PROTOCOL TITLE: MI-CBT Adherence Program for Lifestyle Interventions in Older Adults

NCT: 04817176

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1.0 Study Summary

Study Title	Pilot Trial of a Motivational Interviewing and Cognitive Behavioral Therapy (MI-CBT) Ketogenic Nutrition Adherence Program for Older Adults
Study Design	Block Randomized Pilot Pragmatic Clinical trial completed virtually through HIPAA Compliant Zoom
Primary Objective	Assess feasibility and acceptability of all protocol components of a pilot pseudo-pragmatic trial testing a 6-week telehealth KNA program compared to a KN information only group for older adults with MCI in the FSU SeniorHealth clinic to prepare for a full-scale trial.
Secondary Objective(s)	Assess signal of initial effect of the KNA program on important clinical outcomes and adherence relative to a KN information-only condition.
Research Intervention(s)/ Investigational Agent(s)	Using a centralized telehealth approach, the KNA program will consist of 6 weekly group meetings, which will take place via HIPAA-compliant Zoom. The group will be co-led by a clinical psychologist and a nurse practitioner with expertise in nutrition. Approximately half of each session will be devoted to providing nutrition information and half devoted to psychoeducation, MI activities, and CBT skills. Participants assigned to the KN-only group will also attend weekly group meetings with information about how to adhere to KN and how to track macronutrients, food intake, and ketone levels. Participants will be provided with the same participant binder as the KNA group with informational handouts and KN recipes, but without the MI-CBT handouts. Participants will be asked to track their food intake and daily ketone levels, and will be provided with the option of attending a weekly Zoom meeting where they may ask questions about KN and receive additional nutrition information as needed. These optional meetings will be offered for 6 weeks.
IND/IDE #	
Study Population	Older adults 60+
Sample Size	N = 60
Study Duration for individual participants	1 year, including pre/post assessments; intervention is 6 weeks.
Study Specific Abbreviations/ Definitions	KN = ketogenic nutrition; KNA = ketogenic nutrition adherence; MCI = Mild Cognitive Impairment; PCT = Pragmatic clinical trial

2.0 Objectives*

- **Objective 1:**

Assess feasibility and acceptability of all protocol components of a pilot pragmatic trial testing a 6-week telehealth KNA program compared to a KN information only group for older adults with possible or pre-MCI in the community and at a senior health clinic to prepare for a full-scale trial.

Specifically, we will examine the feasibility of the recruitment, retention, assessment, electronic health record (EHR) downloads, and intervention delivery methods through the FSU SeniorHealth™ clinic. If we determine it is not feasible to recruit the full sample through this clinic, we will expand recruitment to the community.

We hypothesize that

- *The study protocol (MI-CBT KNA program) will result in high patient retention (90%) and patient attendance of intervention sessions (80%), and*
- *A centralized MI-CBT telehealth delivery approach will be associated with high intervention acceptability ratings from patients and key stakeholders.*
- *MI-CBT KNA program will result in higher adherence to KN compared to the KN information-only group as evidenced by higher levels of ketones at week 6 of the intervention using at-home ketone urinalysis test strips.*

To test these hypotheses, we will use a mixed methods approach using qualitative interviews, quantitative measures of patient satisfaction with the intervention (using the Client Satisfaction Questionnaire) and provider perception of the overall fit of the intervention in the clinic, and of patient intervention attendance and study attrition. Qualitative data from providers and patients will be thematically coded to further examine acceptability and barriers to implementation.

- **Objective 2:**

Assess signal of initial effect of the KNA program on important clinical outcomes and adherence relative to a KN information-only condition.

We hypothesize that *patients in the KNA condition, relative to the KN-only condition, will show 1) higher rates of clinically significant improvements on the RBANS total scale scores, improvements in daily functioning (FSQ), decreases in patient CAIDE risk score, improvements in HBA1C levels and comprehensive metabolic panels, and improvements in self-reported pain using the Rolland-Morris Pain scale, and 2) improved adherence to KN, as evidenced by higher levels of measurable urine ketones in the KNA condition compared to the KN-only condition.*

We will also examine the feasibility of using electronic health record (EHR) data as an additional measure of health, pain, and cognitive outcomes.

To visually examine these hypotheses (as significance testing is not appropriate for a pilot study), we will extract data on clinical outcomes from the EHR to examine patient outcomes before and after engaging in the intervention and to compare group differences.

We expect that patients in the KNA condition will have higher rates of transferring to MCI or normal range on the RBANS and improvements in functional status on the FSQ. Participants in the KNA condition will have reductions in self-reported pain and greater improvements on other health indices. Additionally, we expect higher rates of measurable ketones (trace or higher) in the KNA program compared to KN-only based on daily, at-home urinalysis test strips. Combined, these data will provide important information about the clinical effects of the programs and feasibility of the proposed study components for a larger ePCT.

3.0 Background*

Alzheimer's disease (AD) is the fifth leading cause of death in the United States, and despite decades of research, there are still no effective treatments or preventive interventions. One promising intervention has been nutrition that mimics calorie restriction, such as ketogenic nutrition (KN). Ketogenesis appears to be one of the primary pathways through which calorie restriction provides benefit. Thus, nutritionally dense KN provides many of the physiological benefits of calorie restriction while providing sufficient satiation and nutrition. Specifically, KN may directly target neurobiological mechanisms associated with the development of AD, such as defects in mitochondrial function, cerebrospinal fluid biomarkers, and dysfunctional glucose and lipid metabolism.

Recent feasibility trials of KN in older adults demonstrate substantial improvements in cognitive scores and mood, suggesting that KN is a promising therapeutic for targeting multiple disease markers associated with AD. Ketogenic nutrition (KN) is also a promising intervention that may directly target mechanisms associated with pain in older adults. In fact, in addition to targeting mechanisms associated with chronic pain,[1] KN is associated with a range of benefits across multiple chronic conditions often associated with pain. Despite being a promising intervention, there are significant barriers to testing and implementing nutritional interventions to prevent AD in real-world settings. One of the most challenging barriers is the difficulty of adhering to long-term diet modification, which may be especially challenging to implement in older adults with mild cognitive impairment (MCI).

Clinical psychology offers multiple empirically supported techniques for changing behavior and thinking and maintaining change. Cognitive behavior therapy (CBT), specifically, has documented success in application to adherence to weight loss and diabetes prevention and treatment programs and can be combined with motivational interviewing (MI) strategies to enhance motivation and adherence to lifestyle change programs. MI-CBT skills can be used in a group setting to improve the scale-up of interventions while providing social support and accountability.

Thus, group-based MI-CBT may be key to pragmatically increasing patient adherence to ketogenic nutrition long-term. In sum, the scientific premise is that adherence to nutritionally dense KN may be a powerful therapeutic for older adults with cognitive impairment; however, there remain significant challenges to testing and disseminating a KN intervention on a larger scale. The proposed project will address these challenges by pragmatically assessing the effectiveness of a telehealth KN adherence (KNA) program embedded in a community clinic, FSU SeniorHealth™, on cognitive and health outcomes.

My project will build on basic science and existing feasibility trials to assess whether a KNA program increases adherence and retention in KN intervention studies, while influencing important clinical and patient-oriented outcomes. Further, we will pilot an embedded pragmatic clinical trial (PCT) approach in order to prepare for a full-scale PCT.

Key innovations include:

- Testing the application of MI-CBT behavioral techniques to address major challenges of promising nutrition interventions in older adults with MCI. The MI-CBT skills portion is designed to enhance motivation and remove personal barriers to eating healthy, while reducing conflicts at home and providing a supportive environment.
- Applying a centralized telehealth delivery model in the context of the community and a senior health clinic to assess the feasibility of delivering this type of health-behavior intervention. We will use a centralized delivery model to increase the scalability and fidelity of the intervention and to reduce clinician burden. This pilot will provide data on the feasibility of using an embedded PCT approach to translate our KNA program directly to the community.
- Utilizing existing, embedded clinic data from EHRs to improve the scalability, reduce costs, and reduce the burden on clinicians and patients for completing clinical research. Through the examination of existing data in EHRs, we will be able to reduce study costs for assessment appointments, measures, and researcher and clinician time.

4.0 Study Endpoints*

This study will focus on assessing the feasibility and acceptability of all protocol components of a pilot pragmatic trial, testing a 6-week telehealth KNA program compared to a KN information only group for older adults with possible MCI in the community and at a senior health clinic to prepare for a full-scale trial. We will use a mixed methods approach using qualitative interviews, quantitative measures of provider's perception of the overall fit of the intervention in the clinic, and of patient intervention attendance and study attrition. Qualitative data from providers and patients will be thematically coded to further examine acceptability and barriers to implementation.

We will also focus on assessing signal of initial effect of the KNA program on important clinical outcomes and adherence relative to a KN information-only condition. Data on clinical outcomes will be extracted or requested from patient health records before and after engaging in the intervention and to compare group differences. Patient participants will also complete assessments in-person, following appropriate COVID-19 precautions, pre- and post-intervention.

We expect that patients in the KNA condition will have higher rates of transferring to the normal range on the RBANS, greater improvements in functional status on the FSQ, and greater improvements in self-reported pain and other health indices. Additionally, we expect higher rates of measurable ketones (trace or higher) in the KNA program compared to KN-only based on daily, at-home urinalysis test strips. Combined, these data will provide important information about the clinical effects of the programs and feasibility of the proposed study components for a larger PCT.

5.0 Study Intervention/Investigational Agent

Using a centralized telehealth approach, the KNA program will consist of 7 weekly group meetings across 6 weeks, which will take place via HIPAA-compliant Zoom. The MI-CBT KNA group will be co-led by a clinical psychologist and a nurse practitioner with expertise in nutrition, and the KN information-only group will be led by a nurse practitioner only. Approximately half of each session will be devoted to providing nutrition information and half devoted to psychoeducation, MI activities, and CBT skills. Each group session will be recorded and rated by a trained clinician using a modified MI Coach Rating Scale to measure fidelity to MI-CBT strategies and reviewed with Dr. Naar, a recognized expert on MI and CBT. These recordings will be stored on a secure College of Medicine network drive and will only be used for the duration of the project and reviewed by the study team for quality control and intervention consistency. Any information from these recordings used for research purposes will be fully de-identified, with qualitative information transcribed and coded by the research team. Participants will be compensated $20 each week for their time in the study and completion of weekly "homework" (i.e., food logs, ketone logging, and online survey (MSQ, PHQ-9, pain scale, self-reported weight, daily ketone level, self-reported adherence to KN, self-reported barriers and facilitators to adherence, GAS, group cohesion scale, social support scale, and perceived stress scale.))

KNA Week 1

The first group meeting will consist of a 1.5 hour informational and psychoeducational session to introduce participants to the purpose of the group, the ketogenic nutrition goals, and to the MI-CBT model of behavior change in relation to nutrition. Participants will be given a binder that includes weekly goals, handouts on how to maintain KN, including daily recipes and food lists, as well as MI-CBT handouts and worksheets. Participants will be asked to slowly begin reducing their daily net carbohydrate intake to 125g over the first week.

We will provide individualized recommendations for macronutrient intake based on the net carbohydrate weekly goal and participant health information (e.g., sex, weight, height, activity level). Participants will log macronutrient intake in their food logs in order to ensure that approximately 60% of their diet involves healthy fats (e.g., fish, avocado, olive oils), and to begin learning the general macronutrient content of foods they consume. Participants will have the option of completing these food longs online or using paper copies at home. The focus of these first meetings will be on nutritional education and helping participants identify relevant values, goals, and reasons for committing to make healthy changes.

KNA Weeks 2-4

In 1-hour weekly meetings, participants will learn about the CBT model and relevant skills, with assigned homework. Based on feedback from the feasibility trial, the program will emphasize cognitive restructuring and problem-solving as primary skills, while handouts on additional techniques (e.g., distress tolerance, behavioral activation, mindfulness) will be provided as optional.

These skills will help participants identify health goals, manage triggers for unhealthy eating behaviors, and overcome external obstacles to healthy eating. MI will be employed throughout these sessions, through worksheets as well as reflective listening,

summarizing, affirming, and open-ended questions from the group leaders. Participants will be instructed to gradually reduce their net carbohydrate intake across the first 3 weeks of the program in a step-wise fashion (i.e., 125g in week 1, 75g in week 2, 50g or less in week 3) in order to reduce possible adverse responses to the diet (e.g., GI distress, fatigue). Healthy fat intake is a core component of this program, and participants will be provided with ample instruction on ways to increase healthy fat intake while maintaining a healthy balance of macronutrients (e.g., 60% fat, 30% protein, 10% carbohydrates).

KNA Weeks 5-6

In the final two sessions, the focus will shift to emphasize CBT skills practice, maintenance of goals, sustainment of progress, and social support. Participants will make maintenance plans, learn to manage slips, and continue practicing cognitive restructuring skills. The recommended net carbohydrate intake will be reduced to 20g or less these weeks, depending on individual ketone level and macronutrients.

KN-Only (Condition 2)

Participants assigned to the KN-only group will attend a 1.5-hour informational session as a group, which will provide comprehensive information about how to adhere to KN and how to track macronutrients, food intake, and ketone levels. Participants will be provided with the same participant binder as the KNA group with informational handouts and KN recipes, but without the MI-CBT handouts.

Participants will be asked to track their food intake and daily ketone levels, and will be asked to attend a weekly Zoom meeting where they may ask questions about KN and receive additional nutrition information as needed. These optional meetings will be offered for 6 weeks. The structure of this control condition will allow us to examine of the benefits that an MI-CBT group approach provides for increasing adherence to KN and retention in a KN program, compared to KN education only.

6.0 Procedures Involved*

Design Overview

Preparation. During the first 6 months of the study, my team will work closely with key stakeholders (i.e., clinic director, practice manager, and nurse practitioner) in the FSU SeniorHealth™ clinic to coordinate initial contact with patients about the study. Initial contact will include posting flyers in the SeniorHealth clinic, handing out flyers during appointments, and emailing flyers or calling patients who have consented to be contacted about FSU research studies (a consent process, which is completed as part of the normal SeniorHealth intake packet), posting flyers in the Westminster Oaks monthly newsletter, and patients will be able to fill out a contact card with their name, phone number, and email that will be placed in a locked “drop box” in the SeniorHealth clinic. A study team member will collect these cards weekly to enter into a secure screening waitlist. Patients may also discuss interest with their provider or contact the study team directly using the information on the study flyer. If we are unable to recruit the full sample through FSU SeniorHealth, we will expand recruitment to community older adults more broadly, including individuals from the Institute for Successful Longevity participant registry. Community participants will be recruited through flyers, e-mails, and phone calls. Potential participants will only be contacted through e-mail or phone calls if they have previously provided consent to be

contacted for research purposes. Potential participants will be added to a secure screening waitlist, which will include only their name and phone number. This screening waitlist containing potential participant contact information will be stored in a password protected document. Contact information for potential participants will be destroyed for any participant who does not qualify and consent to remain in the study.

Screening phone call. After confirming interest in being contacted about the study, participants will be contacted by a member of the research team and screened for eligibility. This screening will include a telephone MoCA, sections 1 and 4 from the Functional Status Questionnaire, a brief memory complaint scale, a brief self-rated pain during the past week (0-10), and self-reported height, weight, and age. Participants will also be asked to report any restrictive dietary or medical conditions that may make them unable to change their nutrition. Participants will be compensated with a $5 e-gift card for completing the screening and will be asked to provide their full name and email address to receive the gift card. This contact information will not be retained for future research purposes unless participants consent to be contacted for future studies. All screened participants will be provided with a handout on healthy living designed in collaboration with the SeniorHealth physicians. If participants are eligible, then they will be sent an online consent form via REDCap, which they will read and review using HIPPA-compliant Zoom with a member of the research team before signing. The study team will then complete a final eligibility check of the patient's EHR, self-reported health conditions, or provided health records and review with a SeniorHealth physician to confirm eligibility and ensure participant's safety. The SeniorHealth physician will be blinded to participant identify of non-clinic participants. Participants who are eligible and consent to participate will have screening data linked with other study data, in order to reduce redundancy in assessment measures.

Pre-intervention EHR data download & collection of Health Records(Time 0). FSU SeniorHealth patients will be asked to provide our team access to relevant EHR data. Participants who are not patients at FSU SeniorHealth will be asked to provide the same records if possible, but self-reported health conditions and medications will be accepted. Our team will extract and clean relevant EHR/health data on participants who consent to participate in the study. Data from EHR/health records will be used to conduct a secondary eligibility screening to determine if there are any other major health conditions that will exclude participants from the study. Data requested will only include the minimum PHI necessary to complete the proposed study. Data from the EHR or requested health records will include the following information only from appointments pertinent to the study: patients' problem/diagnostic list, medication list, patient vitals, metabolic panels, HbA1C, potassium, CRP, scores on recent cognitive and psychological assessments (i.e., MoCA, depression inventories), and relevant provider notes about a patient's cognitive functioning and pain. Data from the EHR/health records will be used to calculate a CAIDE dementia risk score (Exalto et al., 2014), which includes age, education, sex, cholesterol, BMI, and systolic blood pressure (See Figure 1). The FSU SeniorHealth EHR is maintained on Athena and thus all the information will be accessed from Athena by the study PI, who is a licensed clinician who has completed the required HIPAA and Privacy trainings required to access this information. These data will include the participants MoCA scores, GDS, and FSQ scores or relevant qualitative data about their activities of daily living, and demographic characteristics. We will also include laboratory results that may be relevant to cognitive outcomes for secondary data analyses, including: HbA1c, glucose, potassium,

blood pressure, and cholesterol. Laboratory data that is pulled from the EHR, will be used as a comparison to metabolic and HbA1c data obtained from a blood draw during two in-person assessments.

Baseline Assessment (Time 1). In addition to embedded EHR and other health record data, we are collecting additional data to evaluate the personal impacts of the intervention. This in-person assessment will include: the Repeatable Battery of Neuropsychological Status (RBANS update – form A), GAS, PHQ-9, FSQ, ISEL, MSQ, CAIDE risk score, OPQOL, GSE, PSQI, SCOFF, social support, self-efficacy, a verbal pain descriptor scale, the Brief Pain Inventory, The WOMAC-Pain scale, the PANAS, PSS, the WHY-MPI, and the Roland-Morris Pain and Pain-related Disability scale, a fasting blood draw for a comprehensive metabolic panel and HbA1C (completed by a certified medical assistant), a weight and body composition assessment, and basic vitals (blood pressure and heart rate). Participants will be scheduled in the morning for these assessments in order to allow approximately 10-hour fasting for the blood draw. This assessment will be completed in-person following COVID-19 precautions (described in section 14), and patient participants will be compensated $30 for their time.

Post-intervention Assessment (Time 2). Participants will complete this assessment in the final weeks of the program, in order to assess participants when they are in ketosis. Participants will be asked to return their ketone logs either electronically, reported over the phone, or via mail to the study PI. The research team will complete qualitative interviews with participants to collect information about barriers and facilitators to completing the program and adhering to KN. Participants will complete the RBANS update – Form B, the PHQ-9, FSQ, MSQ, GAS, CAIDE risk score, OPQOL, PSS, PSQI, social support (ISEL), self-efficacy (GSE), group cohesion, a verbal pain descriptor scale, the Brief Pain Inventory, The WOMAC-Pain scale, the PANAS, the Roland-Morris Pain and Pain-related Disability scale, the WHY-MPI, and participants' global impression of change, a second fasting blood draw for comprehensive panels (completed by a certified medical assistant), a weight and body composition assessment, and basic vitals (blood pressure and heart rate). Participants will be scheduled in the morning for these assessments in order to allow approximately 10-hour fasting for the blood draw. This assessment will be completed in-person following COVID-19 precautions, and patient participants will be compensated $30 for their time.

Post-intervention Assessment (Time 3). Patient participants will complete this assessment approximately 3 months after completing the intervention program, in order to assess long-term maintenance. The research team will complete qualitative interviews with participants to collect information about barriers and facilitators to adhering to KN long-term. Participants will complete the RBANS Update – form C, the PHQ-9, FSQ, MSQ, GAS, CAIDE Risk score, OPQOL, PSQI, social support (ISEL), self-efficacy (GSE), a verbal pain descriptor scale, the Brief Pain Inventory, The WOMAC-Pain scale, the PANAS, PSS, the WHY-MPI, the Roland-Morris Pain and Pain-related Disability scale, the Client Satisfaction Questionnaire (8-item), and participants' global impression of change in pain. This assessment will be completed in-person following COVID-19 precautions and patient participants will be compensated $30 for their time.

Participants who express barriers to completing the 3-month post-intervention assessment in person will have the option to complete this assessment remotely if they

choose to. In the even that a participant chooses to complete the Time 3 assessment remotely, the following procedures will be conducted: a research assistant will schedule a phone call with the participant at a time that is convenient to them to complete the qualitative interviews with participants and collect self-reported height, weight, and ketone test (if available); participants will be asked to complete questionnaires via REDCap by following a link to the survey that will be emailed to them by a team member; lastly, due to the nature of the RBANS, participants who choose to complete the Time 3 assessment remotely will not be asked to complete the RBANS Update – form C. Participants will receive the same amount of compensation, $30, for their time upon completing the assessment procedures.

Post-intervention EHR data download and Provider Assessment (Time 4). Approximately six months post-intervention, we will complete a final data extraction from the EHR for SeniorHealth patients, which will include the same data as Time 0. We will also request updated health records from non-FSU SeniorHealth clinic participants. Additionally, we will complete semi-structed interviews with the clinic providers to assess implementation barriers and facilitators. Providers will also complete quantitative measures on implementation acceptability (i.e., Modified version of the Assessment of Fit Scale for outpatient clinics). Provider participants will be compensated with a $25 gift card for their time.

Weekly Assessments. Throughout the active intervention phase, participants will also complete a weekly online survey to assess information about their weight, health symptoms (MSQ), mood (PHQ-9), anxiety (GAS), stress (perceived stress scale), daily ketone levels, response to adherence and barriers to KN, pain, group cohesion, and social support. Participants will be asked to mail or email their food diaries to the study team each week to assist in monitoring nutritional adherence and safety.

Sources of Materials

Data will be obtained directly from participants, including: survey data, neuropsychological data, and health information. Data will also be collected from FSU SeniorHealth EHRs, but will only include the minimum PHI necessary to complete the proposed study. Data from the EHR will include the following information only from appointments pertinent to the study: patients' problem/diagnostic list, medication list, patient vitals, potassium levels, metabolic panels, HbA1C, CRP, scores on recent cognitive and psychological assessments (i.e., MoCA, depression inventories), and relevant provider notes about a patient's cognitive functioning. Finally, we will complete semi-structed interviews with the clinic providers and patient participants to assess implementation barriers and facilitators. Provider participants will also complete quantitative measures on implementation acceptability (i.e., Modified version of the Assessment of Fit Scale for outpatient clinics). Only Dr. Sheffler and key study personnel will have access to individually identifiable private information (e.g., names, dates of birth, etc.) outside of clinic staff. Staff responses will not be shared with other providers at the clinic. All the information extracted from EHR will be save on FSU's W drive until it is deidentified. Deidentified information will be stored in locked file cabinets, within a locked suite, and transferred to a password protected computer once coded.

7.0 Data and Specimen Banking*

Blood samples will be collected by a certified medial assistant 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) and HbA1c of participants. Samples will be stored temporarily in a -80 F freezer in the phlebotomy lab. HbA1C will be extracted through point-of-care and analyzed immediately. CMPs will be analyzed using a Piccolo Xpress Chemistry analyzer in the College of Human Sciences with the assistance of Dr. Bahram Arjmandi and Neda Akhavan. Samples will be transported in a medical transport cooler by trained research personnel. Once results of the CMPs are returned, these will be coded and stored with other participant data (described below). Biological samples will be disposed of after analysis as biowaste.

Data for Future Use

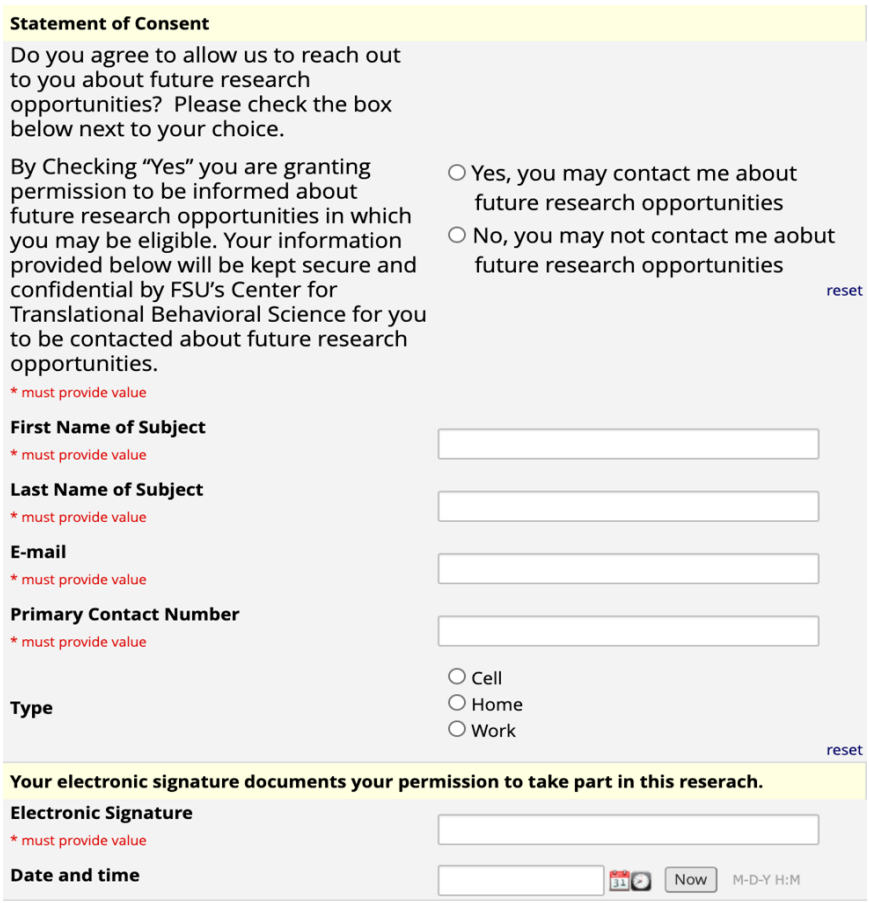
Participants consent to these procedures as part of the consent process.

Data collected during this research study may be used for future research purposes. The data stored will be de-identified. De-identified Data that cannot be linked to participants will be kept indefinitely; this data will be saved for future use and may be shared with other researchers. This data may be used for secondary data analysis to inform future publications examining late-life health and cognition, as well as preliminary data for future grant applications.

At the end of the study data collected may be made available, in accordance with the NIH Data Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing). This data will be saved for future use and may be shared with other researchers. By participating in this study, participants are agreeing to allow us to save and share their data anonymously for research purposes.

We will ask consented participants if they wish to be contacted for future research opportunities. On the Study consent form, we ask participants if they wish to be contacted about future research opportunities in which they might be eligible. For this study, information retained for individuals that give permission to keep their contact information for future research opportunities will include: Names, Email addresses and Working phone number. This information will be collected using a secure REDCap form, only accessible by the study team. Contact information will be stored and maintained in a password protected excel file, and will be kept separate from individual study related information. Access to this information will be limited to only designated study team members throughout the duration of the study.

After consenting to participate in this study, individuals interested in being contacted for future studies will be directed to a secure REDCap form to provide their permission to be contacted, contact information (email and phone) and age. The statement on the Consent form is as follows:



Statement of Consent

Do you agree to allow us to reach out to you about future research opportunities? Please check the box below next to your choice.

By Checking "Yes" you are granting permission to be informed about future research opportunities in which you may be eligible. Your information provided below will be kept secure and confidential by FSU's Center for Translational Behavioral Science for you to be contacted about future research opportunities.

* must provide value

○ Yes, you may contact me about future research opportunities
○ No, you may not contact me aobut future research opportunities

reset

First Name of Subject
* must provide value

Last Name of Subject
* must provide value

E-mail
* must provide value

Primary Contact Number
* must provide value

Type

○ Cell
○ Home
○ Work

reset

Your electronic signature documents your permission to take part in this reserach.

Electronic Signature
* must provide value

Date and time

Now M-D-Y H:M

All screened individuals will be asked if they are interested in being contacted about future research studies. Only by answering "Yes" to interested in future research studies, they will be asked by the study team member conducting the screener to provide their contact information (email and phone) and age. The statement on the Study Screener form is as follows: "Would you like to be contacted for future studies?"

The study team will carefully review and document which participants granted permission for the study team to retain their information. Participants who say "yes" will have their information stored in a password-protected file, separate from the study data, and accessible to only trained members of the study team. Participants may request to be removed from the mailing list at any time, in which case a note will be made for data cleaning to remove that individual when data is cleaned.

*Sharing of Results with Subjects**

Participants will not receive diagnostic feedback about their performance on the phone cognitive assessments or results of any biological or emotional testing. Participants may of course request to view their own medical records through the FSU SeniorHealth Clinic as part of their usual care; however, the study team will not release individual results of testing to participants through the study.

8.0 Study Timelines*

See table below.

Timeline for proposed research activities

Year 1	1	2	3	4	5	6	7	8	9	10	11	12
Submit IRB application	X											
Refining implementation with key stakeholders	X	X	X									
Cleaning and standardizing the EHR		X	X									
Training workshop for clinic staff			X									
Standardize clinic procedures for screening	X	X	X	X	X	X						
Initial screening and recruitment (build waitlist)						X	X	X	X	X	X	X
Resubmit K23 application											X	X
Recruitment calls												X
Year 2	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Pre-intervention EHR data extraction (groups 1&2; T0)	X											
Baseline phone assessments: groups 1&2 (T1)	X	X										
Intervention period			X	X								
Post-intervention phone assessments (T2)				X								
Post-intervention EHR data extraction (T3)					X	X	X					
Pre-intervention EHR data extraction (groups 3&4; T0)					X							
Baseline phone assessments: groups					X	X						
Intervention period							X	X				
Post-intervention phone assessments (T2)									X			
Post-intervention EHR data extraction (T3)									X	X	X	
Data cleaning and Manuscript development				X	X	X	X	X	X	X	X	
Develop and submit new NIA application							X	X	X	X	X	X

9.0 Inclusion and Exclusion Criteria*

Study Population

Older adults, between the ages of 60-85, and with possible or pre-mild cognitive impairment (MCI) were chosen in order to specifically assess the effect of the intervention on individuals at higher risk for converting to AD. These individuals may observe the greatest cognitive benefits from the intervention, while not requiring a caregiver or significant other to provide assistance or consent. The ages 60-85 were chosen, as this age range is often where early signs of dementia begin to emerge on neuropsychological testing.

Inclusion Criteria

To meet eligibility for inclusion in the intervention, participants must be 60-85, meet criteria for possible mild cognitive impairment, have a Telephone MoCA score >12, be English speaking, and have internet access with video conferencing, and report interest in participating in a nutrition intervention. In addition to the criteria above, a subsample of 20 participants will be selected based on self-reported pain on the Rolland-Morris pain scale (A1) of 3 or greater during the past week.

Exclusion Criteria

Participants will be excluded if they report any exclusionary health or major psychiatric conditions as determined by their physician at the FSU SeniorHealth clinic (e.g., Type 1 diabetes, schizophrenia etc.), are under-weight based on BMI, have a diagnosable major neurocognitive disorder, or if they report use of prescriptions that may interact with their ability to adhere to the diet (e.g., insulin, MAOIs, immunosuppressant etc.). Those deemed unable to provide informed consent based on the telephone cognitive screener (MoCA<12) will be excluded.

10.0 Vulnerable Populations*

Participants, age 60-85, years may enroll in the proposed study. We will not include any participants who are unable to provide consent. Of note, a mild neurocognitive disorder (MNCD) also known as MCI 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 licensed clinical psychologist with a specialty in geropsychology and will rule out individuals who do not have capacity to consent via a telephone cognitive screener.

Potential harms from participating in this study are not greater than those encountered in everyday life, standard medical care, or during the performance of routine physical or psychological evaluations. Participants will be assured that their information will be kept confidential to the best of the study team's ability, and the responses they provide will have no impact on their relationship with any academic or health institution. The study team will screen potential participants for possible dementia in order to ensure participants have the cognitive capacity to provide consent to participate.

11.0 Local Number of Subjects

We are seeking to enroll a maximum of 60 participants and a minimum of 40 participants.

12.0 Recruitment Methods

Recruitment methods will be employed to engage up to 60 participants (aged 60–85), to participate in this study. Recruitment materials include a study informational flyer (see attached), which will be posted throughout the community at locations that provide permission to post the flyer. The flyer may also be handed out directly to interested individuals. The flyer will contain information about the nutrition program, research, and study team contact information. The research team is available to answer questions about the study including participant responsibilities, benefits, risks, and alternatives.

We will work with our stakeholders/partners at FSU SeniorHealth™ clinic to increase awareness regarding the study. They will receive a study packet, including study summary, a participant study information sheet, and study team contact information. We will ask them to refer the participants to the study and to distribute study information to interested participants. Interested participants will receive a study information sheet and study team contact information which will include a website link to the primary study screener for eligibility determination and subsequent enrollment. They will also be asked to share a link on their website regarding our study.

Additionally, the PI and trained study team members on the project may hand out flyers and collect contact information from interested individuals during community events and community talks. With participants' permission, any contact information collected will be added to a protected online document for participants interested in being contacted about potential research participation and physical copies will be destroyed.

Preliminary screen. After confirming interest in being contacted about the study, participants will be contacted by a member of the research team and screened for eligibility. This screening will include a telephone MoCA, sections 1 and 4 from the Functional Status Questionnaire, a brief memory complaint scale, self-rated pain during the past week (0-10), and self-reported height, weight, and age. Participants will also be asked to report any restrictive dietary or medical conditions that may make them unable to change their nutrition. Participants will be compensated with a $5 e-gift card for completing the screening and will be asked to provide their full name and email address to receive the gift card. This contact information will not be retained for future research purposes. All screened participants will be provided with a handout on healthy living designed in collaboration with the SeniorHealth physicians. If participants are eligible, then they will be sent an online consent form, which they will read and review using HIPPA-compliant Zoom with a member of the research team before signing. For participants who are patients at FSU SeniorHealth, the study team will then complete a final eligibility check of the patient's EHR and review with the physician to confirm eligibility and ensure participant safety. For participants who are not patients at FSU SeniorHealth, we will request patients provide a copy of their most recent medical records, including health conditions, medications, and recent lab work – this step will be optional. The study team will determine final eligibility of these patients based on self-reported health conditions or review of the records they provide. Participants who are eligible and consent to participate will have screening data linked with other study data, in order to reduce redundancy in assessment measures. Patients and participants who have previously provided consent to be contacted for research may be called or emailed to assess interest in the study if they are not screened during their normal clinic visits. From this sample, we will recruit up to 60 patients who meet criteria for possible MCI (e.g., MoCA score of 18-25 and some self- or other-reported changes in daily living due to cognition). 20 participants will be selected based on self-reported pain of moderate intensity or greater in addition to the other inclusion criteria. There will be two intervention conditions: 30 patients will be randomly assigned to the 6-week KNA group program and 30 to the KN-only condition. All patients will be given the option of signing up for one of three start dates for the programs, with 10 patients maximum in each group. These conditions are designed to determine whether MI- CBT strategies improve adherence to KN, thereby enhancing the benefits compared to providing KN information alone. Key stakeholders in the clinic will be engaged early in the project to increase buy-in to the intervention and to introduce staff to the project.

Recruitment call. The group leaders and study coordinators will call potential participants to provide more information about the respective programs and to determine the patients' interest and availability to participate. A log will be maintained that will track the calls made by the group leaders to provide information regarding the study to prospective participants. The log will include the number of times they were contacted, date they were contacted on, name of the person contacted or spoken to and their initial and final response. Individuals who indicate that they would like to join the study will be provided with detailed study information; additionally, SeniorHealth patients will be asked to provide verbal and electronic written

consent and signed HIPAA authorization. After a final eligibility review of the EHR (for SeniorHealth patients) and self-reported health conditions, participants will then be randomly assigned to a condition.

13.0 Withdrawal of Subjects*

A participant meets the criteria for "premature discontinuation" if they withdraw from the study before completion. Premature discontinuation would include participants who decide to voluntarily end their participation early for any reason, as well as participants who may be withdrawn from the study based on an adverse response to the intervention and consultation with the MD, Dr. Paul Katz. Participants may choose not to attend some sessions or complete all assessments, but they will not be compensated for assessments they do not complete. Participants will not be involuntarily removed from the study for missing sessions or assessments if they indicate that they would like to remain in the study. If a participant fails to attend 2 consecutive appointments and assessments without notifying the study team, we will reach out to them up to 3 times via phone and/or email to assess their interest in continuing in the study. No response from the participant will be considered a premature discontinuation, and they will be withdrawn from the study. Completion represents completing the assessments in addition to the intervention. There are no alternative treatments or procedures for participants that choose to withdraw from the study, other than care as usual. Participants will be reminded that their participation is voluntary and they may choose to end participation in the study at any time.

14.0 Risks to Subjects*

We are only recruiting individuals without unstable chronic medical conditions for this nutrition intervention (e.g., significant gallbladder problems, cancer, Type 1 diabetes). Further, participants who are underweight based on BMI will be excluded (BMI<19). Individuals with these conditions will be screened out in the initial call prior to completing the consent process.

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 the study team 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, Dr. Paul Katz, for a clinical decision.

Participants will be asked to provide two fasting blood samples for assessment of metabolic panels and HbA1c. There may be slight discomfort when inserting the needle. Even with precautions, minor bruising and swelling around the puncture site can occur. Because every person's veins are different, and veins move frequently, bruising can occur even with the most experienced phlebotomists. Participants will be required to fast for 8-12 hours prior to the blood draw. The primary risks associated with fasting may include lightheadedness. Thus, we will provide snacks for participants after the blood draw is complete.

Other risks include mental fatigue from completing some potentially challenging cognitive tasks.

Protection against Risk

Participants will be given the option to end participation at any time with no penalty for doing so. Participants may take breaks from testing as requested or choose not to answer sensitive questions.

For the intervention portion, participants will be closely monitored by the group leaders 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 and nurse practitioner on the team for a clinical decision.

Physical copies of all tests and measures will be stored in locked cabinets in a secured suite in Research Building B at Innovation Park or maintained in the SeniorHealth clinic (for SeniorHealth patients only). 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.

Prior to the blood draw CMAs will wash and sanitize hands then don gloves. Gloves will stay on for the duration of the blood draw. Once the blood draw is complete the needed will be capped and disposed on in the appropriate sharps container. CMAs will keep gloves on until the draw area is sanitized and disinfected. After the area has been cleaned appropriately, CMAs will doff gloves, dispose of them in a biohazard bag and wash hands. Biological samples will be stored in a -80 F freezer in a locked phlebotomy lab at the Center for Translational Behavioral Sciences. Only the study PI and CMAs on the team will have access to this laboratory. Samples will be disposed of as biowaste after analysis.

Participants are permitted to participate in in-person study activities if they have completed a full COVID-19 vaccination series. At screening, participants may share information with the research team regarding their COVID-19 vaccination status; however, based on IRB guidance this is their decision and is not a requirement. If participants choose to disclose their COVID-19 vaccination information the study team will make note of it in the study records. If participants indicate that they are not vaccinated or will not be vaccinated by the start of the study and fall within a "high-risk" category, they will be deemed ineligible to participate in the in-person portions of the study. To maximize participant safety to protect against COVID-19 or Coronavirus, COVID-19 precautions will still be implemented for fully vaccinated participants. These precautions include, wearing a mask at all times, maintaining social distancing when possible, having hand washing and sanitizing stations readily available, and cleaning and disinfecting frequently touched surfaces and objects. Participants and members of the research team will be told to stay home if they are feeling sick. Participants and study team members will wear masks (over nose and mouth) for the duration of all in-person contact, and extra masks will be made available to participants if needed. All frequently touched surfaces (doorknobs, tables, handles, light switches etc.) will be cleaned and disinfected before and after participant contact. Gloves will be worn while surfaces are being disinfected and hand will be washed for at least 20 seconds when cleaning is finished and gloves have been removed. All research personnel with participant contact will have completed a full COVID-19 vaccination series.

15.0 Potential Benefits to Subjects*

A goal of the current study is to assess whether ketogenic nutrition may be beneficial for memory and pain severity in older adults and whether the use of an MI-CBT group approach may improve adherence to this type of nutrition. Previous research has demonstrated that a low-carbohydrate diet has multiple benefits on cognitive functioning, pain, and other health factors in older individuals. Thus, participants will be provided with a supportive environment for making this diet change as well as empirically validated cognitive behavioral skills for behavior change in general.

During the proof-of-concept preliminary trial, participants reported improvements in energy stability, alertness, blood glucose levels, and mood. Participants may experience improvements in their cognitive status and will be closely monitored by health professionals.

16.0 Data Management* and Confidentiality

Data acquired from this study will consist of qualitative and quantitative data gathered from the 3 assessments and EHR stored on Athena only, as well as data collected from clinic staff about their experience being involved with the intervention from a clinical standpoint. *Data will only include the minimum PHI necessary to complete the proposed study. Data from the EHR will include the following information only from appointments pertinent to the study: patients' problem/diagnostic list, medication list, patient vitals, metabolic panels, HbA1C, CRP, potassium levels, scores on recent cognitive and psychological assessments (i.e., MoCA, depression inventories), and relevant provider notes about a patient's cognitive functioning.*

All reports, and other study related material will be identified by a coded number only, to maintain participant confidentiality. All records with personally-identifying information will be kept on FSU's W Drive and once it has been deidentified, it will be transferred in a locked, limited access area (such as a locked file cabinet). Forms containing data/information, will be coded by a unique number and stored on a password protected computer and College of Medicine server. The encrypted REDCap database used to collect data will be collected and stored digitally on a password protected computer and College of Medicine server. Participant identity will be kept confidential in presentations or publications of the results of this study.

Data will be collected using FSU REDCap platform or via telephone and will be stored using unique ID numbers which will be kept separate from contact information and other study data. They will be saved in separate locked or password protected files. Data will undergo initial coding to understand reoccurring themes and ideas by exploring word frequencies and definition of concepts. This data will be exported into SPSS for quantitative data analysis. Results from the quantitative data analysis will be integrated with that of the qualitative data analysis to generate the final product. Data from completed study assessments will be linked using a coded participant number. Data collected from patient EHR or provided health records will be stored on a separate HIPAA Compliant server (W Drive) at the FSU College of Medicine. Data will only be moved from this server if all personal identifying information has been removed and coded. Once PHI has been removed and data is coded, it may be stored with other coded data on a separate, secure College of Medicine server. Only study team key personnel will have access to the data.

All computer entry and networking programs will be done with coded numbers only. Data collected for this study is coded and confidential where only the study team will be able to link the participant data to identifying information. However, research information that identifies the participant may be shared with the FSU Institutional Review Board (IRB) and

others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of the National Institutes of Health (NIH) and the Office for Human Research Protections (OHRP).

Information will be kept confidential – we will only use this information to contact participant for the purposes of this study. After the conclusion of the study and related data analysis, data will be de-identified. Data that cannot be linked to an individual (i.e., de-identified data) will be kept indefinitely; this data will be saved for future use and may be shared with other researchers.

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

The data and safety monitoring plan will involve routine (i.e., quarterly) monitoring by the research team of:

- Removal of direct identifiers from information gathered;
- Documentation of access to data;
- Security of the database with participant identifiers and the documentation of investigator access to this database;
- Any conditions that may negatively impact the confidentiality of information.

Data collected from the EHR will only include the minimum PHI necessary to complete the proposed study.

18.0 Provisions to Protect the Privacy Interests of Subjects

Given the nature of the intervention as a group intervention run through the participants' health clinic, complete privacy cannot be guaranteed, as both providers and other intervention participants will interact with the participants. Participants will be made aware of these limitations to privacy during the initial consent process. Outside of the participants clinical provider and intervention group, only individuals on the study team will have access to identifiable information.

Data collected from the EHR will only include the minimum PHI necessary to complete the proposed study.

During phone assessments, every effort will be made to ensure that the participant is in a quiet room, free of distraction or individuals not involved in the study. Participants may be contacted via phone or email during their engagement in the study, and they will be made aware of the limitations to privacy and confidentiality posed by these forms of communication during the consent process.

Participants will be identified by a unique study ID. All study information will be kept confidential and only accessible by the study team. All electronic documents will be password protected and maintained by key study personnel. The file linking the participant ID with identifiable information will be kept until that participant has completed data collection and then deleted. The full dataset, without identifying information, will be kept for 10 years on a password-protected computer.

The Zoom group sessions recordings will not be used for research purposes. These will only be stored for the duration of the project and then deleted. These will only be used for PI training in Motivational interviewing skills in supervision with Dr. Sylvie Naar, a co-investigator and mentor on the training grant that funds this project. Zoom sessions will be recorded using FSU HIPAA compliant zoom and the recordings will be automatically stored locally on the PI's college of medicine laptop and then moved to the secure FSU W drive. The recordings of the Zoom group sessions will be deleted after each supervision session is complete.

19.0 Compensation for Research-Related Injury

Participants will not be compensated for research-related injury, and this will be clearly indicated on the consent form.

Data collected from the EHR will only include the minimum PHI necessary to complete the proposed study.

20.0 Economic Burden to Subjects

N/A

21.0 Consent Process

Consent will be obtained following *the* "SOP: Informed Consent Process for Research (HRP-090)." Given that the study is a telehealth intervention, consent will be obtained in two ways. First, participants will be sent a link to an FSU REDCap form that will include the complete consent document and a text box for an electronic signature. Additionally, participants will be mailed or emailed a copy of the consent form for their records. Participants will review this consent document on the phone or via video call through HIPAA Compliant Zoom with a research team member prior to providing an electronic signature. The research team member will ask basic questions about the study to ensure that the participant understands their role and the extent of the study before providing consent. Please see attached consent document for more details.

22.0 Process to Document Consent in Writing

Our consent process will follow the "SOP: Written Documentation of Consent (HRP-091)." However, all consent processes will be documented electronically, rather than using a physical copy. The full consent form (see attached) will be reviewed with the participant telephonically or via HIPAA Compliant Zoom by a trained research team member. Participants will be asked to electronically sign and date the consent form only after they have reviewed the form with the researcher, have demonstrated their understanding of the research procedures, and have had an opportunity to ask questions about the study. Documentation of consent will be stored electronically using the FSU REDCap platform. During the consent process, participants will be asked if they are interested in being contacted for future studies, and their contact information will be stored in a password protected file.

23.0 Setting

All intervention and assessments will be completed either telephonically or virtually using HIPAA Compliant Zoom.

All data will be gathered and analyzed by faculty and staff at Florida State University's Center for Translational Behavioral Science at 2010 Levy Ave Building B, Suite B0266, Tallahassee, FL 32310 and FSU SeniorHealth™ clinic at 4449 Meandering Way, Tallahassee, FL 32308.

24.0 Resources Available

Center for Translational Behavioral Science (CTBScience) is a university center, affiliated with the FSU College of Medicine. This facility provides 6 faculty offices, 4 research core offices, a program manager office, two shared postdoc offices, offices for a research coordinator and research assistants, and a shared space for students and staff working with faculty. The center also houses 4 multifunctional participant spaces, 2 of which can function as working sleep laboratories equipped with state-of-the-art sleep diagnostic equipment, video monitoring / recording capability and 2 of which have the ability to be used as both assessment rooms and therapy rooms. Further, the center houses a conference room with video conferencing capabilities and a community space that functions as a group meeting room and/or classroom.

Within its three cores (Management Core, Methods Core, and Tech Core), the Center has a dedicated clinical trials coordinator, administrative coordinator, grants contracts administrator, data manager, biostatisticians, and a communications expert as well as access to FSU's IT, library, and other administrative resources. CTBScience also hosts the Adolescent Trials Network (ATN) Scale It Up Center's Analytic Core, Implementation Science Core, and Management Core, with dedicated faculty members assisting with protocol development, recruitment and retention, sustainment, study management, data management and analysis, and dissemination. There is a Youth Community Advisory Board (YCAB) nation-wide for the ATN, and an ATN Bioethics Working Group, which is made up of a team of national ethics experts.

The Management core, along with the study team will maintain responsibility for the overall conduct and implementation of the study. The study team is responsible for data management, analysis and reporting. The Protocol Leads are responsible for scientific leadership and dissemination. Moreover, Dropbox is utilized to facilitate the storage and sharing of study-related documents, which further informs protocol personnel about any updates to research procedures.

The **SeniorHealth clinic** will not provide physical resources, other than provider participation in giving patients study handouts to assess interest. The FSU SeniorHealth clinic is partially virtually and partially in-person, which partners with patients' primary care physician to optimize the patient's health and wellness. These geriatric physicians

provide health assessment and management for older adult patients. All study sessions, and assessments will be completed virtually, and all records will be accessed through a secure portal.

25.0 Multi-Site Research*

N/A