Musical Engagement of brain LObes in Alzheimer's Disease patients studY (MELODY)

Protocol Number: Pro00115303

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STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the protocol, applicable state, local, and federal regulatory agencies, the International Council on Harmonization Good Clinical Practice (ICH GCP), and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

The investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of the clinical trial have completed Human Subjects Protection and ICH GCP Training.

ABBREVIATIONS

AD	Alzheimer's Disease
AE	Adverse Event
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CRF	Case Report Form
DRE	Disease-Related Event
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
fMRI	Functional Magnetic Resonance Imaging
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MMSE	Mini Mental State Examination
NCT	National Clinical Trial
NIH	National Institutes of Health
NINCDS-ADRDA	The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
OHRP	Office for Human Research Protections
PI	Principal Investigator
SAE	Serious Adverse Event
SIB-8	8-item Severe Impairment Battery (SIB-8)
SOA	Schedule of Activities
SSS	Stanford Sleepiness Scale
US	United States

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Musical Engagement of brain LObes in Alzheimer's Disease patients studY (MELODY)

Study Description: This is a controlled, single-blind, cross-over study design with 10 subjects suffering from moderate to severe Alzheimer's disease (AD) without neuropsychiatric symptoms of dementia designed to evaluate global clinical impact and level of arousal (physiological state of being alert, awake, and attentive) when subjects are exposed to emotionally impactful music compared to control intervention.

Objectives:

Primary Objective:	To measure the global clinical impact of music in subjects suffering from moderate to severe AD as measured by the Clinical Global Impression of Change (CGIC).
Secondary Objective:	To measure the impact of music on the level of arousal in subjects suffering from moderate to severe AD as evaluated by the Stanford Sleepiness Scale (SSS).

Endpoints:

Primary Endpoint a:	Change in clinical outcomes as measured by the CGIC 2 hours and 10 minutes from the onset of the first exposure.
Primary Endpoint b:	To evaluate changes in the modulation of brain networks via exposure to music and their association with global clinical impact using functional magnetic resonance imaging (fMRI) in subjects suffering from moderate to severe AD.
Secondary Endpoint a:	Change in level of arousal as evaluated by the SSS 2 hours and 10 minutes from the onset of the first exposure.
Secondary Endpoint b:	To evaluate changes in the modulation of brain networks via exposure to music and their association with level of arousal using fMRI in subjects suffering from moderate to severe AD.

Study Population: 10 males or females from all ethnic backgrounds suffering from moderate to severe AD aged 55-90.

Phase: Pilot

Description of Study Intervention: This is a randomized, cross-over study to measure global and clinical impact and level of arousal in subjects suffering from moderate to severe AD when exposed to emotionally impactful music compared to control intervention. In partnership with the study partner (a person who spends 10 hours or more a week with the subject and can reliably report on the subject's condition), three tunes will be chosen for the purposes of the study. The tunes chosen will need to be related to a past meaningful, positive experience of the subject, as determined by the subject and the subject's study partner. The pieces will be restricted in duration to between 1.5 and 2 minutes each. A piece will be chosen at random and will be saved on a portable device, and subjects will be asked to listen to the melody using high quality (Bose), over-ear headphones. The total exposure time will be 10 minutes each hour over a three-hour period. The melody will be repeated as many times as

necessary to complete the 10-minute period. The control intervention will involve listening to nature sounds at the same duration and administration scheme. fMRI will be used to identify how brain networks are modulated via exposure to this music and how they associate with the clinical findings.

Study Duration: The total study duration will be approximately 6 months.

Participant Duration: The duration for each participant will be 5 visits over approximately 5 weeks, with each visit scheduled one week apart and each visit lasting approximately 4 hours.

1.2 SCHEDULE OF ACTIVITIES (SOA)

Visit:	Screening	Baseline	Visit 1	Visit 2	Visit 3
	Day 1	Day 7 +/- 3 days	Day 14 +/- 3 days	Day 21 +/- 3 days	Day 28 +/- 3 days
Activities:					
Informed Consent	X				
NINCDS-ADRDA Alzheimer's Criteria for possible and probable AD	X				
Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)	X				
Mini Mental State Examination (MMSE)	X				
Eligibility Criteria	X				
Auditory Assessment	X				
Demographics	X				
Medical History	X				
Vital Signs	X				
Timed Up and Go (TUG) Test	X				
MRI Metal Screening Questionnaire	X				
Establishment of study music interview		X			
Randomization		X			
Auditory intervention (music or nature sounds)			X	X	
Clinical Impression of Change (CGIC)		X	X	X	
Stanford Sleepiness Scale (SSS)		X	X	X	
Severe Impairment Battery, 8-item (SIB-8)		X	X	X	
Adverse Events (AEs)		X	X	X	X
Compliance Assessment			X	X	X
fMRI					X

2 INTRODUCTION

2.1 STUDY RATIONALE

Evidence suggests music is a powerful tool to stimulate brain activity[1], but quantitative efficacy research of music as an intervention, especially in the treatment of degenerative brain disorders, is mixed at best. Further, more research is needed to understand the biological mechanism by which music stimulates brain function.

This study will address both issues. First, by conducting a randomized, cross-over study to measure the global clinical impact and level of arousal in subjects suffering from moderate to severe AD when exposed to emotionally impactful music compared to control intervention. Second, by using fMRI, a brain mapping technique, to identify how brain networks are modulated via exposure to this music and how they associate with the clinical findings.

2.2 BACKGROUND

There are an estimated 6.2 million Americans aged 65 and older living with Alzheimer's dementia today[2]. Approximately one-third of these individuals fall into the moderate to severe range of the illness. Currently, physicians are unable to offer these patients any means to alleviate their symptoms other than the two classes of approved medications which provide limited symptomatic relief and a newly approved disease modifying treatment that, although approved, has yet to find its way into clinical practice. Recently, a number of reports show evidence that music may provide an effective intervention for these individuals[3]. However, most patients do not receive this treatment because there is not robust research to support music as an intervention. If music stimulation proves to be an effective biologically based intervention, we expect the scientific community and third-party payers to re-evaluate the role of music as a treatment for these patients.

A number of important factors provide the scientific basis for this proposal.

1. Several experiments using brain imaging techniques have shown that music is a strong stimulator of brain activity. The initial activation is in the areas of the brain that we know process music and sound and allow us to appropriately perceive sounds and tunes (auditory association area). Specifically, this takes place in the superior temporal gyrus of the temporal lobe. It is important to note that brain activation generated by music appears to be substantially stronger if the sounds are associated with previous emotional experiences. For example, the music that an individual heard at their wedding will generate stronger brain activity than a tune for which they have no emotional connection.

2. Brain stimulation from music can also expand to other networks of the brain through the process of entrainment. Entrainment is a principle of physics that allows for synchronization of activity of entities in close proximity. This principle has recently been shown to also apply to biological entities such as the brain. fMRI is an ideal approach to understand synchronization among functional brain networks. This approach can also be applied to studies that use continuous stimulation paradigms such as listening to musical pieces. It is important to note that if effective, this process should generate brain activation in minutes rather than days or weeks.

3. The areas of the brain that are initially activated by music do not seem to be affected by neurodegenerative disorders or are only affected in the late stages of these disorders, including AD. This

phenomenon offers a unique opportunity to use these "unaffected brain areas" as an initial point for brain activation.

4. Further supporting the concept of expansion of music activation in the brain (perhaps through the process of entrainment) are preliminary studies supporting music as a strong stimulator of brain activity in cognitively impaired subjects. A number of anecdotal reports and uncontrolled trials have provided optimism for the use of music to stimulate brain activity in patients suffering from neurodegenerative disorders[4].

Based upon both literature review and experiential interventions with music and subjects with degenerative brain illness, this research team has identified the following hypotheses:

Using a crossover design, stimulation with preferred music will lead to improvement in global clinical measures as assessed by CGIC and a higher level of arousal compared to stimulation with nature sounds in the same subjects. Stimulation with preferred music as opposed to nature sounds in the same subjects will demonstrate greater connectivity with brain networks associated with arousal as demonstrated by fMRI.

Below we summarize the scientific background in more detail.

1. Music is a strong stimulator of brain activity.

Our understanding of music as a strong stimulator of brain activity emerges with the availability of neuroimaging techniques. The primary auditory cortex (transverse temporal gyri) lies in the superior temporal gyrus of the temporal lobe and extends into the lateral sulcus and surrounding temporal cortex[5]. Therefore, we expected this to be the main area stimulated by music. Interestingly, studies have shown that other large areas of the brain are also stimulated by music. Recent findings reveal that the amygdala (the center that regulates emotions), cingulate cortex (a major hub to integrate sensations), hypothalamus (area responsible for hormonal production), hippocampus (memory), insula (responsible for the physical manifestation of emotions like shaking when we are nervous), nucleus accumbens (related to sleep), and orbitofrontal cortex (center for integration of emotion and memory) are all potentially active when music is processed[6].This activation of nonauditory areas of the brain by music has positive consequences and can explain some of the commonly observed changes in behavior and emotion that music evokes. Specifically, positron emission tomography (PET), fMRI, and studies of brain lesions have shown that these areas of the brain stimulated by music are also responsible for core emotional and cognitive responses[7,8,9]. These types of responses can trigger endocrine or hormonal changes, and the release of the associated neurochemicals can also affect emotion and cognition[10]. Therefore, we can hypothesize that music, while primarily affecting the auditory areas of the brain, has the ability to also affect other nonauditory areas, resulting in changes in emotion, cognition, and other physiological functions by same mechanism.

2. Through the process of entrainment, the areas of the brain that are stimulated by music can spread the activation to other brain networks.

Entrainment is defined by a temporal locking process in which one system's motion or signal frequency entrains (synchronizes with) the frequency of another system. This process is a universal phenomenon that can be observed in physical (e.g., pendulum clocks) and biological systems (e.g., fireflies). Resent research however has shown that the same principle applies to the brain, allowing sensory areas to stimulate other areas of the brain

such as motor, emotional, and cognitive networks. It is therefore possible to conceive that stimulation of the auditory areas by music can reverberate through entrainment across different areas in a given brain network. In other words, the auditory cortex can serve as a conduit for engaging brain networks involved in arousal. For that to occur, the primary areas being stimulated by music need to be unaffected or relatively preserved by the neurodegeneration process observed in disorders like AD[11].

3. The key areas of the brain activated by music do not seem to be affected by neurodegenerative disorders or are only affected in their late stages.

Dementia of AD is a disorder characterized by losses in cognitive function and emotional control resulting in the individual's inability to function independently at his or her normal level[12]. These symptoms are thought to be a reflection of the loss of neurons in brain areas responsible for multiple brain functions such as memory, executive function, visual spatial function, language, praxis (our ability to perform complex tasks), and others[13]. The level of lesions in specific brain areas have been strongly associated with changes in specific functions and disease severity[14,15]. A recent study by Akram Bakkour examined the potential difference in brain degeneration in older subjects with no Alzheimer 's lesions and those suffering from AD[16]. A study of 142 young controls, 87 older adults, 28 subjects with AD, and 35 older adults with neuroimaging data indicating the absence of brain amyloid (the lesion that characterizes AD) evaluated the areas of the brain that are especially impaired in aging, AD, or both. They found that the specific areas related to auditory perception, and therefore the initial areas where music is perceived, are relatively unaffected in subjects with AD.

4. Further supporting the concept of expansion of music activation in the brain (perhaps through the process of entrainment) are preliminary studies supporting music as a strong stimulator of brain activity in cognitively impaired subjects.

There are numerous anecdotal reports of individuals singing entire songs and performing on musical instruments, even when in late stages of AD. Current research sheds light on this fascinating and pervasive phenomenon of preserved musical memory, thanks to sophisticated 7 Tesla fMRI data[17]. Areas of the brain identified with memory for music include the caudal anterior cingulate cortex and ventral pre-supplementary motor area. Remarkably, as we discussed before, some of those areas are relatively spared from the degeneration common in AD, and show little disruption of glucose metabolism in PET scans[17]. However, brain network connectivity is often compromised in AD; therefore, it is important to find alternative routes for engaging brain networks associated with arousal in AD.

In a meta-analysis of the research on effects of music interventions on healthy older adults who show some cognitive dysfunction, 10 studies reported an aggregate mean improvement of 0.03 (Effect sizes, -0.18 to 0.24, showing decreases as well as increases) on tests of cognitive functioning, while also finding improvement in depression, anxiety, disruptive behavior, and quality of life. These results support the use of a variety of music interventions as a safe, non-invasive, and nonpharmacological approach[18].

Studies of the effects of music on the brain date back to the early 1990s with reports that college students improved their performance on standard tests when they listened to music for 10 minutes prior to the test. This effect was replicated multiple times. Further, studies have shown that the effects of music can be observed in the ascending arousal network, which includes clusters of voxels in the occipital and parietal lobe, including the amygdala. These networks appear to be closely associated with norepinephrine neurotransmission. These observations led to publications by Chabris and Thompson who found that most studies attributing improvements

in memory and other cognitive functions following a music intervention were only the result of an increase in arousal. Given this well-known effect of music on subjects' level of arousal, we hypothesize that our experiments will show a clear and evident increase in level of arousal in subjects after the proposed musical intervention[19-21]. For the purpose of this trial, arousal is defined as a physiological state of being alert, awake, attentive.

The goal of the proposed study is to perform a pilot, single-blind, randomized, crossover, controlled clinical trial to evaluate the efficacy of music stimulation on measures of global clinical improvement and increasing level of arousal. Furthermore, we expect to validate the clinical findings through the evaluation of changes in brain networks using the very same stimulation.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 RISKS TO SUBJECTS

PHYSICAL

Risks associated with increased activity

During the clinical stimulation of the brain using an emotionally impactful musical tune, increased level of arousal and increased desire to move due to music stimulation may result in an increase in a subject's physical activity potentially causing injuries or falls if adequate supervision is not provided.

Risks associated with auditory stimulation

The auditory system may be affected if the experimental music intervention or the control consisting of nature sounds is provided at excess volume.

Risks associated with fMRIs

fMRIs are made without using any ionizing radiation, so subjects are not exposed to the harmful effects of ionizing radiation. But while there are no known health hazards from temporary exposure to the fMRI environment, the fMRI environment involves a strong, static magnetic field, a magnetic field that changes with time (pulsed gradient field), and radiofrequency energy, each of which carry specific safety concerns:

The strong, static magnetic field will attract magnetic objects (from small items such as keys and cell phones, to large, heavy items such as oxygen tanks and floor buffers) and may cause damage to the scanner or injury to the subjects or medical professionals if those objects become projectiles. Careful screening of people and objects entering the fMRI environment is critical to ensure nothing enters the magnet area that may become a projectile.

The magnetic fields that change with time create loud knocking noises which may harm hearing if adequate ear protection is not used. They may also cause peripheral muscle or nerve stimulation that may feel like a twitching sensation. The radiofrequency energy used during the fMRI scan could lead to heating of the body.

Some subjects find the inside of the fMRI scanner to be uncomfortably small and may experience claustrophobia[22].

PSYCHOLOGICAL

Risks associated with assessments and questionnaires

Memory and cognitive testing may cause some individuals to become upset, frustrated, or tired. All participants have the right to decline to answer any questions and may ask to stop testing at any time for any reason.

PRIVACY

Risks associated with loss of confidentiality

In this study, a great deal of information about participant health status will be collected. Study staff at the clinic site will collect personal protected health information, which may include name, date of birth, address, phone number, and email addresses. The site will maintain the personal protected health information in a secure and locked location. All participants will be assigned an individual Study ID and all data collected under this protocol will be associated with that Study ID. The data, associated with the Study ID, will be shared widely, but it will not be possible to identify an individual participant from the data. However, there is a very unlikely possibility of a security failure, in which case the protected health information will be no longer protected.

2.3.2 POTENTIAL BENEFITS

Immediate potential benefits

The collection of information that, if relevant, will be shared with the subject's primary care doctor could prove to be beneficial to the subject. Subjects may also find the experience of listening to music and/or nature sounds enjoyable.

Long term benefits

If the study proves to be beneficial, it may result in a new treatment tool to enhance clinical well-being and level of arousal in this population.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Although there is some risk associated with testing and administration of questionnaires, the benefits of enrolling in this study are far greater as there are currently limited FDA-approved treatments to improve level of arousal and other symptoms in AD.

Evidence has shown that music may provide an effective intervention for individuals suffering AD. Due to the lack of robust research to support music as an intervention, the treatment is offered on a limited basis to these patients. However, if music stimulation proves to be an effective biologically based intervention, it will provide a new approach to treatment for the AD population, including the participants involved in the trial. The value of this innovative information outweighs the risks the subject would be exposed to. The PI and his staff will be attentive to subject risks, and to the potential emergence or presence of psychological issues in connection to a subject's participation in the trial. Specifically, the PI and his staff may be required to do the following to minimize such risks and recognize possible issues:

- At each study visit, inquire of subjects and family members as to whether any significant psychological concerns have arisen concerning the subject's cognitive condition and progression in their disease (when applicable)
- Encourage subjects and family members to call study staff if significant psychological issues should arise in the future concerning the subject's cognitive condition and progression in their disease.

Should study staff determine that a subject has experienced significant psychological issues in relation to their cognitive condition or progression, the PI and his staff will treat this as an AE and ensure that the subject is adequately protected.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To measure the global clinical impact of music on patients suffering from moderate to severe AD.	Change in clinical outcomes as measured by the Clinical Global Impression of Change (CGIC) at the end of the auditory intervention.	The CGIC is a clinical outcome measure with proven validity and reliability and has been used in other studies to evaluate symptoms in AD. This instrument provides a systematic method for assessing clinically significant change in the setting of a clinical trial as viewed by an independent, skilled, and experienced clinician. It has been used as a measure of clinical meaningfulness. Evaluating the endpoints described at Baseline, Visit 1, and Visit 2 will allow for determination of treatment effects.
	To evaluate changes in the modulation of brain networks via exposure to music and their association with global clinical impact using functional magnetic resonance imaging (fMRI) in subjects suffering from moderate to severe AD.	
Secondary		
To measure the impact of music on the level of arousal (specifically alertness) in patients suffering from moderate to severe AD.	Change in level of arousal as evaluated by the Stanford Sleepiness Scale (SSS) at the end of the auditory intervention.	The SSS is an instrument to assess the level of arousal by recording degree of current sleepiness. Evaluating the endpoints described at Baseline, Visit 1, and Visit 2 will allow for determination of treatment effects.
	To evaluate changes in the modulation of brain networks via exposure to music and their association with level of arousal using fMRI in subjects suffering from moderate to severe AD.	
Tertiary/Exploratory		
To measure the impact of music on cognitive function in patients suffering from moderate to severe AD.	Change in cognitive functioning as evaluated by the 8-item Severe Impairment Battery (SIB-8) in subjects suffering from moderate to severe AD.	The SIB-8 evaluates cognitive function in patients suffering from moderate to severe AD and includes subscales reflecting aspects of cognition that are sensitive to change over time. Evaluating the endpoints described at Baseline, Visit 1, and Visit 2 will allow for determination of treatment effects.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a controlled, single-blind, cross-over study design that will enroll 10 subjects suffering from moderate to severe AD with an MMSE of 5-20 and no neuropsychiatric symptoms of dementia. The study is designed to compare the effects of musical intervention consisting of an emotionally impactful tune unique to the subject versus a control intervention consisting of nature sounds.

The study will involve five visits one week apart from each other. The first visit will be a Screening Visit in which informed consent will be obtained, eligibility will be evaluated, an auditory assessment will be administered, and demographics and medical history will be recorded. If eligibility is confirmed, the subject will progress to the Baseline Visit. At the Baseline Visit, the CGIC, SSS, and SIB-8 will be administered, and an interview will be conducted. During the interview, three musical tunes that have a positive meaning to the subject will be identified. After the Baseline Visit and before Visit 1, one tune will be randomly selected out of the three to be used as the experimental intervention.

A randomization program will be used to deliver either the selected musical tune or nature sounds via over-ear headphones at Visit 1. Visit 2, which will occur a week later, will be identical to Visit 1, but the subjects that were originally exposed to music will hear nature sounds and vice versa. Over the course of a 3-hour session during Visit 1 and Visit 2, both interventions will be delivered as 10-minute segments at the top of each hour. After each musical intervention, the subjects will remain in the same research environment and will be free to interact with their caregivers and the staff until the next round of music is performed. The third and final interventional segment will be followed by the administration of the CGIC, SSS, and SIB-8. Finally, at Visit 3, subjects will complete three consecutive 10-minute fMRI scans: resting state (baseline measure), preferred music, and nature sounds, to be administered in a randomized order. The resting state fMRI will serve as the baseline reading. All measures will be done between 9am and 1pm.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Our target population for the study is subjects with moderate to severe AD due to the high prevalence of the disease and the fact that this population was the focus of the preliminary reports cited previously[1,3,4]. The diagnosis of AD will be established using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's Criteria for possible and probable AD[23] and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) per clinical assessment by the PI or another qualified investigator during the Screening Visit.

All research examined clearly states that brain activation via music depends on the type of music that is chosen[1]. This research established that the most effective type of music will be highly individual (AARP GCBH Meeting personal communication). The music to be selected will be different for each subject and will have a special, emotional connection (positive) to the individual participating in the study. Therefore, during the Baseline Visit, the patient's caregiver, as well as the subject, will be interviewed to establish the subject's three favorite tunes. One of the identified tunes will be randomly selected to use as the experimental intervention. Each 10-minute musical exposure will be the same for the unique subject on a given day as described above and the tune will be consistently administered to the subject both during the clinical stimulation and the fMRI scans.

The CGIC will be the primary outcome measure, the SSS will be the key secondary outcome measure, and the SIB-8 will be an exploratory measure. We have chosen the CGIC in an attempt to evaluate the overall clinical impact of music. Secondly, we have chosen the SSS, which has been validated to evaluate level of arousal in this population. Finally, we have chosen the SIB-8 to explore the potential cognitive effect in this population, since it is a validated scale developed specifically for patients in the moderate to severe stages of the disease. The SSS and the SIB-8 have the ability to show changes in short periods of time.

Auditory acuity will be evaluated to determine the intensity of the sound the subjects are exposed to. Specifically, the level of sound the subjects are exposed to will be calibrated in relation to their hearing abilities in order to assure a similar level of music stimulation in all subjects. We will use a well-established hearing test, pure-tone audiometry, to perform this evaluation on the study population[24].

The goal of the fMRI scans is to determine whether the preferred music intervention enhances connectivity with brain networks associated with arousal as compared to pure resting state and nature sounds. The primary outcome measure for connectivity will be a measure of entropy or spread of information from the auditory cortex to other parts of the brain.

Our chosen MMSE score for the study is 5-20 points. The MMSE is a test designed to evaluate basic cognitive functions and is often utilized to gauge the level of impairment in patients with AD. The MMSE is scored is 0-30, with scores of 20 to 24 suggesting mild dementia, scores of 13 to 20 suggesting moderate dementia, and scores of less than 12 suggesting severe dementia.

On average, the MMSE score of a person with AD declines about two to four points each year. As stated, a MMSE score of 20 usually reflects a patient in the moderate stages of the disease where brain degeneration starts to become more pronounced, but where we believe auditory areas remain almost intact. The lower score of 5 reflects the severe stages of the disease where we believe even auditory areas of the brain engaged in music activation will start to be affected, thus scores below 5 will be excluded.

4.3 JUSTIFICATION FOR TREAMENT INTENSITY

In our experience, a minimum of 10 minutes of music stimulation is required to generate an effect. We have observed in our clinical practice the effects of music stimulation in this population start to decline when music is ceased. The effects continue to decrease for approximately 3 hours, at which point we expect the effects will subside entirely. We therefore designed this study to provide music stimulation in 10-minute increments spread across 3 hours to observe if the intermittent stimulation either overlaps (and creates a “dose” increase) or prevents a decline in the effect.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all visits of the study as outlined in the SoA, Section 1.3.

The end of the study is defined as completion of the last visit in the SoA.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Person of any sex/gender aged between 55 and 90
3. Stated willingness to comply with all study procedures and availability for the duration of the study
4. In the opinion of the investigator, has an informant able and willing to provide accurate information about the participant (may be paid or unpaid caregiver)
5. Suffer from moderate to severe AD as established by the study team using the NINCDS-ADRDA Alzheimer's Criteria for possible and probable AD
6. Diagnosis of AD or other type of dementia as defined by the DSM-V
7. MMSE score of 5-20
8. Subject is reported by the study partner to be able to listen to a minimum of 10 minutes of music and a sound in an uninterrupted manner.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Suffer from severe hearing impairment as reported by the informant
2. Lack of ability to tolerate the intervention or the participation in the fMRI portion of the study
3. Presence of neuropsychiatric symptoms of dementia as determined by clinical observation by the PI, including history of agitation and/or combative behavior.
4. Individuals who score ≥ 12 seconds on the TUG Test.

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study

Individuals who do not meet the criteria for participation in this trial (screen failure) because of transient issue(s) may be rescreened one additional time following resolution of these issue(s). Reconsent will be required prior to rescreen.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment

The PI will contact physicians in the Charleston area to provide them with information about the study and request patient referrals of potential subjects. Once a referral has been made, the potential subject will be contacted by

the PI by telephone, the study will be described, and if the subject and study partner express interest in the study, the study coordinator scheduled for a screening visit.

Retention

Due to the short duration of the study, issues with retention are not anticipated.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

This is a randomized, cross-over study to measure global and clinical impact and level of arousal in subjects suffering from moderate to severe AD when exposed to emotionally impactful music compared to control intervention. In partnership with the study partner (a person who spends 10 hours or more a week with the subject and can reliably report on the subject's condition), three tunes will be chosen for the purposes of the study. The tunes chosen will need to be related to a past meaningful, positive experience of the subject, as determined by the subject and the subject's study partner. The pieces will be restricted in duration to between 1.5 and 2 minutes each. A piece will be chosen at random and will be saved on a portable device, and subjects will be asked to listen to the melody using high quality (Bose), over-ear headphones. The total exposure time will be 10 minutes each hour over a three-hour period. The melody will be repeated as many times as necessary to complete the 10-minute period. The control intervention will involve listening to nature sounds at the same duration and administration scheme. fMRI will be used to identify how brain networks are modulated via exposure to this music and how they associate with the clinical findings.

6.1.2 DOSING AND ADMINISTRATION

Over the course of 3-hour sessions at Visit 1 and Visit 2, either the musical intervention or the control intervention consisting of nature sounds will be delivered as 10-minute segments at the top of each hour.

6.2 TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The researcher responsible for randomization will design, implement, and maintain randomization procedures. A software system will generate study assignment. When a treatment assignment is generated, a sound identification number will not be chosen in sequence from the treatment file but rather from the next sequential assignment in the master randomization scheme. Thus, treatment assignment is unpredictable to clinical center staff**.**

This is a single-blind, randomized, cross-over study with raters being blinded to the specific intervention (music or nature sounds) that the subjects receive. The study team will be instructed on the importance of maintaining the blind and special measures will be put in place to avoid inadvertent unblinding. Raters will be unaware if the subjects receive either music or nature sounds. Music will be provided through over-ear headphones to prevent the raters from hearing the intervention being administered and the evaluation will be performed after the intervention is complete.

6.3 STUDY INTERVENTION COMPLIANCE

A compliance assessment will be recorded at Visit 1, Visit 2, and Visit 3. The study staff will ensure that the subject has the headphones appropriately placed on the ears for 10 minutes continuously while the sound is being played and will record this compliance at the end of each session in the Case Report Form (CRF). In the event that the subject is unable to complete the 10-minute period, the staff will remove the headphones, provide the subject with a 30-minute break, then reattempt the 10-minute auditory intervention. If not successful, the subject will be removed from the study and an additional subject will be added.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from the study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

The data to be collected at the time of study intervention discontinuation will include the administration of all end of study outcome measures, if possible.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical AE or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention (development of neuropsychiatric symptoms of dementia)
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on CRFs. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for any of the scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and the study partner to reschedule the missed visit and counsel the participant and the study partner on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant and the study partner (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file.
- Should the participant and the study partner continue to be unreachable, the participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Eligibility Criteria

Eligibility Criteria will be established by the PI using a clinical interview with the subject and informant to establish the NINCDS-ADRDA Alzheimer's Criteria for possible and probable AD and the DSM-V Diagnosis of AD or other type of dementia, the review of medical records, and cognitive assessment using the MMSE.

Clinical Global Impression of Change

CGIC scales have been used extensively as primary outcomes in phase 2 and 3 clinical trials for AD, mild cognitive impairment, and for cognitive enhancers. A CGIC score is intended to be used as a measure of clinically meaningful change, as distinct from an instrument's ability to assess any change. The ADCS-CGIC, the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change is the most commonly used process for obtaining an assessment of clinically meaningful change in clinical trials. The ADCS-CGIC is a systematic method for assessing clinically significant change in a clinical trial as viewed by an independent skilled and experienced clinician. The ADCS-CGIC requires the assessor to consider a number of cognitive, functional, and behavioral areas prior to providing an overall "global" assessment of clinical change. It was designed in response to an FDA request and on the basis of a survey of Alzheimer Disease Cooperative Study clinicians. It is performed by interviewing the patient to assess function and mental status and the informant, using a worksheet that comprehensively lists relevant symptoms potentially useful in judging clinically meaningful change, and allows for notes for future reference- it takes approximately 20 minutes per interview.

The Stanford Sleepiness Scale

The SSS was developed by Dement and colleagues in 1972 and is a one-item self-report questionnaire measuring levels of sleepiness throughout the day. The scale, which can be administered in 1-2 minutes, is generally used to track level of arousal at each hour of the day. The scale has been validated for adult populations aged 18 and older. The SSS is used in both research and clinical settings to assess the level of intervention or effectiveness of a specific treatment in order to compare a client's progress.

The Severe Impairment Battery (8-item)

The SIB evaluates cognitive abilities at the lower end of the range. There are 40 items, and it takes approximately 20 minutes to complete. It is composed of very simple one-step commands which are presented in conjunction with gestural cues. Example questions include:

- 'What's your name?'
- 'Please write your name here'
- 'What do you call the thing you drink coffee from?'

The SIB is divided into scorable subscales, each sampling within the range expected of the severely-impaired individual. The six major subscales are attention, orientation, language, memory, visuospatial ability and construction. There are also brief evaluations of praxis and the patient's ability to respond appropriately when his/her name is called (orienting to name). In addition, there is an assessment of social interaction skills.

The range of possible scores is 0-100. There is no cut-off for normal as the test should only be used with patients known to be severely impaired. However, it is possible to grade the severity of impairment by rating those who score less than 63 on the SIB (corresponding to less than 4 on the MMSE) as 'very severely impaired'. A recently derived 8-item version of the SIB — the SIB-8 — which takes about 3 minutes to administer, may represent a more convenient tool for use in clinical practice. Very good internal consistency/agreement and strong correlations between the SIB and the more rapid and convenient SIB-8 indicate that the SIB-8 may be a useful and efficient clinical proxy for the full SIB in evaluating treatment response in patients with advanced AD.

8.2 SAFETY AND OTHER ASSESSMENTS

NINCDS-ADRDA Alzheimer's Criteria for possible and probable AD research diagnosis

- The PI or another qualified investigator will apply the NINCDS-ADRDA Alzheimer's criteria to make a research diagnosis of the subject's AD status as possible or probable AD.

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) research diagnosis

- The PI or another qualified investigator will apply the DSM-V criteria to make a research diagnosis of the subject's AD status.

Mini-Mental State Exam (MMSE)

- The MMSE will be performed with the subject and assesses orientation, immediate and delayed recall, concentration, language, and construction skills on a 0-30 scale of correctness. An MMSE score between 5-20 indicates subject eligibility.

Auditory Assessment

- An audiologist will perform pure-tone audiometry, where the subject will be instructed to raise their hand (or point to the appropriate ear) when they hear a tone.

Vital signs

- Vital signs (i.e. sitting pulse and sitting blood pressure) will be obtained by trained study personnel.

Timed Up and Go (TUG) Test

- The TUG Test measures the time (in seconds) taken for an individual to stand up from a standard armchair, walk 10 feet, turn, walk back to the chair, and sit down. It is a commonly used scale for measuring functional mobility and risk of falls.

MRI Metal Screening Questionnaire

- The MRI Metal Screening Questionnaire will be performed to determine if the subject has any metal items in their body that may be harmful in the scanner or may interfere with the MRI examination.

Recording of AEs and SAEs

- See Section 8.4 for AE and SAE recording and classification.

Assessment of intervention adherence

- A compliance assessment will be recorded at Visit 1, Visit 2, and Visit 3. The duration of time that the subject adheres to the established procedures of the intervention will be logged during each visit on a CRF.

Functional Network Analysis

- MRI scanning includes collection of a high-resolution T1-weighted MPRAGE (TR=2.3s, TE=2.23ms, flip angle=8°, 192 sagittal slices, FOV=256x256mm), followed by a 10-minute resting state fMRI scan and two 10-minute stimulation scans (nature sounds/preferred music; acquisition parameters: 3 mm^3 voxels, TR=1.1s, TE=30 ms, flip angle=65°, 51 axial slices, matrix=64x64, 375 time points, acceleration factor=3). Gradient field maps will also be collected. More information about fMRI resources will be provided upon request.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

AEs are any untoward medical occurrences associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). AEs the PI deems related to study procedures, related to the

study intervention, and/or medically important for an individual participant, regardless of causality, will be tracked during this study.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An AE or suspected adverse reaction is considered "serious" if, in the view of the PI, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

SEVERITY OF EVENT

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures and cause some interference with daily activities.
- **Severe** – Events incapacitate a participant in daily activities and may require systemic drug therapy or other treatment. Of note, the term "severe" does not necessarily equate to "serious".

RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to the study intervention assessed by the PI who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study intervention must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

EXPECTEDNESS

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant.

All AEs not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, PI's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the

event. All AEs occurring during the course of the study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

The PI will monitor the study procedures for this trial for overall safety and scientific relevance on an ongoing basis. The PI will evaluate each AE and SAE for safety and causality. All AEs and SAEs will be recorded and reported to the IRB on a regular basis.

8.3.6 REPORTING EVENTS TO PARTICIPANTS

Subjects, their study partners, and, if so desired by the subject and their study partner, the subjects' primary care physician will be informed of all AEs and SAEs as per GCP guidelines.

9 STATISTICAL CONSIDERATIONS

Initially, baseline variables and outcomes (Clinical Global Impression of Change, Stanford Sleepiness Scale) will be summarized using descriptive statistics for each intervention. For the primary comparison of outcomes between visits 1 and 2, general linear mixed models will be constructed. GLMMs are an excellent means of accounting for clustering (correlation) of observations within subjects over time, which naturally occur as a part of crossover designs such as this. The models for CGIC, SSS and SIB-8 will include main effects for sequence (intervention order), period (a subject's first or second trial), and intervention (music vs. nature sounds), along with random subject effects. Since this is a pilot study of n=10, the focus will be on estimating group differences as opposed to formal hypothesis testing. The estimates provided by the GLMMs will be vital for designing a future more definitive crossover trial.

For fMRI analysis based on data from Visit 3, we will use analytic methods similar to those used in our prior publications of functional network connectivity[25-29] and similar to other studies[30]. Briefly, following fMRI preprocessing and nuisance signal regression, residual time series from each of 294 brain regions (nodes) will be submitted to partial correlation to establish the connectivity between each pair of nodes in the network, controlling for connectivity of all other nodes. These pair-wise correlations then serve as edge weights in the calculation of graph-theory measures like diversity coefficient.

The Brain Connectivity Toolbox (BCT)[31] will be used to calculate diversity coefficient after establishing the community structure in each participant using modularity and consensus functions. Modularity will be run 1000 times for each subject, and the consensus community structure, as implemented in the BCT, will be determined. The diversity coefficient of the auditory cortex will be the primary measure of interest. The higher the diversity coefficient of the auditory cortex, the greater the spread of information to other networks in the brain [JL2] [a3]. Visualization of the connectivity of the auditory cortex as measures by diversity coefficient is expected to reveal greater connectivity with frontal and fronto-parietal networks associated with arousal in the preferred music condition compared to continuous resting state or nature sound conditions. A separate GLMM will then be used to determine whether the diversity coefficient differs by intervention; this model will include main effects for

sequence (intervention order) and intervention (because there is only one MRI session, period is not applicable), along with random subject effects.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

If the subject meets these basic criteria, the PI will present an Informed Consent Form (ICF) to both the subject (and if applicable the subject's legal authorized representative) and the caregiver/informant to participate in the study. After the Informed Consent is fully discussed, and all questions are answered, another designated investigator determines whether the subject has the capacity to provide their own informed consent. For those subjects with Decision Capacity, the subject will then sign their own ICF. For those subjects without Decision Capacity, the subject's legal authorized representative by SC state law will be asked by the investigator obtaining consent to sign the ICF, with verbal assent from the subject.

The PI will also present the HIPAA Authorization form, which will be fully discussed with the subject. All questions will be answered by the PI and the specifics of the Notice of Privacy Practices will be explained. The subject and the subject's legal authorized representative (if applicable) will sign the HIPAA Authorization form thereafter. A copy of the signed ICF, the signed HIPAA Authorization form, and the Notice of Privacy Practices will be given to the subject.

Decision Capacity

Decision capacity is determined every time an informed consent is executed, regardless of subject's clinical presentation. Subjects are evaluated by a clinician (MD or master level clinician) independent of the study team to determine if they have decision capacity. If the subject does not have decision capacity, a legally authorized representative (spouse, all next of kin, or individual with healthcare power of attorney) will be required to review and sign the Informed Consent.

The decision capacity determination will be completed on a separate form which states the study subject's ability to make a decision regarding participation in the study and then dated and signed by the clinician who made the determination.

Decision capacity process will be repeated for any new informed consents using the same procedures as above.

Research subjects are free to withdraw informed consent at any time if they desire to do so. Appropriateness of a research subject's involvement in a research study is evaluated on an ongoing basis by the PI.

It should be noted that the ability to provide informed consent is based on decision capacity at the time of administration of the informed consent, not on the severity of the disease. If the subject has agreed to participate in the study and the study procedures, the subject will not need to be reassessed for decision capacity given the short duration of the study.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the PI and his staff and their interventions. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the subject.

All research activities will be conducted in as private a setting as possible.

Representatives of the IRB or regulatory agencies may inspect all documents and records required to be maintained by the PI. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Medical University of South Carolina. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by the Medical University of South Carolina research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Medical University of South Carolina.

10.1.3 KEY ROLES

Principal Investigator	Co-Investigator	Safety Monitor	Biostatistician
Jacobo Mintzer, MD, MBA	Jane Joseph, PhD	Olga Brawman-Mintzer, MD	Paul Nietert, PhD
College of Health Professions	Department of Neuroscience	College of Health Professions	Department of Public Health Sciences
Medical University of South Carolina	Medical University of South Carolina	Medical University of South Carolina	Medical University of South Carolina
151 Rutledge Ave A,	135 Cannon Street	151 Rutledge Ave A,	135 Cannon Street,
Charleston, SC 29403	Charleston, SC 29425	Charleston, SC 29403	Suite 303 MSC 835
843-367-4260	843-792-7683	843-367-4270	Charleston, SC 29425
mintzerj@musc.edu	josep@musc.edu	mintzero@musc.edu	843-876-1204
			nieterpj@musc.edu

10.1.4 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

Data safety and monitoring will be carried out to ensure and maintain the safety of our participants. Safety monitoring is the process during the study that involves the review of accumulated outcome data to determine if any of the procedures practiced should be altered or stopped. Due to scope and limited risk of the protocol as well as lack of significant risk of listening to music intervention, no Data Safety Monitoring Board is required. However, the study Safety Monitor will be responsible for monitoring the safety of the study and complying with the reporting requirements. Continuous, close monitoring of participant safety will include prompt reporting of safety data (i.e., adverse/serious adverse events) to the MUSC IRB. Serious adverse events will be reported to IRB within 48 hours of the time project staff become aware of the incident. Safety Monitor will review study data and procedures if early termination of the study, amendment to the protocol, or changes to the data collection plan are needed. Should the protocol or data collection plans be amended as a result of data review, the IRB will be notified and the amendment approved prior to study amendment implementation. In addition, the participants will be notified of any significant new findings that develop during the course of research (e.g., other potential risks) that may affect their wish to continue participation in the study.

10.1.5 QUALITY ASSURANCE AND QUALITY CONTROL

The data system will employ double data entry and range checks to reduce the occurrence of data entry errors. The Data Management Team will also develop and periodically run data quality query programs on all the accumulated data to check the logic and consistency of data between forms and provide additional means of detecting errors. Queries generated during this process will be sent to the clinical center where personnel will attempt to resolve the queries. Any changes to the data will be made on the CRFs and in the data system. All changes made to the data system will be logged and information including data systems operator making the change, details of change, date, and time will be recorded.

10.1.6 DATA HANDLING AND RECORD KEEPING

DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data Security and Protection

Prior to completing any protocol procedures:

1. The PI and the coordinator have complete the Collaborative Institutional Training Initiative (CITI) course on protections of human subjects in research. The CITI was founded in March 2000 as collaboration between the University of Miami and the Fred Hutchinson Cancer Research Center to develop a web-based training program in human research subjects' protections.

2. The PI has successfully completed training for administering the MMSE, TUG, MRI Metal Screening Questionnaire, CGIC, SSS, and SIB-8.

The PI is trained to perform vital signs.

This is a single site study, and individual data will not be shared with any other research site. The data collected will not contain any identifiers. No identifying data is shared with any source outside the local research team without specific release of information from the subject.

Data will be stored in a locked office within a locked suite only accessible to authorized personnel. The research data will be stored and managed in REDCap, a secure web-based database system designed for clinical research studies.

Types of Raw Data

Raw data will be results of CGIC, SSS and SIB-8, along with fMRI results. The study coordinator will develop and maintain common study documents including the protocol, manuals, template consent documents, and policy and procedures memoranda. These documents will ensure that study participants are enrolled, treated, and followed according to the same procedures. The study coordinator will also maintain an official study chronology of important events occurring during the trial, including protocol revisions and serve as the repository for study documents. The PI will monitor submission of the common study protocol to clinic IRB and compliance with study procedures. Study personnel will be trained and certified in study procedures for treatment and data collection before the study begins and training will be reinforced as indicated.

Standards to be used for raw and meta-data format and content

Prior to initiation of participant recruitment, the Data Management Team will develop detailed methods for data collection. Data will be recorded on CRFs. The study coordinator and psychometrician will have primary responsibility for developing, testing, and maintaining the CRFs in collaboration with the PI. Forms will be identified by a participant study ID number and an alpha code to prevent personal identifiers from being transmitted to the Data Management Team. Data will be entered into a data system and the Data Management Team will oversee data storage. Backup files of the database will be stored at regular intervals in a secure, off-site location, to permit regeneration of the database in the event that it is destroyed. CRFs will be available through the study website in real-time. A study investigator will maintain a clinical chart for each participant that will contain source documents including clinical information and progress notes.

Plans for archiving the raw and meta-data, and for ensuring continuous access

The research data will be stored and managed in REDCap, a secure web-based database system designed for clinical research studies. The REDCap database will be developed by the study team, with oversight from the biostatistician (Dr. Paul Nietert). REDCap will facilitate data archival, data analyses, and data sharing.

STUDY RECORDS RETENTION

Study documents should be retained for 25 years.

10.1.7 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or the International Conference on Harmonization Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 days of identification of the protocol deviation, or within 21 days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the Data Management Team. Protocol deviations must be sent to the reviewing IRB per their policies. The PI is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.8 PUBLICATION AND DATA SHARING POLICY

Dissemination Plan

This study will be part of the Alzheimer's Clinical Trials Consortium (ACTC). This trial is committed to the open and timely dissemination of research outcomes. The study abides by the principles for sharing of research data as described in the NIH Public Access Policy on data sharing. Data sharing is essential for further translation of research results into knowledge, products, and procedures to improve human health. The researchers endorse the sharing of final research data to serve these and other important scientific goals.

Data Sharing

This project will facilitate sharing of software, archived study datasets (including images), assessment instruments, forms, and procedures through the web-based tools of the ACTC. The ACTC web portal will include clear access to inventories of resources and request procedures. All ACTC archival datasets will be included on the Global Alzheimer's Association Interactive Network (GAAIN); ACTC data can be accessed via the GAAIN platform; full or partial archived datasets can be shared via the dedicated ACTC Dataset- Sharing Portal.

10.1.9 SHARING OF RESULTS WITH SUBJECTS

If the study staff learn anything about a subject from the study activities that could be important to their health or standard of care, the information will be provided to them. Otherwise, they will not receive their study results.

Changes in their cognitive testing scores that warrant further evaluation will be discussed with them.

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