagnosed with a neurocognitive disorder, but have been disproportionately neglected in research.[8] Despite this underrepresentation, basic science, as well as large epidemiological studies over the past several decades have illuminated a wide range of risk and resiliency factors for late-life cognitive decline for both minority and Caucasian populations.

For example, it is well accepted that **carriers of an ApoE €4 allele, compared to carriers of €2 and €3 alleles, are at the greatest risk for developing AD**;[9] yet, having an ApoE €4 allele is not sufficient to develop AD. The expression of this genetic risk is

influenced by a wide range of environmental risk factors, ranging from stressful life events to diet and exercise.[10-11] **A ketogenic diet, in particular, holds promise for addressing deficiencies linked to the ApoE €4 allele**.[9,12-13]

ApoE is involved in lipid metabolism, and the ApoE €4 allele is not as efficient as other variants; thus, researchers have indicated that genotype should be taken into account when applying a dietary intervention for AD.[9] In addition to lipid metabolism, glucose metabolism may be another contributor to neurodegeneration due to decreasing metabolic efficiency with age.[14] For example, researchers have demonstrated that a high-glycemic diet (e.g., high sugar/carbohydrate) is associated with accumulation of amyloid plaques in cognitively normal adults.[15] A diet high in healthy fats and low in carbohydrates (i.e., ketogenic) induces the creation of ketone bodies, which can be processed by the brain in place of glucose. Further, ketone supplements, specifically, appear to improve cognitive functioning, even when a normal diet is maintained.[16-17] The effect, however, is weakened in individuals with an ApoE €4 allele;[17-18] ketone supplements do not account for the potential benefits of healthy fats and reduced carbohydrate intake on APOE functioning – an effect only diet change may produce. **The ketogenic diet shows promise in addressing problems in lipid metabolism and may circumvent inefficient glucose metabolism**, which indicates diet as a potent therapeutic intervention for cognitive functioning.[10-11] The ketogenic diet has already proven a powerful therapeutic tool in pharmacoresistant epilepsy and is being studied for its effect on tumor growth in cancer.[19]

Less attention has been given to the potential therapeutic effects of a ketogenic diet in individuals with mild neurocognitive disorder (MNCD) and AD. A small feasibility study demonstrated that the ketogenic diet can successfully improve cognitive scores in older adults with mild AD (N=10 completers) across a 3-month span, although all four patients with moderate AD dropped out before completing the trial.[15] Additionally, ketone supplements to a normal diet have shown small, but positive effects in improving cognitive functioning scores in individuals with AD without an ApoE €4 allele.[16] These findings demonstrate that ketosis is generally beneficial and such a trial is feasible; however, implementation may be challenging in patients who are already diagnosed with AD. Further, given the evidence of an interaction between ApoE and ketone bodies[9,20,21], feasibility studies and future clinical trials should experimentally assess the cognitive effects and neural correlates associated with a ketogenic diet in humans.

In sum, there is significant and growing evidence that adherence to a ketogenic diet may be an effective behavioral intervention for AD. While previous studies have identified the basic mechanisms and interactions of a ketogenic diet with ApoE and lipid and glucose metabolism, feasibility testing in diverse human samples remains in the earliest phases of translational science. The current project will translate these findings into a new behavioral intervention to prevent AD using the *NIH ORBIT model* for early phase translational behavioral studies. This model includes Phase 1a: Define the Intervention, Phase 1b: Refine the Intervention, Phase 2a: Proof of Concept, and Phase 2b: Pilot Study.[22] Phase 1a of this model (Defining the intervention) is underway. We have already recruited over 300 participants for the initial phase to identify a sample meeting our study criteria. Additionally, we have teamed with a community clinic to modify an existing ketogenic group intervention for application in research with older individuals. **The current study builds on both the basic science and existing**

feasibility trials to implement an intervention that would take into account genetics, neurophysiological correlates, and other psychosocial factors in a diverse, high risk older adult population. Especially important to the current application is the inclusion of neurophysiological assessment to identify neural correlates and improve assessment of intervention effects.

Measurement of Intervention effect and Identification of Neural Correlates

The existing literature suggests a link between the APOE genotype and risk for AD—and further implicates a ketogenic diet in ameliorating this risk. One of the primary goals of the current study is to extend this work to neural measures linked to both APOE genotype and AD in a diverse population. To this end, a key component of the current proposal involves the use of electroencephalogram (EEG) to assess neurophysiological risk for AD and potential changes in neural measures post-intervention. This is a significant addition insofar as neural measures derived from EEG are ideally suited to assess neurocognitive risk factors linked to APOE and MNCD – and are an appropriate target for assessing the impact of a ketogenic diet. Further, EEG assessments may not be prone to the biases inherent in many neuropsychological tests, making it ideal for assessing more diverse populations.

In previous EEG studies, AD has been associated with reduced amplitude of the P300 event-related brain potential[23-24], as well as delayed latency of the P300.[23-25] The P300 is one of the most robust and commonly studied event-related brain potentials (ERPs). It is typically elicited in either auditory or visual oddball tasks, in which participants must count or respond to an infrequently presented 'target' stimulus and ignore a more frequently presented 'standard' stimulus. The P300 is evident as a parietally-maximal positive deflection that peaks a few hundred milliseconds after stimulus onset. A shorter latency of the P300 has been associated with faster decision-making and quicker information processing[26], whereas a larger P300 amplitude has been associated with better cognitive abilities (i.e., attention, memory). The P300 effects seen in AD reflect delayed information processing and reduced cognitive abilities – and appear irrespective of task modality.[23]

Importantly, the ApoE genotype has also been associated with deficits in the P300: ApoE €4 carriers are characterized by reduced amplitude of the P300 event-related brain potential[27-28], as well as delayed latency of the P300.[28-30] Other studies have found that positive familial risk for AD is related to delayed latency of the P300.[29,31] Collectively, these data strongly suggest that abnormalities of the P300 may be a risk factor for AD, and may further mediate the association between ApoE €4 and AD risk. One primary aim of the current grant application is to replicate these associations in our sample—to demonstrate that the ApoE €4 genotype is associated with a reduced amplitude and delayed latency of the P300. Our second aim is to collect pilot data to determine whether a ketogenic diet would 'normalize' P300 abnormalities – and if it would do so more among ApoE €4 gene carriers. Our working hypothesis is that a reduced and prolonged P300 will be characteristic of ApoE €4, and that a ketogenic diet will normalize these deficits. If confirmed, these data would provide mechanistic data that P300 abnormalities could be a novel target for a ketogenic diet intervention to reduce risk for AD.

2.0 Study Endpoints*

Proof of Concept. Assess the feasibility, acceptability, and preliminary effects of implementing a ketogenic dietary intervention for older adults at high risk for AD. Hypothesis 1: We expect that interdisciplinary collaboration and a patient-centered approach will increase acceptability to a ketogenic diet, as evidenced by an 80% dietary adherence rate. Hypothesis 2: We expect preliminary evidence that adherence to the ketogenic diet will improve cognitive performance on memory tasks, and the diet may have a greater impact on cognitive scores (i.e., RBANS) for ApoE €4+ participants.

Examine the intervention effect on neural correlates of AD and ApoE €4. Hypothesis 1: Ketogenic Diet will reduce P300 latency and increase P300 amplitude Hypothesis 2: The impact of the ketogenic diet on P300 latency and amplitude will be larger among ApoE €4+ carriers.

We will examine whether variability in the p300 relates to cognitive measures, and if it better differentiates ApoE genotype and the impact of a ketogenic diet than cognitive measures. Hypothesis 1: MNCD will have increased latency and reduced amplitude p300 relative to healthy controls. Hypothesis 2: among MNCD, ApoE €4 genotype will be associated with increased latency and reduced amplitude p300.

3.0 Study Intervention

As previously described, we are assessing the feasibility of implementing a 6-week ketogenic dietary intervention. Our primary outcomes involve the assessment of adherence and acceptability of the diet, and our secondary outcomes involve assessing neuropsychological changes and neural correlates of ketosis.

The dietary intervention will consist of weekly group meetings for 6-weeks, which will take place in the CTBScience conference room. Our consultant, Patrice Bullock, MSN, FNP-C, who specializes in functional medicine and the impact of diet on health, will lead the group meetings via video conference. The meetings will be co-led by the PI, Julia Sheffler, Ph.D., who will assist with collection of in-person assessments, distribution of group materials, and group facilitation.

In the first week of the intervention, there will be 2 meetings. Prior to the first meeting, participants will provide a blood sample to assess their metabolic profile. The first meeting will be a 1.5 hour informational session to provide participants with materials (i.e., informational handouts, recipes, food logs, ketosis test strips). The second meeting of the first week will consist of a 1-hour video conference designed to answer remaining follow-up questions, assess issues that might arise early in the diet, and provide additional support. The remaining 5-weeks will consist of 1-hour, weekly group meetings in the CTBScience conference room. Participants will be asked to return their ketosis logs, and complete weekly assessments (i.e., Health profile screener, weight and vitals assessment, food and ketosis log, and self-evaluation of their adherence and obstacles to adherence). These 1-hour meetings will provide additional information about adhering to a ketogenic diet, identifying barriers and solutions to adherence, and providing group support and accountability. These meetings will provide time for participants to ask questions and to discuss any adverse reactions to the diet. These meetings will also provide the researchers an opportunity to complete

brief health assessments in order to identify any physical adverse reactions. These will be reported to the FNP-C to determine if additional assessments may be required. Adverse responses to the diet will be identified by the FNP-C and the consulting M.D., Dr. Paul Katz. Participants will be compensated $50 each week for their time and for the purchase of any additional groceries required for dietary adherence. Thus, participants will be compensated $300 for their total time spent in the intervention.

As described below in the Procedures section, there will be pre-assessment and post-assessment appointments around the intervention to provide additional data on neuropsychological and neurophysiological outcomes associated with the diet. Participants will be compensated an additional $75 for the pre-assessments (RBANS, EEG, & blood draw) and $75 for a post-assessment (RBANS, blood draw, and EEG), and $50 for completing the 1-month follow-up.

COVID-19 Updates: The dietary intervention will consist of weekly group virtual meetings, which will take place via HIPAA-compliant Zoom. The meetings will be led by PI, Julia Sheffler, Ph.D. and a nurse practitioner who will still be mailing informational handouts and ketone test strips to the participants prior to the meetings, so participants may request clarification if needed. Blood sample collection, weight, and vital assessments are suspended in accordance with the recent restrictions. However, if these restrictions are lifted in time, we will proceed with these final blood sample, weight, and vital assessments in-person, but on an individual one-on-one basis. We may request that participants provide their most recent standard bloodwork from their primary care physician at the start of the intervention; however, this will remain optional. Weekly food logs and paper assessments will be mailed to the participants in addition to weekly compensation checks. If COVID-19 restrictions are not lifted prior to the end of the intervention, post-intervention neuropsychological assessments will be completed via telephone, while paper pre- and post-intervention assessments will be adapted into Qualtrics or telephone interviews.

4.0 Procedures Involved*

Screening call:

Participants who completed the previous phase of the study and indicated that they would like to be contacted for future studies will be first screened based on APOE e4 status. Participants who meet all eligibility criteria based on the survey, genetic testing, and neuropsychological testing (i.e., meet criteria for MNCD, 5/10 APOE e4+, 5/10 APOE e4-, no exclusionary health conditions or significant dietary restrictions based on nurse practitioner's discretion, and interest in completing a dietary intervention). The call screening script is attached.

Pre-intervention Assessments:

All participants will complete two pre-intervention assessment appointments. These appointments will be scheduled within 2 weeks of the first intervention group meeting. This appointment will include: consenting, brief neuropsychological testing (*The Repeatable Battery for the Assessment of*

Neuropsychological Status - RBANS), and the emotion battery of NIH toolbox. The total meeting should last approximately 1 hour. These meetings will be completed by a clinical psychologist or a Ph.D. level clinical psychology graduate student.

The second visit will involve completing an EEG, which will involve picture and audio memory tasks. Each appointment will last approximately 1-hour. Participants will be compensated $75 total for both appointments.

COVID-19 Updates: If in-person restrictions are lifted by the end of the six-week intervention, post-intervention EEG and follow-up assessments will be completed on an individual basis, while we continue to take necessary safety and hygiene precautions outlined in the original protocol. Neuropsychological assessments will be completed via telephone using a battery of pre-standardized assessments. Otherwise, the EEG post-intervention assessments will not be completed, and all assessments will be completed via HIPAA-compliant Zoom or telephone.

Given that all participants have already enrolled in the trial, we will also complete individuals calls to these participants to explain the changes in the protocol and to obtain verbal consent to continue in the study. We will test each participants capability to use the video conferencing software prior to the first group meeting.

Intervention:

Week 1: Participants will be asked to come to the center approximately 1 hour prior to the group meeting to complete pre-intervention health assessments. These assessments will include a blood draw for comprehensive metabolic profiles (completed by a certified phlebotomist), a weight and body composition assessment, basic vitals (blood pressure and heart rate), and a health profile screener (see attached). Participants will also be given a food diary and ketone test strips for recording level of ketosis and net carbohydrate intake throughout the intervention trial. **Of note, weight, vitals, and the health profile screener will be administered at each weekly meeting to monitor participant well-being.**

The first group meeting will consist of a 1.5 hour informational session to provide participants with materials and to introduce them to the diet and diet plan in detail. The meetings will be led by a certified Nurse Practitioner via video conference. The PI, Julia Sheffler, will be present in-person as well to help facilitate the group. Participants will be given an opportunity to ask questions and complete and to provide feedback about the session. Participants will be encouraged to track their diet until the next session, and to slowly begin reducing their carbohydrate intake. Participants will be compensated $50 for their time and to purchase any additional groceries.

A second group meeting will be scheduled later in the same week in order to give participants an opportunity to attempt reducing carbohydrate and increase healthy fat intake across multiple days. This meeting will be offered to provide

additional assistance and for participants to ask questions or voice concerns after attempting the diet on their own. This meeting will be semi-structured, with the goal of providing support.

Week 2-4: After the first week, the following meetings will consist of 1-hour weekly group meetings. These will be designed to answer questions, provide additional dietary information, and to provide general support for increasing adherence. In week 4, participants will be reminded of the upcoming post-assessments and will begin scheduling appointments. Participants will be reminded that they should be in ketosis when completing the post-intervention assessments. Each week, participants will be compensated $50, and will be asked to record ketone level on a daily basis.

Week 5-6: The group meetings will continue as usual in the final weeks; however, during this time, participants will be scheduled to complete post-intervention neuropsychological testing. Testing will be completed during the active intervention in order to assess individuals who are actively in ketosis. In the final session, participants will be asked to come early or stay late to complete a follow-up blood draw (by a certified phlebotomist). The final session will conclude with qualitative feedback about the intervention program in order to inform future studies.

Follow-up intervention Assessments: All participants actively engaged in the intervention by week 4 will complete 2 follow-up appointments during the final 2 weeks of the intervention. The first visit will repeat the brief neuropsychological test (RBANS) and the NIH toolbox. The second visit will involve completing a follow-up EEG, which will involve picture and audio memory tasks. Each appointment will last approximately 1-hour. Participants will be compensated $75 total for both appointments.

1-Month Follow-up Assessment: All participants will be contacted 1 month after completing the final group meeting to repeat the brief neuropsychological test (RBANS) and the NIH toolbox, as well as to respond to brief semi-structured questions about their experiences since ending the intervention. Participants will be compensated $50 for completing this appointment.

COVID-19 Updates: If COVID-19 restrictions are not lifted, the dietary intervention will consist of virtual group meetings, which will take place via HIPAA-compliant Zoom. The meetings will be led by PI, Julia Sheffler, Ph.D. and a registered nurse practitioner, who will mail informational handouts and ketone test strips to the participants prior to beginning the intervention. Online assessments will be sent using email prior to each meeting, so participants may request clarification if needed. Blood sample collection, weight, and vital assessments are suspended in accordance with the recent restrictions; however, if these restrictions are lifted, we may proceed with these assessments in-person on an individual, one-one-one basis, with additional safety precautions and sanitation taken. We will request that participants provide their most recent standard bloodwork from their primary care physician; however, this will remain optional.

Week 1: Prior to the first meeting, participants will be mailed the ketone test strips, informational handouts and food diaries to monitor carbohydrate intake over the course of the intervention. They will complete a 1.5-hour virtual group meeting, which will act as the initial informational session. A second meeting will be scheduled with participants within this first 7-day period to give participants the opportunity to begin reducing carbohydrate intake and to ask follow-up questions. This meeting will retain the original goals of providing support and giving the participant the opportunity to ask questions after attempting the diet on their own.

Week 2-4: After the first week, subsequent meetings will be 1-hour long and will retain the original goals of providing support and answering dietary questions. Participants will still be asked to record ketone levels on a daily basis.

Week 5-6: These final one-on-one HIPAA-compliant Zoom meetings will collect qualitative feedback as previously mentioned and will omit the blood-drawings.

The follow-up intervention assessments and 1-month follow ups will continue as planned, but will continue with online and telephone-based assessments rather than in-person.

If COVID-19 restrictions are lifted prior to the end of the program, post- and follow-up intervention assessments and 1-month follow ups will be conducted as individual, one-on-one in-person assessments.

5.0 Data and Specimen Banking*

Blood samples will be collected in a phlebotomy lab at the Center for Translational Behavioral Science. Samples will be labeled and identified only by an ID number. These samples will be used to assess comprehensive metabolic profiles (CMPs) of participants. Samples will be stored temporarily in the phlebotomy lab and then will be transported via medical transport cooler to the lab on FSU campus for analysis. If immediate analysis is not possible, samples will be stored in a –80 F freezer at the Translational Science Laboratory at the College of Medicine in a locked suite until analysis is possible. Once results of the CMPs are returned, these will be coded and stored with other participant data (described below).

Specimens will not be released to participants or entities outside the study. If the Nurse Practitioner on the study identifies concerning findings in regards to the participants' comprehensive metabolic profiles or other health data, she will notify the study team's M.D. consultant for a clinical decision on recommendations. If necessary, participants will be notified that follow-up with a physician may be indicated, and they will be given the option to sign a release of information (see attached) to have this information shared with their physician for follow-up. Findings will be faxed directly to their physician.

6.0 Sharing of Results with Subjects*

Participants will not receive diagnostic feedback about their performance on the RBANS, NIH toolbox, or EEG results. If participants request information about their performance on the memory tasks, the researchers will provide general feedback about whether the participant performed the same, better, or worse at follow-up compared to baseline. Participants will be told that fluctuations in performance are normal and are not necessarily indicative of a problem.

If the Nurse Practitioner identifies concerning findings in regards to the participants' comprehensive metabolic profiles or other health data. Participants will be notified that follow-up with a physician may be indicated, and they will be given the option to sign a release of information (see attached) to have this information shared with their physician for follow-up. Findings will be faxed directly to their physician.

7.0 Study Timelines*

Recruitment will not begin until Fall 2019. Participation in the full study participation in the full study will require a maximum of 15-weeks for participation from the first in-person appointment to the last.

8.0 Subject Population*

Participants will include individuals between the ages of 60 and 75 years; however, we will allow participants over the age of 75 if they completed the initial screening survey when they were 75. That is, some individuals may have had a birthday since initial screening, and we will still include these individuals if they meet other study criteria. The sample will be randomly selected from participants who complete a previous screening study who expressed interest in participating in a dietary intervention. Inclusion criteria for the intervention are: meet criteria for a MNCD, no self-reported dietary restrictions or health conditions/medications that might interact with a ketogenic diet, and interest in completing a dietary intervention to improve cognitive functioning. In addition to the total sample inclusion criteria, half the sample will also be selected based on their ApoE €4 status. We are specifically interested in targeting older adults who are at high risk for developing AD, but have not progressed to a diagnosable major neurocognitive disorder.

We will not include any of the following as participants in the current study:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

9.0 Vulnerable Populations*

We will not include any participants who are unable to provide consent. Of note, a mild neurocognitive disorder is characterized by slight decline in cognitive functioning, which require compensatory strategies to retain independence. Individuals with MNCD are able to live and function independently and are able to provide consent to participate. The PI is a trained clinical psychology with a specialty in geropsychology and while rule out individuals who do not have capacity to consent via previous screening studies.

10.0 Local Number of Subjects

Our goal is to recruit 10 participants to complete the intervention, as this is a small feasibility study.

11.0 Recruitment Methods

Participants will be recruited from a previous screening study (IRB approved: STUDY00000213), where they provided consent to be contacted for future research studies. Participants will be called by one of the key personnel and will provide verbal consent to complete a brief screening (see attached script). Participants who qualify based on this telephone screener will be scheduled for the initial assessment appointment.

Participants will be excluded from the study if they identify an unstable chronic medical condition, such as kidney/renal disease or failure, congestive heart failure, heart disease, heart rhythm irregularities, severe lipid dysfunction or deficiencies, unstable gallbladder disease, Chron's disease, ulcerative colitis or other serious GI disorder, including history of ostomy, Type 1 and Type 2 diabetes requiring insulin, chronic auto-immune disorders, active psychosis or serious unstable psychiatric conditions, or any other significant surgery or chronic health condition that may interfere with their ability to alter their diet, as determined by a certified nurse practitioner. Further, participants who report using the following medications will be excluded: insulin, diuretics, antipsychotics, MAOIs, narcotics, immunosuppressant medications, or others at the nurse practitioner's discretion.

12.0 Withdrawal of Subjects*

Participants will be withdrawn from the study based on the investigator's discretion. The consultant leading the intervention is a registered Nurse Practitioner who will assist in monitoring the participants' vitals each week. Participants who experience significant adverse responses to the diet (as determined by a nurse practitioner or MD) will be withdrawn from the intervention. If a participant is withdrawn due to health, they will be provided partial compensation and provided the option of completing follow-up assessment appointments.

13.0 Risks to Subjects*

Intervention Risks: We are only recruiting healthy individuals with no unstable chronic medical conditions for this diet (e.g., gallbladder problems, Type 1 diabetes). Thus, primary risks associated with changing diet may include,

gastrointestinal upset (i.e., bloating, diarrhea, gas, and constipation), change in weight, headache, and fatigue. Participants will be closely monitored by a nurse practitioner on a weekly basis to assess any adverse response to the diet. If a significant adverse response is reported or identified, the team will consult the MD consultant on the team for a clinical decision.

EEG Risks: There is a small possibility of mild skin irritation (redness) where the electrode contacts the skin. This is rare and usually temporary.

14.0 Potential Benefits to Subjects*

A goal of the current study is to assess whether a ketogenic diet may be beneficial for memory in older adults. Previous research has demonstrated that a low-carbohydrate diet has multiple benefits on cognitive functioning and other health factors in older individuals. Thus, participants will be provided with a supportive environment for making this diet change. Participants may experience improvements in their cognitive status and will be closely monitored by health professionals.

15.0 Data Management* and Confidentiality

In regards to the data analytic plan, we will complete descriptive analyses of the sample and correlational analyses of outcomes. Regression, ANOVA, and t-tests may be used.

Physical copies of tests and measures will be stored in locked cabinets in a secured suite in Research Building B at Innovation Park. Data from these physical copies will be coded and transferred to electronic spreadsheets, which will be password protected and stored in encrypted locations. All identifiable participant data will be stored separately in a password protected document. Data will be connected to an ID number rather than participant information.

Data will be entered by a research assistant and checked by the PI for consistency.

If data or specimens require transport from one study location to another (I.e., innovation park to college of medicine), these will be transported only by study key personnel directly from location to another.

16.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

Weight and basic vitals assessments and the health profile screener will be administered at each weekly meeting to monitor participant well-being. These will be reviewed by the Nurse Practitioner on the study at each weekly session. She will determine if additional follow-up or referral is warranted. If the Nurse Practitioner identifies a potential adverse response, she will notify the M.D. consultant for further review and a clinical decision on course of action. The IRB will be notified in the case of any adverse event.

COVID-19 Updates: Although we may not be able to conduct the weight and basic vitals assessments if COVID-19 restrictions are not lifted by the end of the study, we will be asking participants to disclose any discomfort or adverse

experiences they might be having throughout the duration of the study. We will also ask participants to self-monitor weight and health information and to self-report these each week through the online questionnaires. These will still be reviewed by the Nurse Practitioner following the original protocol. We will also introduce the option for participants to provide their most recent standard bloodwork from their primary care physician to attain some indication of their baseline health status.

17.0 Provisions to Protect the Privacy Interests of Subjects

Research records will be kept confidential to the extent allowed by law. Research records will be numerically coded to remove any identifying information. Only the researchers in this project and the research sponsor will have access to this data. Anonymized information derived from the research records may be used more broadly for publications and product development efforts, and as a result will not necessarily be kept confidential. The research team will not request to access existing patient records covered by HIPPA or other entities. All information collected during the study will be at the participants' discretion.

If a participant reports feeling discomfort at completing a task or item, they will be given the option to skip the item or task. Participants will be reminded that their participation is voluntary and there is no penalty for leaving the study.

18.0 Compensation for Research-Related Injury

Engaging in a monitored low-carbohydrate diet should pose no more risk to participants than encountered in daily life. Similarly, risks for the EEG portion of the study are minimal and clearly laid out in the consents and in other sections of this protocol. We state the following about compensation:

"Medical Treatment: FSU, its agents, or its employees do not routinely compensate for or provide free care for human subjects in the event that any injury results from participation in a research project. If you become ill or injured as a direct result of participating in this study, contact your regular medical provider. If you have insurance, your insurance company may or may not pay for these costs. If you do not have insurance, or if your insurance company refuses to pay, you will be billed. Funds to compensate for pain, expenses, lost wages and other damages caused by injury are not routinely available."

19.0 Economic Burden to Subjects

Participants will be required to supply their own transportation to and from appointments. No other economic burden to participants is expected.

20.0 Consent Process

We will follow the "SOP: Written Documentation of Consent (HRP-091)." Participants will receive a separate consent form for the intervention portion of

the study. This consent is attached. The consent process will take place in a research office at the Center for Translational Behavioral Science and will be completed by the PI or a trained research assistant.

Participants are being selected for the current study based on results of neuropsychological testing from a previous, related study. Thus, the cognitive status of participants as cognitively capable of providing consent will be determined by a clinical psychologist (the study PI). If there is concern during the study that a participant no longer has capacity to provide consent to participate, a brief cognitive assessment will be completed (I.e., the Montreal Cognitive Assessment & judgment questions) to assess whether their cognitive status has precipitously declined. If a participant is identified as no longer having capacity to participate, they will be removed from the study and provided with community referrals.

COVID-19 Updates: Participants will be re-consented and provided with updated information regarding study procedures as they adjust to follow recent restrictions. They will be given the option to reconsider their participation given these changes now, as well as throughout the study's completion. However, participants will be made aware that if COVID-19 restrictions are lifted before the end of the study, they will be asked to come in for in-person follow-up assessments. The study team will take the greatest care to ensure the safety of our participants. **Even if restrictions are lifted, we will continue to screen all researchers who may have contact with participants, we will limit any physical contact with participants unless we obtain PPE, and we will take additional safety and cleaning measures for all surfaces and participant areas.**

21.0 Process to Document Consent in Writing

We will follow the "SOP: Written Documentation of Consent (HRP-091)." Participants will receive a separate consent form for the intervention portion of the study. This consent is attached.

22.0 Setting

Participants will be recruited from a previous study via phone contact. Only participants who expressed interest in being contacted will be recruited.

The majority of participant interactions will occur at the Center for Translational Behavioral Science at Innovation Park Campus.

COVID-19 Updates: If Covid-19 restrictions are not lifted before the end of the intervention, all participant interactions will occur via telephone and HIPAA-compliant Zoom to maintain social distancing practices.

23.0 Resources Available

We are proposing to recruit a total of 10 participants, with at least 5 being APOE 4+. Participants will be selected from eligible participants from a previous, related study who express interest in completing the dietary intervention. As part of an initial screening/recruitment study, we have surveyed over 500 participants. The next screening study will recruit a subsample of these individuals for neuropsychological testing and APOE sequencing. The current study will further select from this subsample.

The current PI will devote up to %50 time to conducting the current research study. The Center for Translational Behavioral Science is currently being equipped with a phlebotomy room, which will be used for health assessments and blood draws. We will also have a conference room equipped with video conferencing to complete the intervention. Participant rooms in the center will be used for completing assessments in a quiet environment. Our center will be sharing a space with Dr. Greg Hajcak's EEG lab, where the follow-up EEGs will occur.

Our team consists of multiple clinical psychologists, a nurse practitioner, Geriatrician M.D., geneticist, research methodologist, and a Ph.D. level registered dietician. These study personnel will be available for consultation in the case of any adverse event.

Our team has met multiple times to develop the current grant and after award to plan the project. A copy of this protocol will be shared with all key personnel.