Internet-based Conversational Engagement Clinical Trial
NCT0287192
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OREGON HEALTH & SCIENCE UNIVERSITY

Minimal Risk Research Protocol

I. Protocol Title: Internet-based conversational engagement clinical trial (I-CONECT) in socially isolated adults 75+ years old: A multi-center, assessor-blinded, randomized, 12-month, parallel group, efficacy study

Remote Protocol for subjects enrolled after March 2020, or whose study participation timeline was significantly impacted by COVID-19.

Aims for additional analyses proposed in the NIA-funded secondary data analysis (RF1AG072449; Funding period: 04/15/21-03/31/24. Title: Identification of Mild Cognitive Impairment using Machine Learning from Language and Behavior Markers).

Short Title: I-CONECT

II. Objectives

We hypothesize that increasing social interaction in older adults with normal cognition or mild cognitive impairment (MCI) could improve or sustain cognitive function. Increasing daily social contact through communication technologies could offer a cost-effective home-based prevention program that could slow cognitive decline and delay the onset of dementia.

Aim 1: To examine the efficacy of our intervention using cognitive test scores.

We will examine changes in subject performance from baseline to six months to test the efficacy of a high engagement dose of the intervention on the following primary and secondary outcome measures.

Primary outcome measure from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) Version 3 In-Person and Telephone Administered Cognitive Battery:

1. In-person Montreal Cognitive Assessment (MoCA) score using only pre-pandemic cohort, with a sensitivity analysis using all the randomized subjects by imputing missed items in Telephone administered MoCA (pre and post-pandemic cohorts combined).

Secondary outcome measures:

1. Language-based executive function score: Category Fluency Animals from the UDS V3
2. Learning and episodic memory: Craft Story Immediate and Delayed Recall (verbal episodic learning and memory) from the UDS V3

For the above secondary outcomes, test scores based on in-person and telephone versions are combined (pre and post-pandemic cohorts are combined) due to the proximity of assessment protocol via two modalities.

We hypothesize the intervention group will show **either** improvement **or less decline** in these global and domain-specific cognitive functions compared to the control group.

Aim 2: Exploratory analysis: To examine the efficacy of our intervention on emotional well-being, resting-state fMRI (5 large networks), and functional measures.

Changes from baseline to Month 6 in the psychological well-being assessed by the NIH Toolbox Emotion Battery (emotion items total score), resting-state functional MRI (5 large networks) and IADL using OTDL-R (the Revised Observed Tasks of Daily Living) will be examined.

Aim 3: Exploratory analysis: To examine whether the intervention could lead to changes in speech and language characteristics over time.

There is a need to develop ecologically valid outcome measures sensitive to trial effects. Previous studies from our group showed that speech and language characteristics (e.g., word counts, sentence complexity) differentiated participants with MCI from those with intact cognition cross-sectionally.

We will record and analyze subjects' conversational sessions during the trial to examine whether algorithms used for the cross-sectional analyses can detect changes in speech and language characteristics induced by the intervention over time. We hypothesize that speech and language characteristics among participants with MCI will increasingly resemble those observed among the subjects with intact cognition over time.

Aim 4: Exploratory Analysis: Early identification of MCI using I-CONECT and CART data (IRB# 17123) (secondary data analyses).

We hypothesize that the integration of language markers from all available video chat audio recordings can improve MCI screening accuracy. Specifically, we will:

1. Identify MCI by applying machine learning methods to I-CONECT language markers. We will develop predictive models characterizing MCI using natural language processing (NLP) and machine learning (ML) algorithms to extract linguistic variables from the transcribed dialogues and acoustic variables. We will then link the variables with the cognitive status (MCI/normal cognition) and use the language markers to develop ML algorithms that fuse the information from the two modalities (linguistic and audio) to carry out early identification of MCI.
2. **Identify MCI by using the behavioral markers collected in the CART (IRB 17123). The similar machine learning methods will be applied to this data set which includes highly frequently in-home monitored data such as computer usage, walking speed and variability, time out of the house. .**
3. Fuse CART digital biomarker data and I-CONECT language markers to further boost the model screening performance.

III. Background

In recognition of the COVID-19 public health threat, Oregon Health & Science University suspended all in-person, n*onessential research on human subjects* on March 15th, 2020. The governor of Oregon went on to issue a stay-at-home order shortly thereafter. These restrictions lifted enough to permit remote trial

conduct and contactless materials delivery to subjects by June 8th. However, given the ongoing pandemic and uncertainty around possibly future COVID-19 restrictions, as well as the high-risk nature of our subject population (adults age 75 and older), it became necessary to adapt the protocol for remote conduct.

IV. Study Design

This study is a two-arm randomized controlled trial.

Participants will be randomized in a 1:1 ratio to the experimental or control conditions balancing the following factors:

- Cognitive status (healthy normal vs. MCI)
- Age (age 75-79 vs. age 80-84 vs. over 85+)
- Education (high school completion vs. below high school education)
- Sex (male vs. female)
- Mean Montreal Cognitive Assessment (MoCA)

Subjects will complete in-home assessments at the 6-month time point. All subjects will receive a follow-up telephone call approximately one month after the intervention period concludes. Subject participation in the study will last approximately seven months including the screening and follow-up period. In total, there are approximately four scheduled assessment calls (if assessment time points are split into multiple calls), plus additional technology troubleshooting calls, depending on group allocation.

A. Intervention Group

Half of participants will be randomized to the experimental group, the study intervention group. These subjects will engage in video chat conversations with study staff using an online video communication platform. Each video chat session will be 30 minutes long. Subjects will also receive a weekly telephone call, lasting approximately 10-15 minutes, to assess health and social activities.

The intervention period will last 24 weeks. Subjects in the intervention group will receive four chats per week (a high dose of the video chat intervention) for 24 weeks. The video chat frequency will then taper to a decreased dose of two chats per week during weeks 25 and 26 of the follow-up period.

B. Control Group

Half of participants will be randomized to the control group. For the length of the intervention period and for two weeks of follow-up, subjects will receive a weekly telephone call, lasting approximately 10-15 minutes, to assess health and social activities.

C. Blinding

1. Assessor Blinding

Staff conducting cognitive assessments will be blinded to subject group assignment. Subjects will be instructed and reminded to maintain blinding throughout the study.

The Social Isolation Assessment requires asking about conversation frequency. To preserve blinding to subject group assignment, conversation frequency should **not** be assessed at the Month 6 time

point by the blinded assessor. The conversation frequency portion of the assessment should be done by study staff who are not blinded to subject group assignment.

2. Intervention Staff Blinding

Staff administering the video chat intervention will be blinded to subject cognitive status (normal vs. MCI).

3. Investigator Blinding

Investigators will not be blinded to subject allocation, however when making ongoing eligibility or subject termination decisions, investigators should attempt to discuss the situation and make ongoing participation determinations without awareness of subject group assignment to the degree possible (i.e. by not referencing the subject's ID number or identity while assessing the situation with staff).

V. Study Population

A. Number of Subjects

The targeted study population remains as described in the main I-CONECT study protocol. We anticipate enrolling approximately 40 subjects across study sites under this Remote Protocol.

B. Inclusion and Exclusion Criteria

Inclusion Criteria:

1) Age 75 or older
2) Consent to participate in the study
3) Socially isolated, defined by **at least one** of the following:
    i. Score ≤12 on the 6-item Lubben Social Network Scale (LSNS-6)
    ii. Engages in conversations lasting 30 minutes or longer no more than twice per week, per subject self-report
    iii. Answers "Often" to at least one question on the Hughes et al. Three-Item Loneliness Scale
4) Adequate vision to use study technology and complete all neuropsychological tests throughout the study, defined by the following:
    i. Able to see well enough to read a newspaper, wearing glasses if needed but not using a magnifying glass
5) Adequate hearing to use study technology and complete all neuropsychological tests throughout the study, defined as:
    i. Able to hear well enough to complete the telephone screening
6) Sufficient ability to understand English in order to complete protocol-required testing
7) Normal cognition or mild cognitive impairment (MCI), as assessed by the trial neuropsychologist
8) Sufficiently able to comply with protocol assessments and procedures, in the opinion of the investigator

Exclusion Criteria:

1) Identified as having dementia based on either of the following criteria:
    i. Self-reported diseases associated with dementia, such as Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, normal pressure hydrocephalus, or Parkinson's disease
    ii. Diagnosis of dementia by trial neuropsychologist
2) Anticipating major change in living arrangement within the upcoming year
3) Severely depressed, operationally defined as a 15-item GDS score > 7
4) Significant disease of the central nervous system, such as brain tumor, seizure disorder, subdural hematoma, or significant stroke, per subject report
5) Current (within 2 years of screening) alcohol or substance abuse
6) Unstable or significantly symptomatic psychiatric disorder, such as major depression, schizophrenia, posttraumatic stress disorder, or bipolar disorder
7) Unstable or significantly symptomatic cardiovascular disease, such as coronary artery disease with frequent angina, or congestive heart failure with shortness of breath at rest
8) Unstable insulin-dependent diabetes mellitus, defined as meeting any of the following criteria:
    i. Received a diagnosis of Type 1 Diabetes
    ii. Started taking insulin within 3 months of the screening visit
    iii. Been hospitalized for hypoglycemia within one year of screening
9) Active systemic cancer within 5 years of the screening visit (Gleason Grade < 3 prostate cancer and non-metastatic skin cancers are acceptable)
10) Surgery that required full sedation with intubation within 6 months of screening (sedation for minor procedures is acceptable)
11) More than one overnight hospital stay within 3 months of the screening visit
12) Any other condition that, in the opinion of the investigator, is severe enough to cause study participation to have a negative impact on participant or study team rights or wellbeing.

Due to COIVD-19 risk, research personnel (including internet vendors) may be prohibited from entering the home to install new internet connections. In addition to the above criteria, subjects may be required to have a pre-existing internet connection and be willing to allow the use of this connection for study purposes (e.g. video chat).

C. Vulnerable Populations

Decisionally impaired adults will not be included in this study. Eligibility criteria require that participants have normal cognition or MCI, based on neuropsychologist diagnosis. Subjects with MCI have no more than minimal cognitive impairment and are still able to provide informed consent.

Study staff conducting the informed consent process will thoroughly review the consent form at screening and will assess comprehension in the following areas:

- The nature of the research
- Consequences of participation for the subject's own situation and health condition
- The difference between research and clinical care
- Alternatives to participation
- Potential risks involved in the study

- Procedures to follow if the subject experiences discomfort or wishes to withdraw
- The voluntary nature of participation

If potential participants cannot sufficiently answer related questions (indicating risk of decisional impairment), they will not be consented or enrolled into the trial.

Cognitive status will be reassessed by the trial neuropsychologist at the 6-month time point. If it is determined that the participant has developed dementia, study activities and assessments will cease and study equipment will be returned.

Other vulnerable populations, such as prisoners, will not be included in this trial.

D. Setting

This is a multi-center trial involving Oregon Health & Science University (OHSU), University of Michigan (UM), and Emory University. OHSU will function as both a research site and the coordinating center for the trial; sites may conduct the study under OHSU Institutional Review Board (IRB) oversight or local IRB oversight. Massachusetts General Hospital will function as the statistical analysis and data management center.

Subject recruitment will occur for the Oregon site primarily in the Portland area and nearby counties, for the Michigan site primarily in Detroit and nearby counties, and for the Georgia site in the Atlanta metro area and nearby counties. Study staff will conduct research activities (i.e. telephone pre-screenings, data management, data analysis) at the OHSU Layton Aging & Alzheimer's Disease Center, the UM Michigan Alzheimer's Disease Center and School of Nursing, and Emory's Goizueta Alzheimer's Disease Research Center, or working remotely in accordance with those institutions' policies. Video Chats will be conducted by study staff working remotely from their homes or offices. Screening calls, assessment calls, and technology-related calls for installation and repairs will be completed remotely via phone or video chat.

E. Recruitment Methods

Recruitment methods will remain as described in the main I-CONECT study protocol.

This study will **not** recruit in any way that requires in-person contact with potential subjects while applicable COVID-19-related physical distancing mandates remain in effect.

F. Compensation

All participants who consent to participate will receive $50 for Screening. Screen failures who have formally consented will still receive this compensation. Participants will receive $50 if they complete testing at the Month 6 time point. Payments will not be pro-rated in the event that a subject discontinues the study early for any reason.

If it is necessary for the study to use a participant's existing personal internet connection for the study video chat device, the study may reimburse the participant for the cost of their internet up to $35 per month. If a subject receives this reimbursement and completes the study, their total study compensation will be $520.

G. Consent Process

Prior to obtaining full informed consent, subjects will undergo a telephone pre-screening during which

basic eligibility will be assessed. Data may also be collected and used prior to consent as described in the Recruitment section of this protocol. Collection of protected health information (PHI) prior to consent for this study will be covered by an IRB-approved waiver as required by the reviewing IRB.

Subjects will be consented at Screening. Study staff will explain the consent process and study procedures in lay terms, and will administer a series of questions to confirm comprehension. Subjects will be given ample time to review the consent form and have any questions answered prior to providing consent. **Consent will be obtained prior to any other study procedures at Screening.**

Consent will be collected remotely over the phone due to COVID-19 safety, so subject signature to document informed consent will not be obtained. Informed consent will be documented by the study staff, who will document the conversation and sign the consent form to indicate that informed consent was obtained from the subject. A copy of the form signed by study staff will be provided to the subject.

Study staff will minimize the possibility of coercion or undue influence by informing participants during the consenting process that participation in the study is voluntary and that they may quit at any time. Compensation has been limited to reduce the possibility of inappropriate financial influence. Ongoing consent will be reflected as subjects voluntarily continue to keep study appointments. Subjects will be informed of changes to the protocol or study procedures that may impact their risks or trial participation, and will be formally re-consented as required by the IRB.

Study staff conducting the video chat interventions will be asked to provide characterizing information and complete a personality questionnaire. Staff will be provided with a Consent Information Sheet; documentation of study staff consent will not be obtained.

VI. Procedures

A. Subject Characterization

1. Demographics (NACC Form A1) *Screening*

Subject demographic information will be collected.

2. Social Isolation Assessment *Screening, Month 6, Follow-Up*

To assess level of social isolation, subjects will be asked about their conversation frequency, and the Lubben Social Network Scale (LSNS-6) and Hughes et al. Three-Item Loneliness Scale will be administered. The LSNS-6 is a 6-question assessment of social engagement and social isolation in older adults. The Three-Item Loneliness Scale[1] is a brief, three-item measure of subjective feelings of general loneliness, designed to be administered via telephone or self-administered. Together these social isolation measures will be used to determine subject eligibility at Screening.

The Social Isolation Assessment requires asking about conversation frequency. To preserve blinding to subject group assignment, conversation frequency should not be assessed at the Month 6 time point by the blinded assessor. The conversation frequency portion of the assessment should be done by study staff who are not blinded to subject group assignment.

3. The Neuroticism-Extraversion-Openness Five-Factor Inventory (NEO-FFI) *Baseline, Month 6*

[1] Hughes, M. E., Waite, L. J., Hawkley, L. C., & Cacioppo, J. T. (2004). A Short Scale for Measuring Loneliness in Large Surveys: Results From Two Population-Based Studies. *Research on aging*, *26*(6), 655–672. doi:10.1177/0164027504268574

The NEO-FFI is a self-report personality inventory. The questionnaire will be provided for subjects to complete independently at the Baseline and Month 6 time points. If the subject does not successfully complete the questionnaire on his or her own, the questionnaire will be completed with staff assistance.

4. **Genotyping** *Baseline*
   A single saliva sample will be self-collected to measure APOE4, a genetic risk factor for Alzheimer's disease. Participants will be permitted to opt out of sample collection and genetic testing. Participants will not be given the results of their genetic test. If it is not possible to obtain a saliva sample at the designated time point, collection may be re-attempted at a future time point. If a saliva sample is determined inadequate, an additional sample may be requested at a future time point.

B. Administrative Procedures

1. **Pre-Visit Stability Screening** *Screening, Month 6*
   At the beginning of every assessment call, study staff will compete the Pre-Visit Stability Screening. Subjects will be asked about their health, routines, and substance use.

   Based on the participant's responses, study staff will assess whether reasonably reliable data can be collected, and determine if the call be rescheduled and/or if data collected should be flagged during analysis for any reason. This screening facilitates consistency of testing conditions across all assessment calls.

   If time point assessments are split into multiple visits (e.g. multiple visits for screening, or multiple visits for Month 6), this screening should be administered at each visit.

2. **Subject Contacts** *Screening*
   Subjects may choose to provide contact information for a contact person the study team may call in the event the study team cannot successfully reach the participant. Subjects may choose to provide contact information for their primary care physician, if they would like their physician to be notified in the event that clinically relevant information is noted in the course of the study (e.g. the subject is assessed as developing dementia).

3. **Resource Provision** *Month 6, Failed Screening, Early Termination/Withdrawal*
   At the Month 6 time point, study staff will provide participants with post-study resources for social engagement, and will encourage participants to utilize the resources. Subjects will also receive this information if they fail screening, or if their participation is terminated early or they withdraw from the study. If participants become depressed, as evidenced by their scores on the Geriatric Depression Scale (GDS), staff will provide information about mental health resources and may refer the subject to the subject's primary care physician. Subjects should be encouraged to utilize the provided resources again at the final follow-up call.

C. Cognitive & Functional Assessments

1. **Neuropsychological Battery** *Screening, Month 6*

   Subjects will receive the Uniform Data Set (UDS) Version 3 Telephone Administered Cognitive Battery, or T-Cog, after the COVID-19 pandemic started. This battery is the telephone version of the National Alzheimer's Coordinating Center (NACC) UDS Version 3, used by the Alzheimer's Disease Centers (ADC) program of the National Institute on Aging (NIA).

The battery consists of brief measures of attention, processing speed, executive function, episodic memory, and language. Tests include: Craft Story Immediate Recall, Blind/Telephone MoCA, Number Span Forward, Number Span Backward, Category Fluency (Animals), Category Fluency (Vegetables), Oral Trail Making Test Part A, Oral Trail Making Test Part B, Craft Story Delayed Recall, Verbal Fluency (F), and Verbal Fluency (L).

Administration of the battery will be audio recorded. Due to the need to ensure appropriate delay timing for memory assessments, the neuropsychological battery assessments must be completed in the order presented above.

The battery data measured at the Screening time point will be used as the subject's baseline for data analysis.

2. **Clinical Dementia Rating (CDR) (NACC Form B4, Adapted)** *Screening, Month 6*

   The CDR assesses dementia symptoms in a variety of domains and provides an overall rating of dementia symptom severity. Due to the socially isolated nature of the population, the CDR assessment will be limited to the subject. No informant will be used. It will be used in conjunction with the neuropsychological battery to identify participants as having normal cognition, MCI, or dementia, and to determine participant eligibility.

3. **The NIH Toolbox Emotional Domain** *Baseline, Month 6*

   The NIH Toolbox is a proctored (i.e., requires active administrator participation) assessment program administered via electronic tablet. To adapt this assessment to be conducted remotely, subjects will complete only the emotional domain of the Toolbox as questionnaires.

   The toolbox measure of emotion includes four general domains: negative affect (anger, fear, and sadness), psychological well-being (positive affect, general life satisfaction, and meaning & purpose), stress & self-efficacy (perceived stress and self-efficacy), and social relationships (social support, companionship, and social distress).

D. Subject Health Assessments

1. **Subject Health History (NACC Form A5, Adapted)** *Screening*

   Subject medical history will be collected, including substance use history.

2. **Medication Assessment** *Screening, Month 6*

   A list of the subject's current medications and general information about medication habits will be collected.

3. **Geriatric Depression Scale (GDS) (NACC Form B6)** *Screening, Month 6, Follow-Up*

   The GDS is a self-report assessment of depression. If the subject scores ≥ 2 on the suicide ideation subscale of the GDS, the subject will be assessed for possible suicidal ideation using a depression safety tool, and staff will take appropriate follow-up actions per the tool's guidance.

   The GDS will be used to assess subject eligibility at screening. If subjects are excluded due to high GDS score, depression resources will be provided and the subject may be referred to their primary care provider.

4. **Family History of Dementia** *Baseline*

   Subject family history of dementia will be collected.

5. **Physical Evaluation Form (NACC Form B1)** *Baseline*

   The subject will self-report on height, weight, vision and hearing.

E. Eligibility *Following clinician diagnosis*

A telephone pre-screening will be conducted to assess preliminary subject eligibility. If successful, a full Screening visit will be conducted to further assess eligibility.

If the subject is determined to be ineligible during Screening, the visit will be ended at that point. Otherwise, final study eligibility will be determined upon clinician diagnosis of subject cognitive status following the screening assessments. If a subject is found ineligible, staff will provide the subject with a list of resources for social engagement.

Previously ineligible subjects may be rescreened for participation in the study if their eligibility status is believed to have changed. Their subject identification code will be kept the same; a new code will not be assigned. If fewer than 6 months have elapsed since the original administration of the Screening cognitive assessments, the neuropsychological battery will not be repeated due to possible learning effects. The original scores will be used. Subjects will not receive additional compensation for rescreening. Other Screening procedures will be repeated per the Schedule of Events, including collection of informed consent.

F. Clinician Diagnosis (NACC Form D1) *Within 1 week of Screening, Month 6*

Once all Screening procedures have been completed, subject CDR and neuropsychological test results should be evaluated by the study site's designated neuropsychologist within approximately one week. The clinician will complete a clinician diagnosis, which identifies participants as having normal cognition, MCI, or dementia. Subjects must have normal cognition or MCI to be eligible to participate in the study. Subject MCI will be further characterized as amnestic or non-amnestic. If the site neuropsychologist is uncertain about the diagnosis, (s)he may consult with the designated trial neuropsychologist at other study site(s). The clinician diagnosis will be reconfirmed within approximately one week after the Month 6 assessments to monitor the subject's cognitive status, as this study will not include subjects with dementia.

G. Randomization *Following eligibility determination*

Subjects with normal cognition or MCI per clinician diagnosis will be randomized to the intervention group or to the control group once the clinician diagnosis is available to confirm subject eligibility. This should be completed as soon as possible once the required eligibility confirmation is available.

Randomization to the control group or intervention group will occur prior to the Baseline visit, but subjects should not be notified of their group assignment until after the Baseline visit to help prevent the subjects from inadvertently unblinding the assessment staff.

If subjects are randomized but then withdraw and do not complete the Baseline visit, they will be removed from the randomization program to ensure study arms remain balanced. These subjects will be classified as drop-outs prior to randomization, as they are not informed of their group assignment.

If cohabitating subjects enroll in the trial, forced randomized will be used to assign the subjects to the

same study condition.

H. Intervention Period

The 24-week intervention period will begin once the Baseline procedures are complete. The intervention period will always start on a Monday.

For all subjects, Week 1 of the intervention period will start no more than two Mondays after the last Baseline-period procedure (the Baseline assessment or the technology installation, as applicable).

If a subject's Week 1 Day 1 is delayed more than 6 months from the date of their Screening visit, the subject will be rescreened. See section VI. E. Eligibility for rescreening details. Screening and Baseline data will be recollected.

1. **Video Chat Intervention** *Week 1 through Week 24*

   The study intervention consists of structured 30-minute video chats between participants and study staff. Video chats will be conducted remotely using an online audio and video communication platform and a video chat device installed in the subject's home. The video chats will be audio and video recorded.

   Novel conversation stimuli are provided for each chat, focusing on a theme with three possible topics and corresponding photos, to be visually presented to the participant during the chat via the video chat device. Stimuli include questions targeting three domains of cognition: episodic memory, semantic memory, and executive function. Stimuli will be used to initiate each chat, however subjects may direct the conversation as they find interesting or engaging. Study staff will attempt to maintain a neutral or positive chat tone.

   The full chat intervention will last for 24 weeks. Chats will occur four days per week.

   Chats will be scheduled at consistent times throughout the subject's participation in the study. Chats may be rescheduled as needed. If a given day's chat cannot be successfully rescheduled, the chat will be considered missed. Chats missed due to planned holiday office closures will not be considered protocol deviations. If a technical issue renders a video chat impossible for a given day, the chat may be conducted via telephone.

   After every chat, study staff will complete a questionnaire assessing qualitative aspects of the chat such as perceived subject engagement level. Adverse events incidentally noted during intervention delivery will be handled as described in the Data & Safety Monitoring Plan (DSMP).

2. **Positive and Negative Affect Schedule (PANAS)** *Weekly During Intervention Period & Dose Tapering*

   The PANAS is a self-report mood questionnaire which will be administered to subjects in the intervention group only. It will be administered at both the beginning and the end of the subject's first video chat session each week.

3. **I-CONECT Weekly Questionnaire** *Weekly During Intervention Period & Dose Tapering*

   Health and social activities will be monitored with a brief survey, the I-CONECT Weekly Questionnaire, administered verbally during a weekly phone call lasting approximately 10-15

minutes. Subjects in both the experimental and control groups will complete these calls. Calls will be audio recorded.

Staff will call the subject at a prescheduled time to conduct the questionnaire. If the subject does not answer, staff may reattempt contact with the subject. If the subject cannot be reached after reasonable attempts, the weekly call will be considered missed.

Adverse events will be noted in the course of conducting the weekly health questionnaire. Adverse events will be documented, assessed and reported per DSMP and OHSU IRB requirements.

4. **Medication Adherence** *Intervention Period Weeks 1-4, Follow-Up Period Weeks 25-27*

   At the OHSU study site, daily vitamin-taking adherence will be tracked as a real-world measure of cognitive function. Subjects will be provided with electronic pillboxes and low-dose (250 mg) vitamin C tablets. Please refer to the Risks and Benefits section for additional information.

   A pillbox will be provided for four weeks of data collection to begin at Week 1 Day 1, and three weeks of data collection to begin at Week 25. An adequate supply of tablets will be supplied with the pillbox.

   Subjects will be instructed to take the vitamin C tablet once per day, as close as possible to the target time of their choice. If the subject misses the target time but remembers to take the vitamin the same day, the subject should take the vitamin as soon as they remember. If the subject misses the target time and does not remember until the next day or later, the subject should skip the missed dose and leave the vitamin in the pillbox. Subjects will be instructed to refill the pillbox on a weekly basis.

   Adherence will be monitored using the electronic pillbox devices, which internally records timestamps when the compartments of the pillboxes are opened and closed. Pillboxes will be returned to the study once each data collection period has concluded.

5. **Qualitative Evaluation** *Month 6*

   This study will use a questionnaire to collect subject feedback about the intervention and study experience. The questionnaire will be administered immediately following the final video chat session of Week 24. Administration and responses will be audio and video recorded.

6. **Intervention Staff Characteristics** *Prior to Interventions*

   Intervention staff will document their age at study start, gender, and previous experience conversing with elders. They will also complete the NEO-FFI personality inventory. No personal health information will be collected from staff.

I. In-Home Technology

1. **Installation** *(~1-2 hours; variable depending on technology)*

   Following the Baseline visit, study technology will be installed for all subjects in the intervention group.

   Study equipment will be provided to subjects for self-install, guided by remote, unblinded

technical staff. Unblinded technical staff will provide device instruction, answer questions, and assist the subject in practicing with the device. Written device instructions will be provided. Staff will inform the subject of study expectations. The video chat device will be on loan for the duration of subjects' participation, and subjects will be instructed to use it for study purposes only.

2. Troubleshooting

Study technology troubleshooting will be done remotely. As-needed technology troubleshooting calls will be scheduled at the subject's convenience. Study staff may replace malfunctioning devices as needed, either by mail or by contactless delivery to the subject home.

3. Uninstallation *(~30 minutes; variable depending on technology)*

At the conclusion of the intervention period, the video chat technology (and vitamin C pillbox, if applicable) and any accompanying study equipment will be returned, either via prepaid mail or contactless pickup from the home. Subjects will self-uninstall equipment for return to the study.

J. Follow-Up

1. Dose Tapering *Weeks 25-26*

Subjects in the experimental group will receive a decreased dose of the video chat intervention in Weeks 25 and 26. They will chat twice per week. They will also continue to receive the PANAS during the first video chat session of the week.

This tapered dose is intended to reduce the risk of loneliness associated with an abrupt end to chats, and to create consistent testing conditions between this remote protocol and the main I-CONECT protocol, facilitating data analysis.

Subjects in both the control and experimental groups will continue to receive weekly health calls during Weeks 25 and 26 as well, mirroring the conditions of the main I-CONECT protocol.

2. Follow-Up Call *Week 28*

Subjects will receive a follow-up call approximately one month after the conclusion of the intervention period (refer to Schedule of Events). If participants become depressed, as evidenced by their scores on the Geriatric Depression Scale (GDS), staff will provide information about mental health resources and may refer the subject to the subject's primary care physician. Subjects will be encouraged to utilize the post-study social engagement resources.

K. Subject Discontinuation

1. Early Termination

If at any point during the study it is determined that the subject no longer fulfills study eligibility criteria, the investigator will assess whether the subject should be withdrawn and may choose to terminate the subject's participation. To the degree possible, the investigators should avoid referencing or considering study group assignment when assessing potential discontinuation. If a subject is terminated for any reason, study staff will arrange for the uninstallation of study equipment from the subject home, and subjects will be provided with post-study resources for

social engagement.

Subject cognitive status will be formally reassessed at 6 months. The subject will be removed from the trial if the study neuropsychologist determines that the subject has developed dementia during the course of the trial. Upon this determination, subject participation in ongoing study activities (e.g., weekly calls, pillbox usage, intervention) will be terminated immediately, and study staff will arrange for the uninstallation of study equipment from the participant home.

If participation is discontinued due to low cognitive test scores, study staff will inform subjects that their scores on memory and thinking tests indicate they should follow up with their primary care physician for further testing and evaluation.

2. Subject Withdrawal

Subjects may discontinue the study at any point in time without any penalty. The subject will be reminded that if he or she chooses not to participate at any time, the decision will not affect his or her relationship with the study staff, community recruitment partners, or study sites. Subjects who choose to discontinue during the intervention period will be asked to remain in the study to complete remaining study assessment visits, rather than withdrawing from the study entirely. Subjects will be asked to provide their reason for withdrawing from the study.

In all instances of subject withdrawal, study staff will arrange for the uninstallation of study equipment from the subject home. Subjects will be provided with post-study resources for social engagement. Subjects may be asked to complete the 1-month follow-up call.

VII. Data and Specimens

A. Handling of Data and Specimens

As this is a multisite study, data will be collected in multiple formats locally at the study sites, e.g. on paper forms or electronically within site systems such as MRI data. In all cases, data will be will be handled, stored, and transmitted in a secure manner, using strategies such as locked physical storage and secure servers, to protect the confidentiality of study data.

1. Paper

Compensation paperwork, signed consent forms, and any other paper study records will be stored in locked locations in restricted-access areas at the study sites. Paper-based data collection forms, such as the CDR worksheet, NACC neuropsychological battery, OTDL-R, and NEO-FFI, will be digitized for data verification and archiving. Once scan quality has been confirmed and documented, the hardcopy paper forms will be securely destroyed.

2. Audio Recordings

Audio data, including audio recordings of video chats, cognitive testing sessions, and weekly telephone calls, will be collected and subsequently uploaded to Box. Once upload is complete and confirmed, the files will be deleted from computer hard drives and/or recording devices used. Encrypted, password-protected computers will be used to transfer audio data from study sites. Audio files will be stored for processing on servers at OHSU's Advanced Computing Center (ACC), which is behind OHSU's main firewall. Staff will access ACC servers using a Virtual Machine.

3. Video Recordings

Video chats will be conducted using Cisco Meeting or Cisco Webex software. Sessions will be recorded on a limited-access server behind OHSU's main firewall. The server can only be accessed by approved study staff using their OHSU network IDs. Videos will be moved from the server to OHSU Box at regular intervals.

4. Electronic Data Capture

Whenever possible, data will be collected using real-time electronic data capture, and this method will be consistent across staff and study sites. This study is using OHSU REDCap for electronic data capture. Electronic data capture may include subject-completed REDCap surveys. Subject-specific survey links may be provided to individual subjects via the subject's email. Staff will use wireless hotspots and encrypted laptops to access REDCap in the field. Paper downtime forms may be used in case of technical difficulties, in which case the paper data handling process will be followed.

5. Electronic Pillbox Data

Data from the electronic vitamin C pillboxes will be transmitted via Bluetooth from the pillbox to a wireless hub in the participant's home. From there, it will be sent directly to servers stored at OHSU's ACC. If self-install is required due to COVID-19 safety, data may simply be stored locally on the pillbox for later retrieval by the study staff.

6. Screening Data

Referrals from the I-CONECT website will be gathered using REDCap public survey links. Information about potential recruits, including PHI, will be stored in REDCap and on OHSU Box. Telephone pre-screenings will be conducted using electronic data capture in a REDCap data form. Once enrolled, participants will be assigned a main trial subject ID code, and their screening data will be entered into the main REDCap study database.

7. Saliva Specimens

Study staff will ship saliva samples via U.S. mail to the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) at Indiana University, per the NCRAD Specimen Collection, Processing and Shipment Manual. Samples will be submitted with the following information: collection date, Subject ID, and the subject's sex, year of birth, ethnicity, and race. In the event that visits must be conducted remotely due to COVID-19 safety, subjects may self-collect saliva samples and mail samples directly to NCRAD, using provided kits and mailing materials.

B. Sharing of Results with Subjects

Data or results will not be shared with subjects.

C. Data and Specimen Banking

Saliva samples will be shipped to the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) at Indiana University. Samples will be submitted with the following information: collection date, Subject ID, and the subject's sex, year of birth, ethnicity, and race. NCRAD will provide the study team with APOE genetic results, and will store the saliva samples indefinitely. Upon completion of the I-CONECT study, NCRAD will make the saliva samples available for future research in accordance with NCRAD policy.

All study data from participants who sign the consent and authorization form, including APOE status and pre-screening data collected under a HIPAA Waiver of Authorization, will become part of a repository maintained under this protocol. Data about potential participants who do not consent to join the study will not be included in the repository and will be destroyed at the completion of the study, though de-identified information related to reasons for screen failures may be maintained for reporting purposes.

All electronic data, including recordings of video chats, will be stored indefinitely on secure, password-protected OHSU servers, OHSU Box, and/or OHSU REDCap. All data will be coded prior to sharing. De-identified datasets are easily exported from OHSU REDCap though the recordings contain voiceprints, images of participants, and content that may identify the participant and therefore cannot be deidentified. Paper-based data collection forms will be destroyed after they have been digitized per the paper data handling process described in this protocol. Upon study closure, sites will send the signed consent forms, compensation paperwork, and other remaining paper source documents to OHSU via a courier service with tracking number and signature required for delivery. All signed paper-based consent forms will be stored in locked locations at OHSU for at least three years after study closure.

Separate IRB approval will be required for each human subject research project using identifiable data from the repository. Investigators wishing to obtain data from the repository for research beyond the specific aims of the original study may contact the repository Guardian and Principal Investigator, Hiroko Dodge, PhD. Dr. Dodge will ensure that data are released according to OHSU policy and this protocol. A repository sharing agreement will be used each time data are released for research purposes. All signed agreements will be electronically kept on file indefinitely on a secure storage server. Dr. Dodge will ensure the security and confidentiality of data and specimens during both storage and transfer. She will maintain a secure list of participants who withdraw their consent, and she will ensure no future use or sharing of their data. Dr. Dodge will track data releases to be reported at annual IRB Continuing Review.

VIII. Data Analysis

The data analysis approach for this Remote Protocol remains as described in the main I-CONECT study protocol. Data for the subset of subjects anticipated to enroll under this protocol (N=40) will be included in analyses as appropriate; this subset of subjects will not have data required for certain planned analyses, such as MRI data, and will therefore be excluded where necessary.

Psychological well-being and person-specific levels of social interaction (i.e., changes in social engagement measured with the I-CONECT Weekly Questionnaire administered weekly via telephone) will be monitored and controlled in the analyses along with other relevant variables, including APOE 4 status.

Video chats will be recorded and analyzed to determine longitudinal changes in speech patterns.

A. Analyses for Primary Outcomes

MoCA test scores (global cognitive function) are our primary outcome.

Secondary outcomes include: neuropsychological test results in the area of language-based executive function, measured by the T-Cog category fluency test (animals), and memory domains measured by

two T-Cog episodic memory tests (Craft Story Immediate and Delayed Recall). We will allocate a type I error rate of 0.05 for our primary outcome. The results will be cross-validated with NIH Toolbox cognitive batteries as exploratory analyses for those who had NIH Toolbox cognitive assessments. Potential mediation variables include the Psychological Well-Being portion of the NIH Toolbox. If Psychological Well-Being shows significant improvement in the experimental group compared to the control group over 6 months (in univariate analysis using $p < 0.05$), the measurement(s) will be examined as potential mediation factors in statistical models as secondary analyses. The Psychological Well-Being portion of the NIH Toolbox consists of 3 measurements: Positive Affect, Life Satisfaction, and Meaning and Purpose. The questionnaire and references for these scales are detailed in: http://www.nihtoolbox.org/WhatAndWhy/Emotion/PsychologicalWell-Being/Pages/default.aspx.

B. Sample Size Estimate

Our previous pilot study (based on a six-week intervention) showed Cohen's d=0.53 when comparing pre-post changes in language-based executive functions (Clinical Dementia Rating 0 and 0.5 groups combined) in the control and experimental arms. The sample size (n=72 completers for each group) in this trial provides 80% power to detect this difference at alpha=0.025, using a two-tailed test (i.e., total type I error rate=0.025), based on simulation results using non-pooled standard deviation (SD).

Two separate hypotheses are proposed. Stage I examines the efficacy of the high dose and Stage II examines the efficacy of the maintenance dose. Participants covered under the current protocol will be included into the high dose analysis

Changes in primary and secondary outcomes between the control and experimental groups will be examined for the efficacy of high dose (month 0 – month 6, Stage I) and maintenance dose (month 6 – month 12, Stage II) using the Mixed-Effect Model Repeated Measure (MMRM) model under ITT. We will conduct per protocol analysis using those who completed at least 80% of targeted conversational sessions (experimental group) and the number of telephone check-ins (control group). The subjects recruited or in trial under the current remote trial protocol will be included where appropriate (i.e., high dose analysis).

Changes in primary and secondary outcomes between the control and experimental groups will be examined for the efficacy of high dose (month 0 – month 6, Stage I) and maintenance dose (month 6 – month 12, Stage II) using the Mixed-Effect Model Repeated Measure (MMRM) model under ITT. We will conduct per protocol analysis using those who completed at least 80% of targeted conversational sessions (experimental group) and the number of telephone check-ins (control group).
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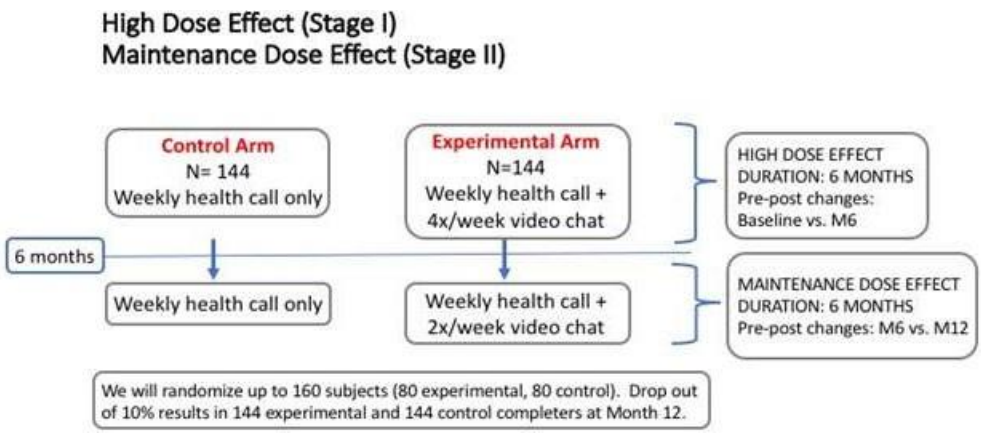

Figure 1. Trial Dose Stages: Sample size for one group (MCI or normal cognition; both groups have the same planned sample size)

Changes in primary and secondary outcomes between the control and experimental groups will be examined for the efficacy of the high dose (Baseline-Month 6, Stage I) and the maintenance dose (Month 6-Month 12, Stage II) using the Mixed-Effect Model Repeated Measure (MMRM) model under intention-to-treat (ITT). We will conduct per-protocol analysis using those who completed at least 80% of the targeted conversational sessions (experimental group) and telephone check-ins (control group).

C. Analyses proposed for the New Aim 4

The analysis of the New Aim 4 investigated the effectiveness of language markers from conversation in detecting early MCI subjects, where the key hypotheses are that 1) data-driven language and acoustic markers are predictive of early MCI subjects, 2) behavior markers from CART study are predictive of early MCI subjects, and 3) fuse both data to further improve the ability of identifying MCI

Aim 4 (1): To validate the first hypothesis of effectiveness of language and acoustic markers, we will first pre-process the data and extract acoustic markers and linguistic markers. We will apply automatic speech recognition (ASR) models to convert the collected conversations to machine-readable text in computer. We will then use OpenSMILE to extract Mel-frequency cepstral coefficients (MFCC) from the raw acoustic recordings as acoustic features in our analysis. For each recording, we will compute various types of feature representations (hand-crafted, statistical, and deep) from the MFCC features and compare them using their quality as evaluated in downstream analysis. Next, we will investigate one conventional bag-of-words feature representation using linguistic Inquiry and Word Count (LIWC) and deep-learning based embeddings.

We will first investigate the correlation of the two linguistic feature representations and their effect on classification performance on MCI detection. We will then compare the inclusion of MFCC features and investigate the effects on the classification performance. For classification models, we will use the de-identified interview data from I-CONECT to assess the performance of the multi-modal predictive models using standard performance measures such as the area under the ROC curve (AUC), sensitivity, specificity, etc. We will randomly divide the data into three sets (80% for training, 10% for validation, and 10% for test), and perform 10-fold cross-validation to minimize the variability in the training set. Stochastic gradient descent will be used for training deep learning models, and first-order gradient descent will be used for non-deep learners. To compare the performance of different algorithms, we will compute the p-value to measure the significance of improvements over the 10-fold evaluations.

Aim 4 (2): To validate the hypothesis of the effectiveness of behavior markers, we will first perform missing value evaluation to estimate the missing values in the sensor-based monitoring data CART. We will use the missing rate as a metric of the uncertainty of the estimation and take the factor into account when making predictions. For modeling with long-term sequences, we will investigate the effectiveness of various imputation strategies, including commonly used smoothing-based imputation techniques (e.g., carrying next forward, carrying last backward, multiple imputation with chained equations, etc.), as well as model-based imputation using matrix completion and deep learning-based imputation methods. After we are done with the imputation, we will then develop a two-level multi-granularity feature extraction process with fine-granularity features describing short-term behavior patterns, and coarse-granularity features describing long-term ones. We will use a denoising autoencorder (DAE) model to extract a low-dimensional latent feature vector, a recurrent neural network to learn the temporal patterns over the fine-granularity features extracted from DAEs. We will then build classification models from the multi-granularity features extracted and study its effectiveness, using the same training-testing scheme (training and testing procedures, evaluation metrics) mentioned above.

Aim 4 (3): By fusing both data using information collected in both data (NACC UDS V3), we will examine whether combining linguistic/acoustic features (coming from I-CONECT) and behavioral markers (coming from CART) can further improve the identification of MCI. We will conduct a joint analysis of language and behavior markers using a novel information fusion framework. In this analysis, we will conduct patient similarity evaluation using NACC UDS data, by using a generalized Mahalanobis distance derived from UDS data. Once the patient similarities are measured, we will use behavior feature vectors from similar patients to construct auxiliary variables. Once done, we will investigate two ways of constructing the enriched feature representations: 1) simple concatenation: the original patient vector representation and the vector representations for similar patients will be simply concatenated to form a long vector which will be feed into the MCI classifiers. 2) hierarchical concatenation: the representations of the similar patients will be aggregated first, and then the aggregated vector will be concatenated with the original patient representation vector. For the classification model, we plan to investigate both conventional models such as logistic regression and decision tree, as well as advanced models such as gradient boosted decision tree and multi-layer perceptron. We will use the same evaluation metrics as done in last hypothesis.

IX. Privacy, Confidentiality and Data Security

Privacy, confidentiality, and data security approaches for this Remote Protocol remain the same as those utilized in the main I-CONECT study protocol.

X. Risks and Benefits

A. Potential Risks to Subjects

1. Privacy

There is a risk of loss of confidentiality. All study personnel will receive training about HIPAA and the responsibilities that accompany the conduct of research. Subject confidentiality will be protected in compliance with OHSU, research site, and HIPAA guidelines.

2. Emotional Risk

Subjects receiving the intervention may feel lonely and isolated at the end of the trial when the intervention has concluded. They may form emotional attachments to the conversation staff and feel a sense of loss or sadness.

Staff conducting the intervention will begin to emotionally prepare subjects to complete the study around Week 12. Staff will remind subjects of this risk and encourage them to consider their options for social connection following the trial over the course of their remaining weeks in the study. Subjects will have a two-week tapering period as they conclude the intervention, to reduce the risk of abrupt transition off of the study.

At the Month 6 visit following the conclusion of the intervention, or if a subject withdraws or is removed from the study early, study staff will provide participants with post-study resources for social connection, and will encourage participants to utilize the resources. Subjects will also receive this information if they fail screening. If participants become depressed, as evidenced by their scores on the Geriatric Depression Scale (GDS), staff may provide information about mental health resources and may refer the subject to the subject's primary care physician.

3. Cognitive Impairment

There is a risk that subjects will develop dementia, becoming decisionally impaired during the course of the study. Should the investigators or staff become aware of a clinically relevant issue in a subject, such as the development of dementia, the investigator or qualified designee will discuss the issue with the subject and refer the subject to follow up with his or her primary care physician. Subjects who develop dementia with be withdrawn from the study.

4. Vitamin C

This study uses vitamin C (ascorbic acid) to assess medication adherence in some subjects. Though generally well tolerated, ascorbic acid may cause gastrointestinal side effects such as nausea, vomiting, heartburn, diarrhea, or abdominal cramps/pain. These effects are primarily observed at high doses. Though this study uses a dose of vitamin C below the tolerable upper intake level of 2,000 mg/day, there may be a risk of these effects, especially if subjects are taking additional vitamin C supplements. High doses of vitamin C may also worsen medical conditions such as gout, cirrhosis or kidney stones. If it is noted that a subject is using additional vitamin C supplementation and/or has a medical condition for which high-dose vitamin C may be contraindicated, the subject may be asked to forgo ingesting the vitamin C pill or may be excluded from pillbox use entirely.

B. Potential Benefits to Subjects

Participants may or may not directly benefit from participating in the study. However, their contribution to research may help further the development of user-friendly, in-home sustainable approaches to improving neurophysiological, cognitive, and emotional health into old age. Ultimately, this research may contribute to the larger goal of delaying the onset of Alzheimer's disease.

XI. Schedule of Events

A. Procedure Timing Guidelines:

- All visits from Screening through the Technology Installation should be completed

approximately **within a ten-week window**.

- **Screening Time Point:** Screening procedures should all be completed approximately **within a two-week window**. Events may be split across multiple days/visits at site discretion to accommodate practical concerns such as participant fatigue, scheduling, or distance from the study center.

- **Clinician Diagnosis: Within approximately one week** of completing final Screening procedures.

- **Baseline Visit: Within approximately one week** following the clinician diagnosis.

- **24-Week Intervention Period:** starts after the final Baseline Period visit. Week 1 of the intervention period will always begin on a Monday.

  Baseline Period visits include the Baseline assessment visit, the technology installation visit (as applicable), and the Baseline MRI (as applicable). For all subjects, **Week 1 will start no more than two Mondays after the last Baseline Period procedure.**

- **Month 6 Time Point:** Procedures should all be completed **within a two-week window**, during intervention period **weeks 25-26**. Events may be split across multiple days/home visits at site discretion.

B. Table: Schedule of Events

	Screening Period		Baseline Period		Intervention Period	Follow-Up Period			
Time Point Name	Telephone Pre-Screening	Screening	Baseline	Tech Install		Dose Tapering	Month 6	Tech Uninstall	Telephone Follow-Up
Approximate Time Required	30 min.	3 hours	30 min.	1-2 hrs.	6-54 hrs.	.5-2 hrs.	2 hrs.	30 min.	30 min.
Scheduling Timeframe		10-Week Window			Weeks 1-24	Weeks 25-26	Week 25-26	Week 27-28	Week 28
Collect Informed Consent		X							
Pre-Visit Stability Screening[r]		X	X				X		
Collect PCP/Contact Information[a]		X							
Demographics (Form A1)		X							
Social Isolation Assessment	X	X					X[t]		X
GDS (Form B6)[p]		X					X		X
T-Cog Neuropsychological Battery[q]		X					X		
CDR (Form B4)		X					X		
Subject Health History (Form A5)		X							
Medication Assessment		X					X		
Subject Compensation		X[b,s]	X				X[c]		
NEO-FFI and NIH Toolbox Emotional Domain Questionnaires[d]			X				X		
Clinician Diagnosis[o]		X					X		
Trial Eligibility Assessment[f]	X	X							
Post-Study Resources		X[e]					X		X
Randomization		X[g]							
Family History of Dementia			X						
Physical Evaluation (Form B1)			X						
Saliva Collection for APOE4			X[l]						
Vitamin C Pillbox[i]				X	X[u]		X[u]	X	
Video Chat Device[j]				X				X	
PANAS[h, j]					X	X			
Video Chat Intervention[j]					X	X			
I-CONECT Weekly Questionnaire[k]					X	X			
Vitamin C Medication Adherence[i]					X[m]	X[m]			
Qualitative Evaluation (Subject)[j]					X[n]				

a) Subjects may choose to provide emergency contact and primary care provider contact information; this is optional.
b) Compensation will be provided to all subjects who consent to participate, including screen failures.
c) Compensation to be provided once all procedures are completed.
d) Questionnaires will be provided for subjects to complete independently. If the subject does not successfully complete the questionnaires on his or her own, the questionnaires will be completed with staff assistance.
e) Resources to be provided at this time point only if subject is a screen failure.
f) Final eligibility assessment to be completed upon clinician diagnosis.
g) Randomization to intervention/control occurs once eligibility is determined, prior to the Baseline visit. Subjects should not be notified of group assignment until after Baseline to prevent them from unblinding the assessment staff.
h) The PANAS will be administered at the beginning and the end of the subject's first video chat session each week.
i) OHSU subjects only.
j) Intervention group only. Control group does not receive.
k) Administered weekly via telephone.
l) This procedure is optional for subjects. If sample cannot be obtained, collection will be re-attempted at a future time point.
m) Occurs daily in weeks 1-4 and 25-27. If the subject misses the target time but remembers the same day, the subject should take the vitamin as soon as they remember. If the subject does not remember until the next day or later, the subject should skip the missed dose and leave the vitamin in the pillbox.
n) To be completed at the conclusion of the Week 24 video chats. Administration and responses will be audio and video recorded.
o) The clinician diagnosis should be completed within 1 week once the time point assessments have been completed. Subjects who are diagnosed with dementia must be withdrawn from the trial immediately.
p) If subject scores 2 or more in response to questions 3, 7, 11, 12, or 14 (the suicide ideation subscale), the Depression Safety Assessment will be conducted.
q) Administration will be audio recorded. Battery assessments must be completed in the required order to ensure appropriate timing for memory assessments.
r) If time point assessments are split into multiple calls, this form should be administered at each assessment call.
s) Subjects will not receive additional compensation for rescreening.
t) To preserve assessor blinding, conversation frequency should be assessed at this time point by study staff who are not blinded to subject group assignment.
u) Pillbox will be installed during Baseline, used at Weeks 1-4, and returned. A pillbox will be provided again for use at Weeks 25-27, and then returned.