Title: IMOVE: A randomized, controlled trial of Improvisational MOVEment for people with memory loss and their caregivers

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Clinical Intervention Study Protocol Template

IMOVE: A randomized, controlled trial of Improvisational MOVEment for people with memory loss and their caregivers

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Tool Revision History

Version Number: 2
Version Date: 09/13/2017
Summary of Revisions Made: Edits were made to clarify study endpoints, randomization scheme, details of statistical methods, and how missing data would be addressed statistically.

Version Number: 3
Version Date: 10/29/2017
Summary of Revisions Made: Edited language about randomization scheme, included information about how data not missing at random would be statistically addressed.

Version Number: 4
Version Date: 11/09/2017
Summary of Revisions Made: Edits were made in response to feedback from Westat to clarify study time windows; add information about planned study sites; add a table of exclusionary medications and renumber subsequent tables; clarify study alert information; add specific laboratory tests; and specified measures for monthly data QA. Additionally, added details about video storage and made minor formatting edits. Increased time since adjudication from 6 months to one year.

Version Number: 5
Version Date: 03/05/2018
Summary of Revisions Made: Clarified inclusion criteria to specify that the caregiver who is a study partner for the person with dementia does not have to be the caregiver who accompanies the person with dementia to the intervention. At the recommendation of the ADC, cognitive testing for study outcomes changed to the Repeatable Battery for the Assessment of Neuropsychological Status, which has minor changes from the originally proposed battery. Added provision that participants who have had a comparable assessment of cognitive status to that provided through our clinics may participate in the study. Moved MoCA to BV1 and moved GDS, GAS, AES, and FES to BV2 for both PWD and CG. Clarified that stroke should be diagnosed by physician. Corrected baseline visit windows. Minor editorial changes.

Version 5.1
Version Date: 07/18/2018
Summary of Revisions Made: All references to Visit 5 were removed.

Version 5.2
Version Date: 07/30/2018
Summary of Revisions Made: Updates were made to inclusion criteria to allow for vascular dementia, lower MMSE cutoff score from 18 to 15, and allow for stroke upon approval of the study physician. These changes are made with the aim of improving recruitment without altering the aims, study design, or risk of the study. Also, the care partner role was modified to accept any person who spends approximately 10 hours per week with the participant, which is the current practice of the Wake Forest Alzheimer's Disease Research Center. Finally, updated the randomization scheme such that it occurs over blocks of 16 instead of 32 dyads to decrease the amount of time between randomization and intervention start date and also to facilitate filling waves in local facilities such as churches or CCRCs.

Version 6.0
Version Date: 11/18/2020
Summary of Revisions Made: Multiple changes are being made in response to intervention interruption due to COVID-19.

- A new consent was added for those whose intervention was interrupted by COVID-19
- Added protocol for collecting as many measures as possible virtually in the event this is necessary if safety concerns for in-person study visits arise.
- Added details for performing intervention arms virtually.
- Addition of an abbreviated screening visit for potential participants who previously completed full cognitive testing over 1 year ago and have an active diagnosis arrived at by as required in the study. The rationale for this is that especially in the case of a dementia diagnosis, it is virtually impossible for cognitive status to improve. Requiring people with established dementia to complete a full battery of cognitive testing can cause extreme distress in the person with dementia and yet provides little meaningful additional information in the context of establishing eligibility for this study. Caregiver concern about potential distress for the person with dementia has caused multiple potential participants not to screen for the study. In the case of an existing diagnosis of dementia, we propose to test global cognition with an MMSE to determine if the participant still falls within the established eligibility range for the study. In the case of MCI, under the guidance of the leadership of our Alzheimer's Disease Research Center (ADRC), we propose to administer the Montreal Cognitive Assessment (MoCA). If the MoCA score is out of range for the study or has changed more than 3 points, a full cognitive testing battery would be performed. It is important to note that cognitive functioning will still be assessed with the RBANS pre- and post-intervention.
- At the suggestion of the study monitor, lab alert values have been adjusted to better align with ranges prescribed by the lab analysis provider (LabCorp). Values requiring alerts and time windows for these alerts were also clarified.

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FREQUENTLY USED ABBREVIATIONS USED IN PROTOCOL (ALPHABETICAL ORDER)

AD	Alzheimer's disease
ADCC	Alzheimer's Disease Core Center
CG	Caregiver
DSC	Digit Symbol Coding
fMRI	Functional Magnetic Resonance Imaging
MA	Movement Alone
MAC	Memory Assessment Clinic
MCI	Mild Cognitive Impairment
MG	Movement Group
MoCA	Montreal Cognitive Assessment
NC	No Contact (control group)
NPI	Neuropsychiatric Inventory
PWD	Person With Dementia
QoL	Quality of Life
RBANS	Repeatable Battery for the Assessment of Neuropyschological Status
SG	Social Group

PRÉCIS

Study Title

IMOVE: Improvisational MOVEment for people with memory loss and their caregivers

Objectives

The overall aim of this proposal is to experimentally determine the independent and combined effects of dance movement and social engagement on quality of life (QoL) in people with mild cognitive impairment (MCI) and early-stage Alzheimer's disease or vascular dementia, and test the neural mechanisms of these effects.

Design and Outcomes

We will use a 2x2 factorial design and randomize up to 120 older adults (age ≥ 60 years) adjudicated as having MCI or early-stage ADRD to one of four 12-week intervention conditions: 1) Movement Group, 2) Movement Alone, 3) Social Group, or 4) No Contact Control.

Active interventions (Movement Group, Social Group, Movement Alone) will occur twice weekly for 1 hour, for a total of 2 hours of intervention each week.

The primary outcome is QoL in the person with memory loss. Secondary outcomes of interest include: 1) gait and balance assessed with an instrumented mat, force plate, Fullerton Advanced Balance Scale and Short Physical Performance Battery; 2) apathy, depression, and other neuropsychiatric symptoms in the person with dementia (PWD); and 3) changes in brain networks, especially somatomotor regions and the default mode network (DMN), assessed with graph theory analysis of resting-state functional magnetic resonance imaging (rsfMRI).

Outcomes will be assessed prior to the intervention, within days 0-7 and within days 1-21 following the last intervention date.

Interventions and Duration

The study will have four arms: 1) Movement Group (MG), 2) Movement Alone (MA), 3) Social Group (SG), or 4) No Contact (NC) control. Participants will be on study for up to 9 months, including time between screening and intervention initiation, and 2 follow-up visits off intervention. All intervention subjects will participate in two 1-hour intervention sessions each week for 12 weeks, for a total of 24 hours of intervention.

The **Movement Group** will participate in 1-hour group improvisational dance movement lessons twice a week for 12 weeks. Improvisational dance movement classes are grounded in 4 principles that shape the tone of the class and result in a sense of social belonging: non-judgment, non-competitiveness, curiosity, and playfulness. Training strategies used to maintain these qualities while moving are active imagination, variability, and pacing. These concepts are described in more detail in section 5.1.

The general class structure has four phases. These include: **(1)** group warm-up in chairs positioned in a circle, **(2)** standing barre with solo- and partnering exercises,

(3) moving as a group through free space (with and without a partner), and **(4)** recuperation and rest. If participants are unable for any reason to perform exercises at the barre or move through free space, all exercises can be adapted for sitting. The choice to stand or walk is always self-selected by the participant. If the intervention is delivered in a virtual environment, the elements of group warm-up, standing barre, moving through free space, and recuperation and rest will still be performed. Participants will complete the movements at home while viewing the instructor and classmates via videoconference. Barre exercises will be adapted to use a chair for the barre. Partnered exercises will be accomplished by interacting with others in the videoconferencing environment. Group movements will be adapted as needed to accommodate movement in the home.

The **Movement Alone** condition is designed to capture the same dance movement and auditory stimuli as the group class without social interaction. Recordings of the dance instructor teaching a dance class will be presented. This will ensure participants hear comparable music and receive comparable verbal auditory cues to prompt dance movements that students in the group class will hear, without interacting with other people. Participants will be asked to follow the same schedule as participants in the Movement Group arm and complete two 1-hour dance sessions per week. If the intervention is delivered virtually, recordings and music will be presented to the participant via videoconferencing software that is monitored and operated by study staff.

The **Social Group** will consist of improvisational party games that foster curiosity and playfulness, use imagery, and encourage non-judgment. Games that may be used include 'Balderdash', 'Wise and Otherwise', 'Pictionary', and 'Tell Me A Story' cards. These games will also use the same core strategies as the dance group. Games will be varied within an hour-long session to incorporate pacing and variability into the social group, akin to the dance group. The social group will occur 2x/week for 1 hour each time and be led by the same instructors who lead the Dance Group, to control for effects of personality of the group leader. If the intervention is delivered virtually, games will be led by the same instructors over videoconferencing software.

The **No Contact** condition captures the condition of no added social contact and no added dance movement. Participants randomized to the No Contact condition will be asked to continue their current disease management and lifestyle for 12 weeks. The condition of not receiving an intervention can have ethical implications and reduce retention rates. Therefore, these participants will be invited to join in a weekly community improvisational dance class after they complete the study, for as many sessions as they would like, or to participate in a MG arm if space allows. If the intervention is delivered virtually, NC participants will be invited to participate in community classes offered with the same virtual format.

Sample Size and Population

We aim to enroll up to 120 people with mild cognitive impairment or early-stage dementia aged 60-85 and their caregivers in dyads (pairs), for a total of 240 individuals. The main outcomes are powered on the number of PWD, as those are the primary outcomes of interest. Participants will be randomized equally to one of the

four groups, for a total of 30 dyads in each group. The target population is people adjudicated as having mild cognitive impairment or early-stage dementia aged 60-85. Cognitive status will be determined by combining information from 1) a cognitive test battery that is either the National Alzheimer's Coordinating Center (NACC) Unified Data Set (UDS) or comparable battery, 2) self-report forms including depressive symptoms, 3) caregiver-report of functional status and neuropsychiatric symptoms, and 4) the Clinical Dementia Rating scale (CDR). We anticipate most study participants will be referred to the study after being adjudicated by consensus using the above information either in the Wake Forest School of Medicine Memory Assessment Clinic (MAC) or the Alzheimer's Disease Core Center (ADCC). Participants from the community can also be included by completing the above testing, being adjudicated as having mild cognitive impairment or early-stage dementia, and meeting study inclusion/exclusion criteria.

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective of this proposal is to experimentally determine the independent and combined effects of dance movement and social engagement on quality of life (QoL) in people with mild cognitive impairment or early stage dementia.

1.2 Secondary Objectives

The secondary objectives of this proposal include assessing the neural mechanisms of the effects of dance movement and social engagement, and to assess potential mechanistic links between functional neuroimaging metrics, behavioral outcomes, and overall QoL scores using structural equation modeling in all groups combined.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Dementia is a progressive decline in cognition that impairs a person's ability to perform activities of daily living. Alzheimer's disease (AD) is the most common form of dementia, the most common neuro-degenerative disease in older adults, and the 6th leading cause of death in the US.[1] It is the only one of the top 10 leading causes of death with no disease-altering treatment or cure, meaning that all current medical treatments for AD are essentially palliative, aimed at controlling symptoms rather than altering the course of the neuropathology underlying the disease. Care for AD and other related dementias (ADRD) was estimated to cost the United States approximately $203 billion in 2013, and that cost is estimated to increase to over a trillion dollars by 2050.[1] Costs for AD are high because of the need for specialized in-home and institutional care as the disease progresses, and also due to increased healthcare costs for caregivers. In addition to lost time at work, the medical costs arising from the stress of dementia caregiving are estimated to be around $9.1 billion a year [1]. Research has convincingly demonstrated that caregivers of a person with dementia face increased levels of stress that tax their health [2-7] above and beyond

caregiving for people with other needs,[1] and to the extent that they may increase mortality.[8]

Neuropsychiatric symptoms (apathy, depression, anxiety) and altered gait and balance are prominent secondary symptoms of AD that increase medical costs and decrease quality of life (QoL) for the person with dementia (PWD) and their caregiver (CG).[9-11] In a report from the Secretariat (Executive Board, 134th Session, December 20th, 2013), the World Health Organization identified a need to integrate evidence-based palliative care services into the continuum of care for serious chronic diseases, including AD. However, two recent NIH workshops identified major gaps in the evidence supporting the wider use of non-pharmacologic activities to ameliorate secondary symptoms of chronic disease. Arts-based activities were identified as particularly understudied for symptom management, given growing evidence that various arts-based activities can improve QoL, relieve symptoms, and reduce reliance on medications.[12] Dance is an arts-based activity that can improve QoL, decrease symptoms of depression, and improve balance in healthy older adults[13-15], those with Parkinson disease,[16-21] and AD.[22, 23] Thus, dance simultaneously addresses two sets of prominent secondary symptoms in AD: 1) gait and balance and 2) neuropsychiatric symptoms.

2.2 Study Rationale

Changes in gait, balance, and neuropsychiatric symptoms that accompany dementia decrease QoL and increase the need for formal care. PWD are at increased risk for hospitalization from falls relative to their non-demented peers.[24-26] The increased risk of falls in PWD is likely due to well-documented changes in balance and gait. In PWD, fall risk is associated with the same measures as in non-demented older adults, such as postural sway, stance, and gait speed.[27, 28] PWD have lower scores on the Short Physical Performance Battery (SPPB),[28, 29] a global measure of mobility disability risk that assesses balance, strength, and gait speed.[30] They also show a 32% increase in postural sway assessed with a force plate.[31] Changes in gait speed are common[29, 32, 33] and can precede dementia onset.[34-40] Other gait changes include increased stride variability,[33] increased compensation movements,[41] and decreased stride length in single and dual-task conditions.[29, 32] Changes in gait are detectable early in the course of AD and decline further as dementia advances.[42, 43] Gait speed changes in PWD correlate with beta amyloid accumulation using positron emission tomography,[44] and increased white matter lesion burden and decreased grey matter in motor-related regions on MRI.[45]

Neuropsychiatric symptoms such as higher levels of depression, anxiety, and apathy are prevalent in PWD, with estimates ranging from 40-73%.[46] There is a clear link between neuropsychiatric symptoms in the PWD and increased CG burden. In one study, subclinical anxiety or depression added 10 hours of caregiving each week, and the added amount of caregiving approximately doubled if neuropsychiatric symptoms reached clinically significant levels.[10] Dementia caregivers are more likely to visit the emergency room or be hospitalized if the person they care for is depressed or has

behavioral disturbances.[11] In addition, caregivers are more likely to place a PWD in a nursing home if they report being stressed by neuropsychiatric symptoms.[9]

Dance can improve symptoms of depression and improve gait and balance. There is growing evidence that dance improves or maintains physical function, mood, and QoL in older adults. In a longitudinal observational study evaluating relationships between leisure activities and risk of dementia, dancing was associated with reduced risk of dementia.[13] Older dancers have better gait and balance in cross-sectional studies,[14, 47] and participating in dance interventions (tango, folkloric) is associated with improved balance and gait[18, 48, 49] mental health and depression,[18, 50, 51] and QoL.[18, 50, 52, 53] In people with Parkinson disease (PD), the second most common neurodegenerative disease in older adults after AD, group-delivered dance classes in ballet, modern dance, Argentinian tango, and other forms of social and ballroom dance improved balance, gait, and QoL.[16-21] A recent review of controlled trials[20] found that in people with PD, dance improves balance and QoL more than common forms of aerobic exercise such as cycling and walking. Evidence of the effects of dance on PWD is limited, yet aligns with the findings from older adults and people with PD. **In PWD, dance can improve QoL, gait and balance,**[54] **and symptoms of depression.[22, 23]**

Improvisational dance may have unique benefits for older adults with neuro-degenerative disease. Improvisation is the ability to create new gestures and movements spontaneously.[55] Improvisation can be a part of many different art forms. However, improvisational dance can be practiced as a specific dance form. The objective in improvisational dance is that choreographed or prescriptive movement is replaced by the possibility for multiple physical responses. Improvisation does not mean that people are free to do whatever they want; material may be unplanned, but it is not random.[56] Instead, improvisation allows movers to make choices within a structured environment of select constraints.[57, 58]

Two key differences that distinguish teaching improvisational dance as the primary dance form from encouraging improvisation around another form of dance are 1) the use of auditory cueing and music, and 2) repetition of choreographed or codified dance movements. In improvisational dance, verbal auditory cueing is used to convey improvisational ideas that elicit movement from students in the class. Because verbal auditory cueing does not instruct explicit movements, participants self-select motor strategies in response to the prompt that vary in terms of shape of movement, spatial usage, and timing. Unlike many other forms of dance or exercise, there are few specific movements that are repeated or over-trained in this form of dance.

Improvisational movement is particularly well-suited for people with dementia because 1) it does not rely heavily on memory; 2) it can be seamlessly adapted to include students sitting, standing, or moving around the room; 3) it is cognitively challenging; and 4) it fosters a social, playful atmosphere.

Duration of Intervention. Intervention duration (8 weeks in the pilot, 12 weeks proposed): The duration of the pilot was largely dictated by our pilot funding timeline, but it is also supported by literature. There is no consensus on optimal duration of a dance intervention with quality of life and biomarker outcomes in

cognitively impaired participants. Determination of optimal intervention time is complicated by the variability in the dance literature in terms of population (Parkinson's disease, stroke, cancer, youth, older adults, etc.), outcomes (gait, balance, UPDRS, falls, depression, various forms of quality of life, etc.), and form of dance studied (Tango, ballroom, social dance, folkloric dance, ballet, etc.).

The literature on Parkinson's disease (PD) and dance is the most established body of work. One study examined effects of Tango on physical function at baseline, 3 months, 6 months, and 12 months.[59] Significant improvement was seen at 3 months and the largest gains in improvements for the Unified Parkinson's Disease Rating Scale (UPDRS) and gait speed were seen by 6 months. This study is in a different population and used different outcome measures than the proposed trial, but supports the idea that collecting data beyond 8 weeks may increase the observed effect size.

We know of only 3 published dance interventions in people with dementia. The first two met twice a week for 6 weeks. One looked at solely qualitative outcomes (n=7),[23] so it is not possible to evaluate magnitude of effect size. The other reported robust effects of poco poco dancing (n=44) versus a relaxation control (n=40) on quality of life measured with the QOL-AD (η^2=0.29, $p<0.001$) in Malaysian older adults with cognitive impairment living in government-run residential homes. However, the authors describe the method as "quasi-experimental" and the methods and population are not thoroughly described.[22] The third study examined the effects of a twice-weekly 12-week salsa dancing intervention in a single 84-year old woman with Alzheimer's disease.[54] Outcomes were measured at baseline, 6 weeks, and 12 weeks. Scores on the Berg Balance scale, 6-minute walk test, 10 meter walk test, and timed up and go test all continued to improve between 6- and 12-week time points. This supports the idea that increasing the length of intervention to 12 weeks may increase the observed effect size.

None of these studies had brain imaging or other biomarker outcomes. A recent review of the effects of dance in older adults found no published trials of neurobiological factors.[60] **The proposed study will provide important, first-ever data about the effect sizes for neurobiological outcomes in a randomized, controlled trial of dance in older adults with cognitive impairment.**

Potential Risks. The movement class has been taught safely to groups with Parkinson disease for 5 years now in the community, and was completed safely in the pilot study by people with early-stage memory loss. However, as with any class that involves moving, there is a risk of tripping, falling, or temporary muscle soreness. To protect against fall risk, all exercises in the movement arms can be adapted for sitting; standing or walking are always optional. Participants will be encouraged to pay attention to their own body and make movements that feel safe for them.

3. STUDY DESIGN

We will use a 2x2 factorial design to test the separate and combined effects of social engagement and dance movement on QoL in 120 community-dwelling older adults adjudicated as having mild cognitive impairment (MCI) or early-stage dementia of the presumed AD, mixed AD/vascular type, or vascular dementia. Participants will be

randomized to one of four 12-week interventions (n=30 PWD per group): 1) Movement Group 2) Movement Alone, 3) Social Group, or 4) No Contact Control. The primary outcome of the study is QoL in the PWD. Secondary outcomes include gait, balance, neuropsychiatric symptoms, and functional brain imaging. Study measures will be collected at an academic medical center. Study interventions will take place in the community, at the academic medical center, or in the case of virtual intervention, in the participant's home environment.

The entire trial will last for 4 years. Enrollment is planned to occur over 3.5 years. Individual participants will be enrolled in the trial for up to 9 months. Study staff will be blind to each individual's group assignment at baseline. Two study staff will be unblinded after baseline testing for the purpose of scheduling and reminder calls during the intervention. Participants in MG, MA, and SG intervention arms will complete two 1-hour intervention sessions each week for 12 weeks, or 24 sessions within 13 weeks (to allow for illness, etc.) before follow-up testing. Participants randomized to the NC arm will be asked to maintain current medical treatment and lifestyle for 12 weeks.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Recruitment. Participants will be recruited through the WFSM Memory Assessment Clinic (MAC) and the WFSM Alzheimer's Disease Core Center (ADCC). The assessments in these two settings are highly overlapping and will ensure consistency in diagnosis. People who are adjudicated within the previous year as having MCI or early-stage dementia of the AD, vascular, or mixed AD/vascular type and their CGs will be invited to participate. The study aims to recruit up to 120 men and women with dementia over 3.5 years. Of the 400 older adults seen annually in the MAC, about 160 are diagnosed with dementia (all causes), 200 with MCI, and 40 are judged to be unimpaired. The recently NIH-funded WFSM ADCC has characterized and currently follows 250 older adults at high risk of or with dementia through their Clinical Core, and over the next year an additional 200 individuals will be added to the cohort. Co-investigator Laura Baker, PhD, is Associate Director of the ADCC and will ensure appropriate participants are available for the proposed study. Additional participants recruited through the community will be adjudicated through the ADCC.

Adjudication of cognitive status. Patients in the MAC and the ADCC undergo a cognitive evaluation that includes a neuropsychological test battery, functional status questionnaires completed by a proxy, and a history and physical by a board-certified geriatrician. Persons without recent imaging or blood work to rule out reversible causes of cognitive impairment receive standard blood assays and an MRI (or CT scan if MRI is contraindicated). After reviewing all data and in consultation with the diagnostic team, dementia experts assign a diagnosis of AD, other forms of dementia, MCI, or normal cognition using Alzheimer's Association/NIA criteria.[61] The cognitive test battery consists of tests of naming, word fluency, working and episodic verbal and visual memory, and global cognition. Depression and other psychiatric symptoms, functional independence, and CG assessment of cognitive and physical function are also assessed with interviews and questionnaires. Participants will be recruited from the MAC or the ADCC after their routine evaluation and diagnostic

classification. New participants recruited from the community will have their intake and diagnostic screening performed through the ADCC. If a potential participant has been previously given an eligible diagnosis of dementia, they may be given an MMSE to confirm they are still within the range of study eligibility rather than a full cognitive testing battery and adjudication. If they have previously received a consensus diagnosis of MCI, a MoCA may be administered to assess current global cognitive function to ensure that they still meet eligibility criteria. If the MoCA results in a score that is outside the eligibility range or changes more than 3 points, a full cognitive screening will be repeated. Once a diagnosis of dementia is given, it is virtually impossible for cognitive status to improve. Requiring people with established dementia to complete a full battery of cognitive testing can cause extreme distress in the PWD and yet provides little meaningful additional data in the context of establishing eligibility for this study. Current cognitive functioning will still be assessed with the RBANS pre- and post-intervention.

4.1 Inclusion Criteria

Participants must meet the following inclusion criteria to participate in this study:

- The person with dementia must be:
    - Age 60-85 years
    - Adjudicated as having mild cognitive impairment or early-stage dementia of the predominantly AD, vascular, or mixed AD/vascular type within 1 year of beginning the study. If adjudication is older than 1 year, it may be repeated, or if the person has been diagnosed with dementia, an MMSE may be administered to confirm the participant falls within the eligibility scores for the study. The adjudication process is described more fully in section 6.2.1.
    - English speaking
    - Able to undergo an MRI scan
    - Have a study partner who is around the PWD approximately 10 hours per week and is willing to be an active study partner
    - Have a study partner(s) who can regularly accompany the PWD to intervention sessions. With approval from the study team, this may be a different study partner(s) than the study partner reporting on the behavior/mood of the PWD. Different partners may accompany the PWD to any given session as long as a partner is present.
    - Not enrolled in an another interventional study for at least 3 months prior to beginning this study.
    - Willing to participate in interventions from home using a virtual platform if public health concerns exist. Access to internet and an appropriate device will be assessed. The study team can provide temporary internet access and a loaned device to support the participant if they do not have technology access and are willing to use

the equipment.

The CG must be:

- Willing to be an active study partner
- Spend approximately 10 hours a week with the PWD
- A caregiver may be younger than the PWD and therefore may have the potential to be pregnant. No contraception is necessary for a caregiver to participate, as they will not be asked to complete any procedures known to present a risk. The MRI will only be completed by the PWD.
- Willing to participate in interventions from home using a virtual platform if public health concerns exist. The study team will provide temporary internet access and a loaned device to support the participant if they are willing to use the equipment.

4.2 Exclusion Criteria

Participants will be excluded if any of the exclusion criteria listed below are present at study entry:

- The PWD has/is:
  - Currently symptomatic or cortical stroke deemed exclusionary by the study physician. Persons with subcortical stroke that is resolved or largely asymptomatic may be included if found to be appropriate by the study physician. Due to the high variability in residual symptoms based on factors such as location, size, and time since stroke, these will be reviewed on a case-by-case basis by the study physician to determine whether these factors may affect study outcomes, aims, or integrity.
  - Other causes of dementia, such as Lewy body, fronto-temporal, or Parkinsonian dementia
  - Other neurological diseases, such as amyotrophic lateral sclerosis (ALS), Parkinson disease, or multiple sclerosis (MS), etc.
  - Any major medical problem that could reasonably affect cognitive or brain imaging measures used to determine eligibility or outcomes, or severely impact attendance, such as current cancer treatment
  - Taking medication that could negatively influence safety during the intervention, such as taking regularly prescribed benzodiazepines during study intervention times (see Table 1 below)
  - Any reason for which the study doctor or personal physician feels that the intervention is contraindicated for the participant.

- Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements
- Unwilling to provide consent or assent for study participation
- Planned extensive travel during the study period

- The CG has/is:
  - Unable or unwilling to be an active study participant
  - Unwilling to provide consent for study participation
  - Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements
  - Any major medical problem that could reasonably affect ability to attend study and intervention visits, such as cancer treatment
  - Taking medication that could negatively influence safety during the intervention, such as taking regularly prescribed benzodiazepines during study intervention times (see Table 1 below)
  - Planned extensive travel during the study period without availability of an alternate study partner

The following medications will be considered exclusionary if they are regularly taken during intervention times:

Table 1. List of medications that are exclusionary if given during intervention times

Benzodiazepines	• Alprazolam *(Xanax)* • Chlordiazepoxide *(Librium)* • Clonazepam *(Klonopin)* • Diazepam *(Valium, Diastat)* • Flurazepam (*Dalmane)* • Clorazepate (*Tranxene)*	• Lorazepam *(Ativan)* • Nitrazepam *(Mogadon)* • Oxazepam *(Serax)* • Quazepam *(Doral)* • Temazepam *(Restoril)* • Triazolam *(Halcion)*
Hypnotics	• Zolpidem *(Ambien, Zolpimist, Intermezzo)*	
Barbiturates	• Phenobarbital	• Pentoparbital *(Nembutal)*
Anticholinergics	• Diphenhydramine *(Benadryl)*	• Hydroxyzine *(Vistaril)*

	• Doxylamine *(Unisom)*

4.3 Study Enrollment Procedures

4.3.1 Identification and recruiting of candidates for trial

Identification and recruitment of potential study participants will occur 4 ways:

- **Referral through the WFSM Memory Assessment Clinic (MAC)**. The MAC is an outpatient clinic staffed by the Section on Gerontology and Geriatric Medicine that specializes in diagnosis of cognitive complaints in older patients. Patients in the MAC undergo a cognitive evaluation that includes a neuropsychological test battery, functional status questionnaires completed by a proxy, and a history and physical by a board-certified geriatrician. Persons without recent imaging or blood work to rule out reversible causes of cognitive impairment receive standard blood assays (including thyroid hormone and vitamin B12 levels) and an MRI (or CT scan if MRI is contraindicated). After reviewing all data and in consultation with the diagnostic team, a diagnosis is made using current criteria. Of the 400 older adults seen annually in the MAC, about 160 are diagnosed with dementia (all causes), 200 with MCI, and 40 are judged to be unimpaired. The MAC neuropsychological test battery consists of the Mini Mental State Exam, Digit Symbol Coding, Category Fluency-Animals, Rey Auditory Verbal Learning Test, Clock Drawing, Rey-Osterreith Complex Figure, Logical Memory I and II, Trail Making Test, and Boston Naming Test. In addition, the Geriatric Depression Scale, Geriatric Anxiety Scale, Katz Activities of Daily Living Scale, the Lawton Instrumental ADL Scale and the Neuropsychiatric Inventory Questionnaire are collected.

  Participants will be recruited from the MAC after their routine evaluation and diagnostic classification. MAC staff will provide a list of patients who have been adjudicated as having MCI or early-stage dementia believed to be primarily of the Alzheimer's, vascular, or mixed Alzheimer's and vascular type. Study staff will review the information provided and contact participants who may qualify for the study to invite them to participate. An Institutional Review Board (IRB)-approved letter will be sent to potential participants to briefly inform them about the study. The letter will be followed by a phone call inviting them to participate. Those who are interested in participating will be screened using an IRB-approved telephone screening questionnaire to assess eligibility.

- **Referral through the Alzheimer's Disease Coordinating Center (ADCC).** Cognitive assessments through the MAC and ADCC are highly overlapping and will ensure diagnostic consistency. The ADCC neuropsychological test battery is based on the Uniform Data Set (version 3) from the National Alzheimer's Coordinating Center (NACC). It is designed to test multiple aspects of cognitive function and typically includes the Montreal Cognitive

Assessment (MoCA), Story Recall, Benson Complex Figure, Trail Making Test, Category Fluency, Phonemic Fluency, Number Span (forward and backward). In addition, function, behavior, and mood are assessed through the Clinical Dementia Rating Scale (CDR), ADL checklist, IADL checklist, GDS, and NPI. Participants referred from the ADCC have had thyroid hormone and vitamin B12 levels measured.

ADCC staff will provide a list of patients who have been adjudicated as having MCI or early-stage dementia believed to be primarily of the Alzheimer's type after adjudication or from existing databases of participants who are enrolled in non-interventional studies or who have completed an interventional study 3 months or more in the past. Study staff will review the information provided and contact participants who may qualify for the study to invite them to participate. An IRB-approved letter will be sent to potential participants to briefly inform them about the study. The letter will be followed by a phone call inviting them to participate. Those who are interested in participating will be screened using an IRB-approved telephone screening questionnaire to assess eligibility.

- **Referral from other clinics.** Participants may be referred from other clinics as long as the adjudication procedure is similar to that used in the MAC or ADCC. These participants must have an appropriate diagnosis after assessments including a cognitive battery, bloodwork, exam by a physician, and neuroimaging.
- **Referral from the community.** Participants who are not part of the MAC or ADCC or who have not been diagnosed with a memory concern may also wish to volunteer for the study. Community awareness of the study may occur through public talks, community contacts, mention in newsletters from the Sticht Center on Aging, press coverage, or IRB-approved advertising, such as fliers. If someone from the community wishes to be part of the study, they will first be adjudicated through the ADCC.
- If a participant has completed a full approved cognitive assessment as described above and received a diagnosis of dementia, cognitive eligibility may be assessed by confirming the diagnosis with an MMSE for individuals with a dementia diagnosis or MoCA for individuals with an MCI diagnosis rather than re-administration of the full cognitive testing battery.

4.3.2 Documentation of ineligibility or non-participation

People who decline to participate will be asked to provide information about reasons for declining. Information from the telephone screening instrument will be data entered into REDCap for the purpose of assessing rate of successful recruitment and barriers to participation, as well as to prevent re-contacting an individual if they are referred more than once. Ability to download identifying information such as name, address, and phone number will be restricted to the PI in REDCap.

People who qualify for the study, but choose not to participate, or who drop out after randomization will be asked to provide reasons for non-participation. This information

will be recorded in the study log and will be data entered into REDCap for the purposes of assessing barriers to participation and reporting on study retention.

4.3.3 Consent procedures

Signed informed consent will be obtained from each subject. The primary outcome for this study is QoL in the PWD. However, the CG will be an active participant. Important data will be collected through the CG about the PWD, and other important data will be collected about the CG for the purpose of testing for alternate hypotheses and controlling for factors such as caregiver personality and mood that might influence the CG's reports about the PWD. Therefore, written informed consent will be obtained from each PWD and CG. The CG will report important information about the PWD including recent cognitive symptoms and mood, as well as medical history for inclusion/exclusion purposes and safety of testing procedures such as MRI. If the CG is incapable of reliably reporting medical history, this information may be collected from a family member via telephone.

The informed consent process will follow the procedures of the WFU IRB. The study interviewers will explain the purpose, methods and extent of the study to prospective participants. The potential participant is asked to read the informed consent form and ask questions. The form is written in simple easy to understand language. We require study staff to review all of the key aspects of the study verbally with the potential participants. Staff then question potential participants to ascertain whether they have understood the information. Potential participants who are illiterate or have impaired vision must have the consent read to them, followed by review of the checklist, opportunity for questions, and discussion. Because participants in this study are at early stages of memory loss, some PWD may have a legally authorized representative while others will not. We will request that the CG be present during consent regardless of whether they are a legally authorized representative or not to make sure the interests of the PWD are protected. The CG will be asked to sign the consent form to document their presence during consent even if they are not a LAR. Consent may be administered virtually following approved IRB protocols if public health concerns exist.

A copy of the signed and dated consent form will be given to participants, and the original document will be placed in subjects' individual study files, which will be stored in a secure location. In compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, we will access personal health information only after obtaining informed consent.

4.3.4 Randomization procedure

After completing the second study visit, participants will be randomized to their study condition (Movement Group, Movement Alone, Social Group, No Contact) through a computerized randomization scheme with blocking stratified by gender. Recruitment will occur in phases. Randomization will be blocked in blocks of 32 that each correspond with a wave of data collection; each block will randomize 4-10 dyads to each of the 4 study groups.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The study will have 4 arms: Movement Group (MG), Movement Alone (MA), Social Group (SG), and No Contact (NC) control.

Dosing schedule. The aim of all 3 intervention arms (MG, MA, SG) is for participants to meet for 1-hour sessions 2 times a week for 12 weeks (24 sessions). Participants will have the option of completing the 24 sessions within 13 weeks to allow for make-up days for missed classes due to illness, weather events, or other conflicts. All efforts will be made to accomplish the full 24 sessions in 12 weeks. An unblinded staff member will contact participants regularly to remind them to attend.

Group interventions will occur in waves. In order to allow adequate resources for pre- and post-intervention testing with a wave study design, entry into MG and SG arms will be staggered across a month if needed. Slightly staggering group intervention entry (and therefore intervention completion) will prevent a situation where follow-up testing might be delayed due to limitations on scanner time or coordinator effort. To accommodate staggering of group intervention entry, group interventions may span 17 weeks in total. Follow-up testing for each dyad will take place between days 0-7 and again between days 1-21 after the last intervention session. Dyads will be asked to continue the intervention to conclusion to maintain a stable group structure.

Location. All interventions will take place in spaces that are safe, well-lit, have convenient parking, and are accessible for a range of mobility. The spaces planned include a local dance studio in close proximity to WFSM (Academy of Dance Arts, 1425 West First Street, Winston -Salem, NC 27101), a space downtown owned by Wake Forest University (WFU Brookstown Campus, 200 Brookstown Avenue, Suite 302, Winston-Salem, NC 27101), space on the WFSM campus (Piedmont Plaza II, 2000 West First Street, Winston-Salem, NC, 27104), and Old Town Recreation Center, 4550 Shattalon Dr, Winston-Salem, NC 27106. Additional spaces may be added as needed to ensure the convenience and safety of participants. For dance interventions, participants will be given options of spaces to dance in that are free from obstacles, have a sturdy chair(s) with no arms, and a means for playing music or recordings of dance instructors.

As of March 2020, all in person visits were suspended due to COVID-19. A pilot study was conducted to validate the administration of the intervention visits via video conferencing software. Dependent upon federal, state, and local recommendations, all intervention visits may be conducted remotely. To ensure safety of all participants, the home environment will be assessed for safety in the same way public spaces are assessed. Study staff will confirm there is enough open, uncluttered space where movement sessions could safely take place in the home. If appropriate chairs are not present, staff will provide them for the duration of the interventions.

Movement Group. The MG will participate in 1-hour group improvisational dance [62, 63] lessons 2x/week for 12 weeks. We have published the dance method and

theory,[62] and describe it briefly here. Improvisational dance classes are grounded in 4 principles that shape the tone of the class and result in a sense of social belonging: **non-judgment, non-competitiveness, curiosity,** and **playfulness**. The following training strategies are used to maintain: **active imagination, variability, and pacing.**

- **Active imagination.** Working with imagery is crucial in improvisatory practice. Verbal auditory cues are used to create movement scenarios that cue or activate the motor imagination. Verbal auditory cueing takes primacy over rhythmic entrainment to music, although the music itself may be used as an improvisatory cue. The teacher calls the cue, may demonstrate an optional response, and asks participants to join in with their own gestural inventions. As an example, students might be prompted during the seated warm-up to recreate a beach scene. Verbal auditory cues direct motor imagination by using rich language to act out a beach scenario - laying down beach blankets, putting on sunscreen, opening a picnic basket, setting out lunch on a blanket, running into the ocean, avoiding the shark swimming towards them, etc.
- **Variability.** The improvisational method does not aim to learn a specific movement pattern and habituate to it. Cues are delivered quickly, one after another.[64] Within an average of two minutes, tasks requiring quicker decision-making are introduced. Physical challenges are advanced by dual- and multi-tasking, such as being asked to direct traffic with the right side of the body while picking apples with the left.
- **Pacing.** This is the rate at which new movement prompts are presented. Quick changes in pace avoid defaulting to habitual responses, thereby facilitating new movement options. Participants cannot rely on copying another, memory, or anticipation to address the motor problem. Verbal cues might be delivered in a rapid-fire manner, for example, to keep participants from reflecting on movement choices, changing their minds, or becoming embarrassed or dissatisfied with the choice made.

Use of music. Music is used in different ways in the class. The playlist is random and variable; it may be unrelated to movement instruction and merely ambient. At other times, the music may be an improvisational cue. As examples, students may be asked to dance what comes to their minds listening to Otis Redding's "(Sittin' on) The Dock of the Bay" and then variations are cued from that initial movement, or "play" an instrument they can hear in a complex piece of classical or jazz music. Sometimes, participants themselves create movement through vocalizing or body-based percussive actions. Portions of the class also happen in silence. Unpublished video analysis of previous studies shows that participants are more likely to improvise than follow (entrain to) the beat of any music played.

Overall class structure. The general class structure has four phases. These include: **(1)** group warm-up in chairs positioned in a circle, **(2)** standing barre with solo- and partnering exercises, **(3)** moving as a group through free space (with and without a partner), and **(4)** recuperation and rest. If participants are unable for any reason to perform exercises at the barre or move through free space, **all exercises can be adapted for sitting**. The choice to stand or walk is always self-selected by the participant. In fact, this adaptation is common in the weekly community class that Ms. Soriano has taught for 5 years. Similar exercises may appear within each phase, creating a progression of motor skills, but the class series does not build

incrementally. Recuperative phases are essential to rest and recover metabolically and cognitively. These movements are slower, simpler, and often more familiar (e.g., seated hamstring stretch). The overall class structure remains the same when the class is presented virtually. However, group movements through free space will be adapted as needed for the home environment.

Movement Alone. The MA intervention is designed to capture the same dance movement and auditory stimuli as the group class without social interaction. Recordings of the dance instructors will be played that include the same range of prompts presented to group classes. This will ensure participants hear comparable music and receive comparable verbal auditory cues to prompt dance movements that students in the group class will hear without interacting with other people. Participants will be asked to follow the same schedule as participants in the MG arm and complete 2 one-hour dance sessions each week. A sample of each subjects' individual dance sessions will be video recorded. This recording will yield data that a trained student or staff member can view and code to document movement fidelity (e.g., that the person has responded to the dance prompts and for the purpose of comparing the amount of quality of movements that occur in individual vs. group dance settings). Study staff will check participants into the rooms and ensure that all equipment is working.

Social Group. As outlined above, four principles guide the overall tone of group dance class: non-judgment, non-competitiveness, curiosity, and playfulness. It is important the social intervention group recapitulates aspects of fun and playfulness as in the MG. Unstructured survey feedback about the dance group included "laughing", "made me laugh and have fun", and "the chance to be more creative and spontaneous." In our pilot study, the individual item on the QOL-AD that increased most in PWD who participated in the dance group was 'Ability to do things for fun'. A traditional education group, as is a control in many exercise intervention studies, would likely not provide such stimulus. Therefore, the social group will consist of improvisational party games to foster curiosity and playfulness, use imagery, and encourage non-judgment. Games that may be used include 'Balderdash', 'Wise and Otherwise', 'Pictionary', and 'Tell Me A Story' cards. These games will also use the same core strategies as the MG. Games will be varied within an hour-long session to incorporate pacing and variability into the social group. The social group will be led by the same instructors who lead the MG to control for effects of personality of the group leader. Social group games have been adapted as needed for use in a virtual environment. As examples, rather than having 'Tell Me A Story' cards dealt onto a shared table, the cards are scanned in and presented on a powerpoint slide. If a game requires physical materials that a participant may not have (for example, a white board), the materials may be purchased by the study team, appropriately sanitized, and delivered to participants prior to group sessions following appropriate health procedures.

Guidelines for Use of Appropriate Supportive Care. All study and intervention staff will be trained in CPR. Interventions will most often occur off the medical school campus. In the event of any emergency that requires medical attention during an intervention, regardless of whether it is related to the intervention, staff will be

instructed to call 911. The participant must agree to call 911 if they are conscious; medical treatment cannot be forced on a participant. This protocol also applies to virtual visits if a staff member observes a medical event that occurs in the home during a study intervention. Study visits will take place on the WFSM hospital campus. For a visit that occurs on the WFSM hospital campus, staff will be instructed to call the internal emergency number, 6-9111. All appropriate reporting procedures described in the DSMP will be followed after any adverse event.

5.2 Handling of Study Interventions

Completion of Study Intervention Accountability Records. Study staff and intervention staff will be responsible for documenting attendance. Each participant will have an attendance form where study staff will note whether or not they attended the intervention that day. In addition, for dance and social groups, the instructor will note a qualitative rating of engagement with the group on a Likert scale from 0-5. Study staff will document attendance of MA participants when they check them into their movement room for in-person intervention or when they log the participant into the videoconferencing software for virtual intervention. There will be a notes section for all participants where any other relevant observations can be recorded. When a session is video recorded, study staff will be responsible for archiving the video within 24 hours of collection and deleting it from the recording device. For participants completing the interventions virtually, on the dates when recording occurs, participants will be asked Likert-style questions about their perceived connection to the group, perceived connection to the instructor, enjoyment, and ease of use of technology.

Mechanisms for blinding study interventions. During screening and baseline visits, e.g., prior to randomization, study staff will be blinded to the randomization scheme. Therefore, group assignment will not be known during testing or assignment to groups. One primary study staff member and one backup team member will be assigned to be unblinded after baseline visits for the purposes of notifying participants of their study arm, coordinating intervention visits as needed, and making reminder calls. Intervention staff will not be performing any research assessments of participants and will not be blinded to group assignment.

Delivering Virtual Interventions

The process for delivering virtual interventions will be similar across intervention arms. Participants will be sent written materials and a video demonstrating how to use the videoconferencing software on their device. Separate instructions have been prepared for a range of brands, internet browsers, and devices. Prior to beginning any virtual intervention, staff trained in using the videoconferencing software will have a call with the PWD and CG to walk them through correctly accessing and configuring the videoconferencing software. This check will include:

- Ensuring video and sound connectivity
- Helping the participants locate a safe and appropriate space for the

intervention

- Helping the participants adjust the video and audio levels so that they can be seen and heard and so that they can see and hear the staff member
- Ensuring the participants know how to change relevant settings within the software, such as the view of the group

Prior to the intervention date, participants will be sent a secure link to the session. Staff will log on approximately 15 minutes ahead of the scheduled session time. A technical support team member will be present to address any technical issues that arise during the session. This team member will have the telephone contact information for all participants so they can be reached if their videoconferencing is not working correctly. A moderator will be present to greet participants as they enter the room, foster conversation, and give study-relevant reminders. An instructor will be present to lead the group. These roles will usually be filled by three separate people. However, if necessary, the role of technical support staff and moderator may be filled by one person. This format mimics the in-person format for group interventions, where a study team member is present to check participants in, a volunteer is usually present to provide additional support as needed, and the instructor is present to lead the group.

Delivering the Movement Group Intervention. Trained dance instructors will be responsible for administering the MG intervention and may be accompanied by assistants. Professor Soriano, the Co-PI, will be responsible for training any other dance instructors in the method they will be using. The instructor arrives prior to the class to arrange the chairs in a circle and prepare the music. Participants in the intervention will arrive at the specified location for class. When they enter the dance room, they will be greeted by the dance instructor and invited to sit and join the group. After the group has arrived, the instructor will begin the class as described above in section 5.1. Upon completion of the class, the instructor will immediately complete attendance sheets.

For virtual sessions, participants will receive a secure link to the movement session. Participants will be allowed to socialize and interact as they would in person until everyone arrives and the instructor is ready to begin the movement class. During the pilot testing of the virtual intervention, structured social interactions were piloted along with unstructured chatting. While some people enjoyed the structured interactions, the overall preference was for unstructured interactions. All other aspects of the protocol will remain the same – the instructor will greet the class by name and will complete attendance sheets and engagement ratings immediately after the class.

Delivering the Social Group Intervention. The same dance instructors who administer the MG will also administer the SG to control for effects of instructor personality. The instructor arrives prior to the class to ensure the room arrangement is correct and any supplies needed for the class are prepared. Upon completion of the class, the instructor will immediately complete attendance sheets.

For virtual sessions, participants will receive a secure link to the social group session. Participants will be allowed to socialize and interact as they would in person until

everyone arrives and the instructor is ready to begin the class.

Delivering the Movement Alone Intervention. Participants will contact study staff to reserve two 1-hour long blocks each week at an available site. Study staff will arrive prior to participants to make sure all equipment for presentation and recording is operating. Study staff will be present to check participants into the room, monitor for any adverse events, and document attendance. After the MA session is complete, study staff are responsible for transferring files if video has been taken to assess treatment fidelity, neatening the space, and locking any doors if necessary.

For virtual sessions, participants will receive a secure link to the virtual movement session. Study staff will greet them and will administer the pre-recorded classes and music through the videoconferencing software. As in the in-person intervention, the study staff will monitor for adverse events, document attendance, video record sessions, and transfer files appropriately.

Delivering the No Contact Control Arm. Participants in the no-contact control arm will be contacted by phone at least once a month by an unblinded study staff member. During this phone call, they will be asked a set of questions about their current health and lifestyle to assess whether they have had any major life events or have made any substantial lifestyle changes. Participants will be reminded to maintain their usual lifestyle.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Because movement classes can be completed seated, all movements are self-selected and voluntary, and the class does not require any strenuous cardiovascular engagement, medical limitations for participation are not extensive. Participants should continue any medications they are taking at enrollment (e.g., that are not exclusions for the study). Participants should always take rescue medications as needed. If a participant changes medications that will affect study outcomes or safety, they should inform study staff. Participants will be queried monthly about changes in health status during routine reminder phone calls and this will be documented.

5.3.2 Required Interventions

Participants are required to participate in the intervention arm to which they are randomized and to notify study staff of any major changes in their lifestyle or health status that might affect their safety to participate or study outcomes.

5.3.3 Prohibited Interventions

Participants are prohibited from participating in other interventional studies while enrolled in this study. They may participate in observational studies. All participants are requested not to begin any major changes in physical activity or diet outside of the study intervention. Participants are prohibited from participating if they are taking any medications during study intervention times that may interfere with their alertness or balance (e.g., benzodiazepines).

5.4 Adherence Assessment

Study and intervention staff will be responsible for documenting attendance. Each participant will have an attendance form where staff will note whether or not they attended the intervention. For dance and social groups, the instructor will note a qualitative rating of engagement with the group on a Likert scale from 0-5. Study staff will document attendance of MA participants upon check in. There will be a notes section for all participants where any other relevant observations can be recorded. Participants will also complete their own attendance sheet to encourage self-awareness of attendance. Good adherence will be defined as attending approximately 85% or greater of intervention sessions (that is, 20 of 24 sessions).

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Table 2. Assessments administered to PWD (including allowable windows)

Assessment	Source Data Type	Baseline 1 w/in 2 mos of phone screen and 14 weeks of intervention start	Baseline 2 w/in 6 wks of intervention start	Follow-up 1 0-7 days after intervention completion	Follow up 2 1-21 days after intervention completion
Alternative Uses Task	Paper		X		X
Apathy Evaluation Scale	Paper		X	X	
Blood draw - biomarkers	Lab Report	X		X	
Consent	Paper	X			
Contact Form	Paper	X			
Demographics	Paper	X			
Expanded Short Physical Performance Battery	Paper	X			X
Falls Efficacy Scale	Paper		X	X	
Fullerton Advanced Balance Scale	Paper	X		X	
Gait Speed/Variability	Electronic	X			X
Geriatric Anxiety Scale	Paper		X	X	
Geriatric Depression Scale	Paper		X	X	
Medical History/RX	Paper	X			
MoCA	Paper	X			X
MRI	Electronic		X	X	
Multisensory Reaction Time	Electronic		X		X
Philadelphia Mindfulness Scale	Paper	X			X
Postural Sway	Electronic	X			X
QOL-AD	Paper	X		X	
RBANS	Paper		X		X
Study Expectations	Paper	X			
Timed Up and Go	Paper	X			X

Table 3. Assessments administered to CG

Assessment	Source Data Type	Baseline 1 w/in 2 mos of phone screen & 14 wks of intervention start	Baseline 2 w/in 6 wks of starting intervention	Follow-up 1 0-7 days after intervention completion	Follow-up 2 1-21 days after intervention completion
Alternative Uses Task	Paper		X	X	
Apathy Evaluation Scale (AES)	Paper		X	X	
Blood draw - biomarkers	Lab Report	X		X	
Consent	Paper	X			
Contact Form	Paper	X			
Demographics	Paper	X			
Expanded Short Physical Performance Battery	Paper	X		X	
Falls Efficacy Scale	Paper		X	X	
Fullerton Advanced Balance Scale	Paper	X		X	
Gait Speed/Variability	Electronic	X		X	
Geriatric Anxiety Scale	Paper		X	X	
Geriatric Depression Scale	Paper		X	X	
Medical History/RX	Paper	X			
MoCA	Paper	X			X
Multisensory Reaction Time	Electronic		X		X
NEO-FFI	Paper		X		
NPI-Q	Paper		X	X	
Philadelphia Mindfulness Scale	Paper	X			X
Postural Sway	Electronic	X		X	
RBANS	Paper		X		X
SF-36	Paper		X	X	
Study Expectations	Paper	X			
Timed Up and Go	Paper	X			X
Zarit Caregiver Burden Scale	Paper		X	X	

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Consenting Procedure

Telephone screening will take place after verbal informed consent using an IRB-approved script and form. Participants referred from the MAC or ADCC will receive an IRB-approved letter in the mail to let them know that study staff plan to contact them by phone about study participation. Study staff will read an IRB-approved telephone screening script and form, and explain that information from the phone screening will be kept for purposes of understanding barriers to study participation and to prevent duplicate contacts.

Written, informed consent will be collected from participants referred from the MAC or ADCC who qualify after telephone screening at the outset of Baseline Visit 1 (BV1). Participants from the community who qualify after telephone screening will provide written, informed consent at the outset of the screening visit (SV). Consent may be administered virtually following IRB-approved protocols if public health concerns exist.

Outcomes for the PWD are the primary target for this study. However, the CG will be an active participant. Important data will be collected through the CG about the PWD. Other important data will be collected about the CG for the purpose of controlling for factors that might influence the CG's reports about the PWD and testing for alternate hypotheses. Therefore, written informed consent will be obtained from each PWD and CG. The PWD and CG have separate consent forms, as study procedures differ. For example, the PWD will receive an MRI scan and the CG will not. If there are multiple caregivers involved in the life of the PWD, a primary caregiver will be identified to report on the mood and behavior of the PWD in baseline and follow-up study visits. If needed, other reliable, involved caregivers may accompany the PWD to intervention sessions. This meets the scientific goals of the study by providing data on the CG reporting on the mood and behavior of the PWD, and meets the goals of the intervention by including a reliable, involved CG in the intervention.

The informed consent process will follow the procedures of the WFU IRB. Study staff will explain the purpose, methods and extent of the study to prospective participants. The potential participant is asked to read the informed consent form and ask questions. The form is written in simple easy to understand language. We require study staff to review all of the key aspects of the study verbally with the potential participants. Staff then question potential participants to ascertain whether they have understood the information. All study staff will be trained to administer the consent including practicing in front of a lead study coordinator and/or the PI. A copy of the signed and dated consent form will be given to participants, and the original document will be placed in subjects' individual study files, which will be stored in a secure location. Consenting will be done with both the CG and PWD present. Because this study targets MCI and early-stage dementia, the CG may be a legally authorized representative for some PWD while others will not yet have a legally authorized representative. In all cases, the CG will be asked to co-sign the consent

form for the PWD, either as a study partner or a legal representative to ensure that the best interests of the PWD are protected.

Documentation of signed consent will be kept by 1) the original consent form, 2) a documentation of consent form that includes the name of the participant, and 3) a documentation of consent form with study number only to be kept with the file in long-term storage.

Screening

Telephone Screening. All participants will be screened over the telephone prior to any in-person screening to reduce burden on prospective participants and study staff by eliminating potential participants with known exclusions. Study staff will use an IRB-approved script and telephone screening questionnaire. Questions will be asked of both the CG and PWD. Follow-up phone calls will be made if needed to speak with both the CG and PWD. Prospective participants volunteering from the community will be asked to complete the Telephone Interview for Cognitive Status (TICS) as a brief cognitive screening tool. Based on published cutoff scores, a TICS score between 34 and 15 will qualify someone to participate in the full cognitive screening. Phone screening will be completed no more than 2 months before the first baseline testing visit.

Adjudication of Cognitive Status. The PWD enrolled in the study is required to meet criteria for Mild Cognitive Impairment or early-stage dementia believed to be either Alzheimer's disease, vascular, or mixed dementia. Participants referred through the MAC or ADCC will have already completed a battery of cognitive, functional, and medical tests and had cognitive status adjudicated by consensus within the past year.

Potential participants who previously completed full cognitive testing, but whose testing is outside of the 1 year time window may be asked to complete a global cognitive screen only (MMSE for those diagnosed with dementia, MoCA for those with MCI). If the results of the global test are within inclusion ranges and staging guidelines, participants will be deemed eligible for full study inclusion. In the case of individuals with MCI, if their score changes more than 3 points or is outside the eligibility criteria, a full cognitive screening will be performed.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

When participants have completed the baseline visits and have been randomized, they will be considered to be enrolled in the study.

Baseline Assessments

Participants who have passed the telephone screening and have been adjudicated to have an appropriate cognitive status will be invited to complete two baseline visits. Participants who were adjudicated through the MAC or ADCC will complete their

written, informed consent at the first baseline visit, as well as complete a thorough medication review and medical history. If an exclusionary medication or diagnosis is disclosed face-to-face that was not reported over the phone, the study visit will be ended and the participant will not be enrolled in the study. Baseline assessments will be completed within the 6 weeks prior to intervention initiation. The exact ordering of tasks may vary to accommodate scheduling needs. For instance, the MRI scan may take place on a third visit if that is preferred by the participant. Any questionnaires administered, such as health history, quality of life, depression and anxiety questionnaires, etc. may be administered via telephone or videoconferencing if needed in response to the current public health situation. Virtual administration of these measures may be used to limit participant time in a clinical setting. If in-person study visits are completely suspended in response to a public health situation, as much data as possible will be collected virtually as close as possible to the appropriate timepoint. If the virtual intervention is able to continue the full duration as expected, the primary outcome (QOL-AD) will be collected per protocol 0-7 days after completing the intervention and any other measures possible to collect will be collected with the timeframe specified per protocol. Because the intervention is virtual, we do not anticipate it will have to be suspended. However, if the intervention is suspended for any reason and is unable to resume, all measures possible will be collected per protocol timeframe treating the day of determination that the study is unable to resume as day 0.

The following assessments of the PWD will take place during Baseline Visit 1 as outlined in Table 2 in section 6.1 after IRB-approved, written informed consent:

- **Fasting blood draw.** Planned lab tests of the blood collected in the morning after fasting will include a basic metabolic panel (BMP), complete blood count (CBC), fibrinogen, total cholesterol, HDL, triglycerides, albumin, DHEA sulfate, insulin, hemoglobin A1c, cortisol, and C-reactive protein (CRP).
- **Quality of Life (QoL-AD).** We will measure QoL in PWD using the QOL-AD, a measure of QoL validated in people with dementia who had Mini-Mental State Exam (MMSE) scores as low as 10.[65-67]
- **Fullerton Advanced Balance Scale (FABS).** Measures balance using 10 different performance-based tests.[68]
- **Postural sway** during quiet stance will be assessed from Center-of-Pressure (COP) trajectory data collected at 100 Hz using an Advanced Mechanical Technology Incorporated (AMTI) AccuSway biomechanics force platform. COP data will be collected in a series of 10 30-second trials. Additionally, we will complete 5 30-second trials on a foam mat placed on top of the force platform. Statistical mechanics techniques will be applied to the anteroposterior and mediolateral [69-74] directions of the COP trajectories; studies have linked these to clinical measures of balance performance and/or fall risk.
- **Gait speed and variability** will be assessed over 4m 4 times at usual pace and 4 times at fast pace using an instrumented mat (GAITRite System), which

provides data on average step and stride length, initial and terminal double support time, and variability in these measures. We will also ask participants to walk at usual pace over the instrumented mat while performing a cognitive task, with no instructions on which task to prioritize.[75, 76]

- **Expanded Short Physical Performance Battery (eSPPB).** The SPPB[30] is a brief test of global mobility function with excellent test-retest and inter-examiner reliability;[77] is sensitive to change;[78] is safe, and is a robust predictor of future physical disability and death.[30] To avoid ceiling effects, we will use an expanded version (eSPPB)[79] . The resulting score is normally distributed, continuous, and shows greater sensitivity to change.[80]
- **Timed Up and Go (TUG)[81].** Measures the time for a participant to rise from a chair, walk 3m, turn, walk back to the chair, and sit. The TUG has been shown to have good specificity and sensitivity for identifying older adults at risk of falling. Participants will also complete the cognitive TUG (cTUG) and manual TUG (mTUG).
- **Philadelphia Mindfulness Scale (PHLMS). [82]** Unstructured written feedback from a previous pilot of this improvisational movement method in community-dwelling older adults suggested that participants showed greater body awareness of self and others, as well as less judgment of self and others. Therefore, we chose to include a mindfulness scale that specifically targets attentional awareness and judgment.
- **Montreal Cognitive Assessment (MoCA)** a test of global cognition

The following assessments completed by the CG will take place during Baseline Visit 1 (BV1):

- Fullerton Advanced Balance Scale
- Philadelphia Mindfulness Scale
- Postural Sway
- Gait Speed and Variability
- Expanded Short Physical Performance Battery
- Timed Up and Go
- Montreal Cognitive Assessment (MoCA)

The following assessments of the PWD will take place during Baseline Visit 2 (BV2):

- **Abbreviated cognitive battery.** We do not hypothesize that dance affects the underlying disease course, and therefore do not expect improved cognition. However, previous work has shown better cognition in older social dancers[13, 83] and improved cognition in response to dance in healthy elderly.[84, 85] To control for any potential relationships between study

interventions and cognition, an abbreviated cognitive battery, the Repeatable Battery for Neuropsychological Status (RBANS) will be administered to CG in Baseline Visit 2 and PWD and CG in Follow-up Visit 2. The RBANS takes approximately 30 minutes to administer, tests multiple cognitive domains, includes parallel forms for repeated test administration, and has been used in multiple clinical trials.[86, 87]

- **Falls Efficacy Scale International (FES). Falls Efficacy Scale International (FES-I)[88].** A 16-item scale to assess fear of falling where higher scores reflect a higher fear and risk of falling.
- **Geriatric Depression Scale (GDS) and Geriatric Anxiety Scale (GAS).**[89] PWD be asked to complete brief screening tools to assess depression and anxiety.
- **Apathy Evaluation Scale (AES).** A short form will be used that has been modified for use with PWD.[90]
- **Alternative Uses Task (AUT).[91]** A commonly used test of divergent thinking that asks participants to list as many uses as possible for common objects. The total number of items generated is the outcome of interest here.
- **Multisensory Reaction Time.[92]** A brief test of reaction time that includes reaction time to visual, auditory and audiovisual stimuli.

MRI scan of brain. The primary outcome of interest is graph theory-derived measures of network structure calculated on fMRI images. PWD will complete 1-hour MRI scans in visits 2 and 3 that will include images needed for primary outcomes (T1-weighted structural image, fMRI images) and images needed for potential alternate hypotheses (e.g., FLAIR images to assess white matter hyperintensity burden, *related to gait in aging)*. The following assessments completed by the CG will take place during Baseline Visit 2 (BV2):

- **Quality of Life (SF-36).** We will measure QoL in CG using the Short Form-36 (SF-36).[93, 94]
- **Neuropsychiatric Inventory Questionnaire (NPI-Q)**. The NPI is designed to assess neuropsychiatric symptoms in PWD with the CG.[95] The NPI-Q includes questions about 12 domains of symptoms: delusions, hallucinations, agitation/aggression, depression, anxiety, elation/ euphoria, apathy, disinhibition, irritability, aberrant motor activity, sleep, and eating.
- **NEO Five Factor Inventory (NEO-FFI).**[96] CG reports can be influenced by personality.[97] Therefore, CGs will complete a personality measure that categorizes personality on: emotionality/ neuroticism, extraversion, openness to new experiences, agreeableness, and conscientiousness.
- **Zarit Caregiver Burden Scale (Zarit CBS) [98].** A 21-item self-report scale where caregivers rate items describing burdensome or stressful situations as occurring 0=Never to 4=Nearly Always. Total scores are categorized as No or Minimal Burden (score = 0-20), Mild to Moderate Burden (21-40), Moderate to Severe Burden (41-60), and Severe Burden (61-88).

- Abbreviated cognitive battery (RBANS)
- Alternative Uses Task
- Geriatric Depression Scale
- Geriatric Anxiety Scale
- Falls Efficacy Scale International
- Apathy Evaluation Scale
- Multisensory Reaction Time

Randomization

Randomization will occur within a week after completing baseline visits and may occur up to 6 weeks before the beginning of intervention.

6.2.3 Blinding

Given the interventional nature of the study, it is not possible to blind participants. However, the 3 interventional study arms will be described neutrally during consent and participants will be assessed in BV1 about their outcome expectations for all 4 study arms to which they could be randomized. For participants whose study intervention was interrupted by the public health restrictions in response to the COVID pandemic situation, study expectation questions will include expectations about the transition to a virtual environment. Study staff administering baseline visits will be blinded to randomization. Two study team members will be unblinded after randomization for the purpose of assisting with scheduling interventions and making periodic follow-up phone calls. The remaining study staff will be blinded to perform follow-up testing visits. The intervention team will not perform any study assessments. The study PI and biostatistician will remain blinded until the database is locked.

6.2.4 Follow-up Visits

Participants will have 13 weeks in which to complete 24 intervention visits. Follow-up assessments will occur after either 24 intervention visits or 13 weeks. The first follow-up assessment will occur between days 0-7 after the completion of the intervention, and the second follow-up visit will occur between days 1-21. The exact ordering of tasks may vary to accommodate scheduling needs. For instance, the MRI scan may take place on a third visit if that is preferred by the participant.

The following assessments of the PWD will occur during Follow-up Visit 1 (FV1):

- QOL-AD
- Fasting blood draw
- Geriatric Depression Scale
- Geriatric Anxiety Scale
- Apathy Evaluation Scale

- Fullerton Advanced Balance Scale
- Falls Efficacy Scale
- MRI scan of brain

The following assessments completed by the CG will occur during Follow-up Visit 1 (FV1):

- SF-36
- Geriatric Depression Scale
- Geriatric Anxiety Scale
- Apathy Evaluation Scale
- Falls Efficacy Scale
- Fullerton Advanced Balance Scale
- Expanded Short Physical Performance Battery
- Zarit Caregiver Burden Scale
- Neuropsychiatric Inventory Questionnaire
- Alternative Uses Task
- Postural Sway
- Gait Speed and Variability

The following assessments of the PWD will occur during Follow-up Visit 2 (FV2):

- Expanded Short Physical Performance Battery
- Postural Sway
- Gait Speed and Variability
- Timed Up and Go
- Alternative Uses Task
- Philadelphia Mindfulness Scale
- Abbreviated Cognitive Battery
- Multisensory Reaction Time

The following assessments of the CG will occur during Follow-up Visit 2 (FV2):

- Abbreviated Cognitive Battery
- Timed Up and Go
- Philadelphia Mindfuless Scale
- Multisensory Reaction Time

Laboratory Procedures

After collection, blood samples will be sent to LabCorb and reports will be returned within 48 business hours. Each week, the study physician or a proxy physician will review the lab report to evaluate for any out of range laboratory values for clinical significance (see Table 4 on page 38). Labs that are out of range will be reported to the participant via a letter within 2 weeks of the clinician's review unless the study physician deems it necessary for participant safety to notify them sooner, which may be done by telephone and/or letter. All participant lab reports will be filed in their study chart. If in-person study visits are prohibited in response to a public health emergency, blood collection may not occur. If it is possible to make arrangements for a safely and professionally conducted in-home blood draw, an in-home blood draw may occur. Lab variables are not a primary outcome. Any missing values will be treated statistically as described in the statistical analyses.

7. SAFETY ASSESSMENTS

Alphabetical List of Expected Adverse Events for Study Interventions

- **Falling.** There is a risk of falling in the movement interventions. If a participant falls during the intervention two or more times during the 12-week period, the option to stand or walk will be removed and they will be asked to remain seated for the remainder of the sessions.
- **Muscle soreness.** As with any movement intervention, there is a risk of muscle soreness for the movement intervention arms. Movement intensity can be reduced if needed to prevent further muscle soreness.
- **Tripping.** As with any movement intervention, there is a risk of tripping. If participants trip, the interventionist will modify instructions as necessary to prevent further tripping.

7.1 Specification of Safety Parameters

There is a small risk of injury during the movement interventions, such as falling or muscle soreness. Risk is minimized in the improvisational dance method by always beginning seated, always having a seated movement option, and encouraging participants to self-select safe and comfortable movements. If a participant falls during the intervention two or more times during the 12-week period, the option to stand or walk will be removed and they will be asked to remain seated for the remainder of the sessions.

Other data collected for use as covariates may result in health alerts. Below is a table of laboratory values considered out of range that would result in notification of the participant. Laboratory values are reviewed by staff using the table below. If a value is out of range, the study physician is notified, and the participant will be contacted within the time period specified by study staff, the study physician, or the PI.

Table 4. Alert Criteria for Blood Tests and MRI

Test	LapCorp Reference Range	Value out of reference range: Participant should be notified at routine visit or within two weeks by a qualified staff member that the value is out of the normal range for all adults and could be discussed with Primary Care Provider (PCP) but may not be medically important. (letter)	Value may be medically significant: Participant should be notified at routine visit or within two weeks by a qualified staff member that the value is potentially medically significant and strongly recommend that it be discussed with PCP. (letter with asterisk)	Value requires immediate notification: Participant should be notified within one working day by a qualified staff member that they should contact their PCP. (This will be recorded and followed as an AE unless the value reflects a known chronic condition or expected value based on current health status)
Blood pressure		SBP > 140mm/Hg or DBP > 90mm/HG	SBP > 170mm/HG or DBP > 100 mm/HG, without symptoms	>170/100 HG with symptoms
Geriatric Depression Scale (GDS)			≥ 5	
MRI abnormality noted by board certified neuroradiologist.		As per notation by neuroradiologist	As per notation by neuroradiologist	As per notation by neuroradiologist
Triglycerides	Normal: <150 mg/dL Borderline-high: 150−199 mg/dL High: 200−499 mg/dL Very high: >500 mg/dL	151-200	201-500	>500
Total Cholesterol	Acceptable: 100−199 Borderline: 200−239 High: ≥240	>199	>240	
HDL	Normal: greater than 35 mg/dl	<35		
$HbA1_c$	Normal: 4.8 - 5.6% Prediabetes: 5.7-6.4% Diabetes: >6.4% Glycemic control for adults with diabetes: <7.0%	≥ 5.7	6.5-10	≥10: report as AE ≥12: report w/in 24 hours

Albumin	Normal: 3.5-4.8 g/dL	>5 or < 3.5	< 3.0	<2
Fibrinogen	Normal: 193-507 mg/dL	<193 or >507	<100 or >700	
CRP	Normal < 10 mg/dL	>10	>10	>100
CBC	Normal WBC: 3.4-10.8 x10E3/uL	WBC >10.8 or <3.4	WBC>12 or <4	WBC>14 or <3
	Hemoglobin females 11.1-15.9 males 13-17.7	Hemoglobin females < 11 or >16 males <13 or >18	Hemoglobin females <10 males <12	Hemoglobin <8
	Hematocrit females 34-46.6 males 37.5-51	Hematocrit females <34% or >47% males <37% or >51%	n/a	n/a
	Normal Platelets: 150-450 x10E3/uL	Platelets <150 or > 450	Platelets <100 or >450	Platelets < 80 or > 500
CMP	Normal: 0.76 - 1.27 mg/dL	Creatinine <0.76 or >1.27	Creatinine >1.5	Creatinine >2
	Normal: 8-27 mg/dL	BUN <8 or >27	BUN >30	BUN >40
	Normal: 134-144 mmol/L	Na < 134 or >144	Na < 134 or >146	Na <130 or >150
	Normal: 3.5 - 5.2 mmol/L	K < 3.5 or >5.2	K < 3.4 or >5.5	K <3.0 or >6
	Normal: 96 - 106 mmol/L	Cl <96 or >106	Cl <98 or >110	n/a
	Normal: 20 - 29 mmol/L	CO_2 < 20 or >29	CO_2 < 20 or >29	CO_2 <18 or >35
	Normal: 65-99 mg/dL	Glucose <65 or >99	Glucose <70 or > 125	Glucose <60 or>500
	Normal: 8.6 - 10.2 mg/dL	Calcium <8.6 or > 10.2	<7 or > 12	> 14
	Normal: 0.0 - 1.2 mg/dL	Bilirubin 0-1.2	>1.5	>3
	Normal: 0 - 40 IU/L	AST 0-40	> 45	>70
	Normal: 0 - 44 IU/L	ALT 0-44	> 50	>70
OTHER	Normal: 20.8 - 226.4 ug/dL	DHEA-Sulfate <20 or >230	n/a	n/a
	Normal: 2.6 - 24.9 uIU/dL	Insulin <2.6 and >24.9	n/a	n/a
	Normal: 6.2 - 19.4 ug/dL	Cortisol (AM) <6.2 or >19.4	<3 or >20	n/a

If the participant has normal vital signs and feels well, there is no need to invoke emergency medical systems

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Participants will be asked at least monthly whether there have been any changes in their health status, medications, or lifestyle. They will be specifically asked about falls. Interventionists will be instructed to report to study staff if a participant mentioned a fall or other health event during class. Participants may also report a fall or other health event to study staff who are checking them into an intervention, during a study visit, or during a reminder call. Unsolicited reports of events will be recorded in the study record.

Any major AE, i.e., any serious injury including all SAEs that are unanticipated, serious, and possibly related to the study intervention will be recorded and reported to the co-PIs immediately after completing any and all actions that are necessary to protect the subject's health and safety. A description of the event and the date and location of the event will be recorded on the AE Reporting Form. The PIs will meet quarterly, or as needed, to review all reported events and these will be compiled and reported in aggregate to the DSMB at each biannual DSMB meeting.

7.3 Adverse Events and Serious Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these regardless of relationship to participation in the study.

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer, and Independent Safety Monitor(s) within 3 days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 7 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor(s), IRB, and other oversight organizations in accordance with their requirements and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the DSMB. The DSMB Report will state that all AEs have been reviewed.

7.4 Reporting Procedures

Study progress and safety will be reviewed monthly and more frequently if needed. Progress reports, including subject recruitment, retention/attrition, and AEs will be provided to the DSMB biannually. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the DSMB and will be forwarded to the IRB and NCCIH. The IRB and other applicable recipients will review progress of this study on an annual basis. The PIs will send copies of signed recommendations from the DSMB to the NCCIH program officer and IRB within 1 month of each monitoring review.

The IRB, DSMB, and NCCIH Program Officials will receive copies of all study monitoring/audit or inspection reports within 14 day of PI receipt. For example, the NCCIH (Westat) monitoring report will be submitted to the IRB and DSMB.

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Daily, Weekly, Monthly	Study Staff (D, W, M); PI (W, M) Study statistician (M)
	Semi-annually	DSMB
Status of all enrolled subjects, as of date of reporting	Weekly	PI, Study Staff
	Semi-annually	DSMB
Data entry quality control checks on 30% of charts	Monthly	Study Staff
Adherence data regarding study visits and intervention	Weekly	PI, Study Staff
	Semi-annually	DSMB

AEs and rates (including out-of-range lab values)	Monthly	PI, Study Staff
	Semi-annually	DSMB
	Annually	NCCIH, IRB
SAEs (unexpected and related)	Per occurrence	PI, DSMB NIH/NCCIH
SAEs (expected or unrelated)	Per Occurrence	PI, Study Staff
	Annually	DSMB, NIH/NCCIH
Unanticipated Problems	Monthly	PI, Study Staff
	Per Policy	IRB

7.5 Follow-up for Adverse Events

The PI 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, study staff will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.6 Safety Monitoring

Independent monitoring of this study will be performed by the WFSM Institutional Data Safety and Monitoring Board (DSMB). The DSMB includes a panel of monitors who are independent of the PI and have previous experience on a monitoring committee. The members of this committee are not associated with this research project, work independently of the PIs, and have not collaborated or co-published with the PIs within the past three years. They are qualified to review the patient safety data generated by this study because of their unique expertise, which includes research ethics and statistics. It is planned that the DSMB will meet biannually to review study progress, data quality, and participant safety, unless at the discretion of the DSMB it is felt that more frequent formal contacts are needed. In addition, an emergency meeting of the DSMB may be called at any time by the Chair or the NCCIH, should participant safety questions or other unanticipated problems arise.

8. INTERVENTION DISCONTINUATION

Participants are free to withdraw from the study at any time and may therefore voluntarily discontinue the study. Anticipated reasons for voluntary withdrawal include dissatisfaction with randomly assigned study group, dissatisfaction with study burden, and change in health status. If a participant does not show up for 3 scheduled and confirmed study visits, or stops answering or returning phone calls from study

staff for 4 weeks, they will be sent a certified letter to sign. If they do not respond to that within a month, they are considered to have dropped out.

Participants may be asked to discontinue the intervention by study staff if they have any change in health status that meets exclusion criteria or is judged by staff, the participant, study physician or personal physician to put the participant at risk during the intervention or testing. An example of this is beginning a new medication that affects alertness or balance during study intervention times. Participants will be screened over the phone monthly by staff with a checklist to assess for any major changes in health status for all 4 arms of the study. Participants in interventions may also mention changes in health status during routine reminder phone calls or to intervention instructors. Although poor behavior is not anticipated, participants may be asked to discontinue the intervention by study staff if they demonstrate any behavior toward study staff, interventionists, or other participants in groups that is inappropriate, threatening, or harmful. Participants may also be discontinued from the study if the study is closed for any reason.

Participants may need to temporarily discontinue the study intervention, for example, due to short-term changes in health or a family emergency. If this temporary discontinuation needs to occur after 10 weeks or more of intervention have been collected, study staff will attempt to collect follow-up measures before study discontinuation. Otherwise, participants will resume the intervention when possible and the gap in treatment will be addressed statistically. If temporary discontinuation lasts longer than a month, participants will be asked to complete follow-up visits as close as possible to the appropriate time points relative to study enrollment and intervention initiation. When participants are ready to resume the study, they will be briefly re-screened to ensure that all inclusion and exclusion criteria are still met.

As this study is a randomized trial, we will attempt to collect data adequate to complete intention to treat analyses. Participants who drop out after randomization will be mailed a letter inviting them to complete any study visits they are willing to complete. Participants who have discontinued the study for any reason (voluntarily or by study staff) will be asked if they are willing to complete follow-up visits 1 and 2 at appropriate time points relative to study enrollment and intervention initiation and will be reimbursed for these visits. If study visits need to be modified for length due to constraints on participants' health or willingness to comply, a reduced battery of follow-up measures may be given that focuses on primary endpoints, such as QoL, balance, and checklists of mood and behavioral symptoms. If participants are only willing to complete one follow-up visit, the visit will be reorganized to include as many primary endpoints as possible.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The study uses a full-factorial design to test the main effects of movement and social engagement and their possible synergistic effect. Suppose Y represents the primary outcome of interest post-intervention, and $Y^{(BL)}$ the outcome at baseline. The

following ANOVA model forms the basis of the power calculations and subsequent analyses:

$$Y_{ijk} = \mu + \beta_1 X_i + \beta_2 Z_j + \beta_3 (XZ)_{ij} + \beta_4 Y_{ijk}^{(BL)} + \varepsilon_{ijk}, \qquad \text{(Equation 1)}$$

where y represents the outcome, X represents the movement component, Z represents the social component, and (XZ) represents the interaction between X and Z, and ε represents random error, with, i, j=1,2, and k=1,.,120. Equation (1) decomposes the response (QoL measure) into the sum of effect of the variables and controls for value pre-intervention. Unlike a classical multi-arm randomized clinical trial, the full-factorial experiment preserves power, which is driven by the total sample size, not cell size. The study design was chosen to maximize power in the short time (3 years) provided by the granting mechanism.

Aim 1: Determine the independent effects of social engagement and dance movement on QoL in people with dementia by assessing the main effects of social engagement and movement. We will use analysis of variance (Equation 1) to assess the main effects of social engagement and movement on QoL. Effect coding for the X,Y variables will be used so that the coefficients β_1 and β_2 in Equation (1) can be directly tested and interpreted respectively as main effects of the movement and the social components. The null hypotheses are that there is no main effect. Statistically, we will test the following two hypotheses: H_0: $\beta 1 = 0$; $\beta 2 = 0$ at the level of $\alpha = 0.05$. Following common practice, we will not adjust for covariates in testing main effects unless severe imbalances occur in cell distributions of demographic variables including gender and age. The synergistic effects of the movement and social engagement can be evaluated by testing the hypothesis: H_0: $\beta_3 = 0$**.**

Aim 2. Assess potential mechanistic links between functional neuroimaging metrics, behavioral outcomes, and overall QoL scores using structural equation modeling in all groups combined. Aim 2 will be tested using structural equation modeling using the path diagram in Figure 2. Movement is hypothesized to exert effects on QoL through changes in somatomotor brain networks, a latent variable comprised of multiple graph theory-derived measures of connectivity in the somatomotor ROI defined in section 3.6.5, including E_{Glob}, E_{Loc}, path length, and degree. Changes in somatomotor network structure are hypothesized to result in improved gait (a latent variable comprised of gait speed, gait variability, and stride length derived from the instrumented mat) and balance (a latent variable including balance measured with the FAB, balance confidence measured with the FES, and postural sway measured with the force plate). Social engagement is hypothesized to alter connectivity in the default mode network, modeled using multiple graph theory-derived measures of connectivity in the DMN ROI, including E_{Glob}, E_{Loc}, path length, and degree. Altered DMN connectivity is hypothesized to result in decreased neuropsychiatric symptoms and increased QoL. Structural equation model (SEM) analysis[99] will proceed in several stages. First, confirmatory factor analytic models will be fitted to the stated indicators for individual latent variables. We will examine goodness-of-fit indexes to determine the appropriate measurement models and refine the measures if necessary. Second, we will assess the consistency between the structural model and the data. Connections that turn out to be not significant will be deleted and reported, and alternative hypotheses will be tested. We expect the

iterative model building effort will result in a final structural model that will offer insight into the mechanism through which improvisational dancing affects overall well-being in the population of people with dementia. We plan to conduct the SEM analysis using Mplus v7.4.

Incorporating Virtual Intervention

For Aim 1, our plan for data analysis would include an adjustment for the possible impact of a different mode of delivery of intervention (virtual as opposed to face-to-face). We will integrate data collected from the virtual intervention into previously collected data to preserve power. A variable indicating the mode of intervention delivery would be included into the regression model described in section 9.1. The revised analysis plan thus might deviate from the original plan that was a priori specified in ClinicalTrials.gov. However, elaboration of our analysis plan at this juncture will prevent data mining activities that could be seen as "data fishing".

Specifically, we would first test whether or not the virtual indicator variable is significant. If both the intervention variable and the virtual indicator are both significant, we would further include an interaction between the variables to the model. The process follows the hierarchical principle for introducing interaction terms. If the interaction term is not significant, then we will not include the interaction term into the final model (but keep the indicator of virtual intervention in the combined analysis). Similarly, we would consider the possible interaction between mode of delivery and baseline outcome QoL measure (section 9.1).

Besides the primary analysis described above, we would further examine the possibility of interaction between mode of delivery and other factors such as age and sex in an exploratory analysis.

For Aim 2, we would first include the indicator variable of mode of delivery into the preliminary SEM model for each individual outcome. The variable would only be retained in the final model for if its effect is statistically significant from the preliminary analysis.

9.2 Sample Size and Randomization

Our pilot data showed a difference of 1.4 on the QOL-AD between the no-contact control and dance group in an 8-week intervention. The pilot did not test separate effects of social engagement and dance movement and was an 8-week rather than 12-week intervention, but the pilot data suggest the amount of change we can expect. For power calculations, we used a conservative estimate of effect size of 0.55 per main effect. The power of the study using a sample size of 30 per cell in the 2x2 factorial design (total N=120) is approximately 85%. A sample size of N=106 is needed to achieve 80% power. The power analysis assumed a 2-sided test at $\alpha = 0.05$, and the calculation was conducted using the SAS macro FactorialPowerPlan.[100] We will collect follow-up data on all participants, even those who do not complete the study,

to the best of our ability for the purpose of completing an intent-to-treat analysis. If sample size is unavoidably reduced as a result of interruptions due to public health concerns, power may be reduced. For example, if N=92, then power is approximately 74%.

Treatment Assignment Procedures

Participants will be randomized to one of the 4 study arms: Movement Group (MG), Movement Alone (MA), Social Group (SG), or No Contact Control (NC). Recruitment will occur in waves. Randomization will be blocked in blocks of 16 that each correspond with a wave of data collection; each block will randomize 4 participants to each of the 4 study groups. Two intervention arms in the study are group interventions. Group interventions pose a unique challenge for study recruitment, because a minimum number of participants is needed at the same time to begin the group. Choosing to randomize over smaller blocks will allow more flexibility with study sites and allow waves to begin more quickly after participants are enrolled in the study. Also, the study proposes that people with dementia will be sex-balanced. It is reasonable that sex-balance will be achieved, as it was in the pilot, because while women are more likely to be diagnosed with dementia, they are also more likely to be caregivers. However, if gender balance is not met in any wave, gender blocking can be employed in the next wave.

Randomization codes will be generated and maintained by the study statistician. The randomization code will be shared with the PI for the purposes of communication with the intervention team about timing of group classes and reserving class spaces. The PI will not be administering baseline or follow-up testing or performing any interventions. If recruitment targets are not being met, planned breaking of the randomization code may occur where an intervention group will be started with a smaller number of participants than intended. In this event, randomization to other study arms will be adjusted to match the intervention group and maintain balance across the arms. Also, later groups may be larger in order to compensate or an additional wave may be added. Randomization will be approximately balanced by sex. Women are more commonly diagnosed with dementia than men, but women are also more commonly caregivers than men. The pilot study was approximately balanced by sex. Therefore, we anticipate that overall, sex will be approximately balanced in PWD in this study and will randomize accordingly.

Given the nature of the intervention, it is not possible for participants to be blinded. Interventionists will also not be blinded. Study staff performing baseline visits will be blinded to the randomization code to eliminate the potential for bias in assignment to treatment arm. Two study staff will be unblinded to the randomization code after baseline testing for the purpose of scheduling interventions and making reminder calls.

Participants will be instructed not to mention their study group to staff prior to beginning follow-up testing. However, unintentional breaking of randomization codes may occur if a participant mentions their study group to the study staff performing their follow-up visit. Also, while most interventions will take place away from the hospital, there is a small chance that study staff blinded to randomization code might

see a participant going to or coming from an intervention session. The influence of potential breaking of randomization code on follow-up data should be minimal because 1) participants will have been fairly randomized at the beginning of the study, which is the primary purpose of randomization, 2) study staff will be trained to administer testing according to protocol and will follow the protocol, and 3) an occasional instance of unintentional breaking of randomization code will not introduce systematic bias into the data. If randomization is unintentionally broken, this will be recorded on a notes page in the participant's study binder.

9.3 Definition of Populations

Intention to treat analysis will include all participants randomized to each arm who have follow-up data. Appropriate efforts will be made to get follow-up measures of at least the primary outcome on all participants. If a participant is lost to follow up after baseline data collection, the participant will not be included in data analysis. See the section on missing value for description for treating missing values due to dropping out after FV1 or partially missing values (Section 9.6). Per protocol analysis will include all participants who completed the trial without major protocol deviations.

9.4 Interim Analyses and Stopping Rules

There are no planned interim analyses or stopping rules due to the brief duration of the intervention and small number of participants in each arm (n=30).

9.5 Outcomes

9.5.1 Primary Outcome

Quality of life (QoL). We will measure QoL in PWD using the QOL-AD, a measure of QoL validated in people with dementia who had Mini-Mental State Exam (MMSE) scores as low as 10.[65-67] This study targets early-stage dementia and MCI, meaning MMSE scores will be 15 or above for all participants, putting them well within the range for the QOL-AD to be a valid measure. We will measure QoL in CG using the Short Form-36 (SF-36).[93, 94] QoL will be measured in BV1 and FV1. The primary outcome will be QoL in the PWD measured with the QOL-AD at FV1.

9.5.2 Secondary Outcomes

Secondary Outcomes of Interest.

Measurements of Gait and Balance. We have proposed improved gait and balance as potential mechanisms through which dance can improve QoL for people with dementia. These measures have been defined above in section 6.2.2.

- **Fullerton Advanced Balance Scale (FAB)**
- **Postural sway**
- **Gait speed and variability**
- **Expanded Short Physical Performance Battery (eSPPB).**

Measurement of Neuropsychiatric Symptoms. We have proposed improvement of neuropsychiatric symptoms, particularly apathy and depression, as a potential mechanism through which dance may improve QoL in PWD.

- **Neuropsychiatric Inventory Questionnaire (NPI-Q).**
- **Geriatric Depression Scale (GDS) and Geriatric Anxiety Scale**.
- **Apathy Evaluation Scale (AES)**.

MRI Neuroimaging. We have hypothesized that behavioral improvements due to dance (gait/balance and neuropsychiatric symptoms) are accompanied by changes in brain function that can be measured noninvasively using magnetic resonance imaging (MRI). The primary neuroimaging outcome of interest is graph theory-derived measures of network structure calculated on resting state fMRI images. The primary imaging metrics of interest are: 1) community structure, 2) global efficiency (E_{Glob}), 3) local efficiency (E_{Loc}), and 4) path length (described below).

- **Acquisition.** A high resolution T1-weighted image will be collected using a 3D volumetric MPRAGE sequence. Images will be immediately re-acquired if artifacts due to motion or other sources are detected. Whole-brain network connectivity will be assessed using blood oxygenation level-dependent (BOLD) imaging during resting state, where participants are asked to view a cross in the middle of a screen with eyes open.[101]
- **Preprocessing.**T1 MRI images will be warped into template space and segmented into grey matter, white matter, and cerebrospinal fluid using publically available software. fMRI data will be aligned to the T1 data, then warped to template space by applying the transforms computed on the T1 data. Distortion correction will be performed using EPIREG in FMRIB's Software Library (FSL).[102, 103] To control for physiological noise,[104] all data will be preprocessed to remove head motion, global, white matter, and cerebrospinal fluid signal.[105, 106]
- **Generation of Whole Brain Network.** Graph theory analysis will be performed in collaboration with the WFSM Laboratory for Complex Brain Networks (LCBN) (PI: Laurienti) using their established methodology.[107-126] Each brain network will be generated from preprocessed, spatially normalized images. The first step in performing the network analysis is to generate a whole brain connectivity matrix, or adjacency matrix. This is a binary n X n matrix, where n = the number of voxels in the fMRI data (~20,000). The matrix notes the presence or absence of a connection between any two nodes (i and j) determined by the correlation coefficient between each node and every other node. These values will be used to produce a correlation coefficient matrix. A threshold is applied to the correlation matrix to dichotomize the data such that values above the threshold indicate that a connection is present. This threshold will be set based on the LCBN's recent work showing a universal relationship between node number and connection density.[112] This process yields the binary adjacency matrix. The binary adjacency matrix defines the *graph* (the nodes and the edges that connect them) for each individual. The diagram in **Figure 1** illustrates a graph; circles represent nodes (voxels) and lines represent edges (superthreshold

correlations). Neuroimaging data typically follow the organization of a small-world network.[127, 128] Small-world networks are characterized by having high clustering of nodes within the network, allowing for local specialization, at the same time as short path lengths, which allow for rapid spread of information. Path length refers to the number of edges that must be crossed to get from one node to another. For example, the minimum path length between A and B in Fig. 1 is 2, and the maximum (without crossing an edge more than once) is 7. Clustering refers to how tightly connected the neighbors of a node are. In Fig. 1, the grey nodes, black nodes, and white nodes form tightly clustered communities within the graph.

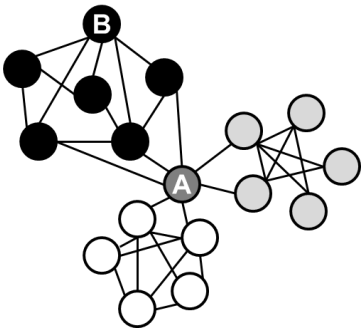

Figure 1. Diagram of a graph

- **Graph theory-derived outcomes of interest.** *Path length* is the number of edges that must be crossed to get from one node to another. Longer path length in people with AD has been associated with slower cognitive performance, beta amyloid deposition, and depression.[129-131]
- *Global Efficiency (E_{Glob})* reflects the efficiency with which information from one node can move through the network.[132] E_{Glob} is scaled from 0 (no long-range information processing) to 1 (maximal distributed processing). Decreased E_{glob} has been associated with aging, cognitive impairment, and depression.[131, 133]
- *Local Efficiency(E_{Loc})* is related to clustering, and reflects the efficiency with which information from one node is propagated to its neighbors.[132] It is also scaled from 0 (no local connectivity) to 1 (maximal local connectivity – all connections are local) and has been observed to change with cognitive impairment and depression.[131]
- *Community Structure/Modularity.* Community structure analyses will be performed to assign each voxel to a network community or module. A community or module is defined as a collection of network nodes that are more interconnected with each other than with the rest of the network. In Fig. 1, the light grey, black, and white nodes form 3 distinct communities more connected within themselves than with the rest of the network. We will compute modularity, or Q,[134, 135] to assess community structure strength in the brain networks using the "Louvain" algorithm.[136] Modularity (Q) ranges from 0 (no community structure) to 1 (perfectly modular network). We will repeat the analysis 10 times on each network and choose the partition with the highest Q value. The consistency of community structure and the strength (Q-value) for each network node will then be assessed across all individuals. Our work shows decreased modularity associated with decreased physical function,[109] and others have shown that cognitive impairment and AD are associated with altered modularity.[130, 137]
- **Regions of interest.** Average values of graph-theory derived outcomes will be extracted from regions of interest (ROIs) using WFU Pickatlas software.[138] The somatomotor region will be defined as the bilateral precentral (primary motor), postcentral (primary somatosensory), and paracentral gyri defined in the automated anatomical labeling (AAL) atlas.[139] The default mode

network (DMN) is a group of brain regions that reliably decrease activation on PET and fMRI scans during a task. These regions of multimodal cortex do not follow clear anatomical boundaries as primary somatomotor cortex does. DMN regions will be defined by a mask of regions deactivated during a sensory attention task[92] that is incorporated into WFU Pickatlas as an ROI.

Tertiary Outcomes

Tertiary outcomes include outcomes measured for the purposes of statistical adjustment, anticipated reviewer concerns/questions, or addressing alternate hypotheses.

- **Demographic characteristics** including age, gender, race, years of education, and employment history will be recorded as covariates.
- **Self-reported medical history** will be used to determine the presence of major medical conditions for inclusion/exclusion. Participants will be asked to bring in all medications and dietary supplements for a "brown bag" review.
- Height and weight will be measured to calculate body mass index.
- Blood pressure
- **NEO Five Factor Inventory (NEO-FFI)**.
- **White matter lesion burden.** Changes in gait and balance are common in AD and are correlated with neurodegenerative processes in the brain such as accumulation of beta amyloid. However, changes in gait and balance are also linked to burden of white matter hyperintensities.[140] Thus, burden of white matter lesions will be assessed by acquiring T2-FLAIR images. The volume of white matter lesions will be calculated using the Lesion Segmentation Toolbox implemented in SPM[141] for use as a covariate.
- **Allostatic load.** Social engagement may change biomarkers of stress, including cortisol and allostatic load,[142-144] a composite measure of blood-based biomarkers associated with chronically elevated stress. Cortisol may be elevated in PWD[145] and is often elevated in CGs.[145, 146] Lifestyle modifications like participating in support groups can reduce stress biomarkers in CGs,[147, 148] and we have pilot data showing that cortisol levels may decline in PWD in response to an engagement group that includes dance movement. Therefore, we will measure and test the effects of stress biomarkers in our model.
- **Effect of the intervention on CGs, and indirect effects on PWD through effects on CGs.** We chose to focus this proposal on the effects of dance on PWD because effect sizes on CGs for QoL, balance, mood, and neural networks were small or absent in the 8-week pilot. Nevertheless, the effect of the 12-week intervention or testing in a larger population might yield benefit for CGs that could influence outcomes. Outcomes of the intervention on CGs will be available to use as covariates to test whether effects on CGs modify effects on PWD.
    - Short Form-36 (SF-36). QoL will be measured in CGs using the SF-36. CGs may also benefit from the intervention.
    - Zarit Caregiver Burden Scale. CG burden will be assessed using the Zarit 22-item CG Burden Scale.[98]

- Mood will be assessed using the Geriatric Depression Scale and Geriatric Anxiety scales as listed above.
- CGs will also be asked to complete assessments of balance, gait, and physical function listed above.

9.6 Data Analyses

Analysis of Aim 1: Determine the independent effects of social engagement and dance movement on QoL in people with dementia by assessing the main effects of social engagement and movement. We will use analysis of variance (Equation 1) to assess the main effects of social engagement and movement on QoL. Effect coding for the X,Y variables will be used so that the coefficients β_1 and β_2 in Equation (1) can be directly tested and interpreted respectively as main effects of the movement and the social components. The null hypotheses are that there is no main effect. Statistically, we will test the following two hypotheses: H_0: $\beta 1 = 0$; $\beta 2 = 0$ at the level of $\alpha = 0.05$. Following common practice, we will not adjust for covariates in testing main effects unless severe imbalances occur in cell distributions of demographic variables including gender and age. The synergistic effects of the movement and social engagement can be evaluated by testing the hypothesis: H_0: $\beta_3 = 0$**.**

Analysis of Aim 2. Assess potential mechanistic links between functional neuroimaging metrics, behavioral outcomes, and overall QoL scores using structural equation modeling in all groups combined. Aim 2 will be tested using structural equation modeling using the path diagram in **Figure 2**. Note that Figure 2 represents a cross-sectional "slice" of the overall longitudinal model of 3 time points. QOL will be modeled longitudinally using longitudinal SEM. With the Markov assumption, we will analyze the data in which QOL is the outcome variable and covariates include both time-varying and non-time-varying measures. Movement is hypothesized to exert effects on QoL through changes in somatomotor brain networks, a latent variable comprised of multiple graph theory-derived measures of connectivity in the somatomotor ROI defined in section 3.6.5, including E_{Glob}, E_{Loc}, path length, and degree. Changes in somatomotor network structure are hypothesized to result in improved gait (a latent variable comprised of gait speed, gait variability, and stride length derived from the instrumented mat) and balance (a latent variable including balance measured with the FAB, balance confidence measured with the FES, and postural sway measured with the force plate). Social engagement is hypothesized to alter connectivity in the default mode network, modeled using multiple graph theory-derived measures of connectivity in the DMN ROI, including E_{Glob}, E_{Loc}, path length, and degree. Altered DMN connectivity is hypothesized to result in decreased neuropsychiatric symptoms and increased QoL. Structural equation model (SEM) analysis[99] will proceed in several stages. First, confirmatory factor analytic models will be fitted to the stated indicators for individual latent variables. We will examine goodness-of-fit indexes to determine the appropriate measurement models and refine the measures if necessary. Second, we will assess the consistency between the structural model and the data. Connections that turn out to be not significant will be deleted and reported, and alternative hypotheses will be tested.

We expect the iterative model building effort will result in a final structural model that will offer insight into the mechanism through which improvisational dancing affects overall well-being in the population of people with dementia. We plan to conduct the SEM analysis using Mplus v7.4. The SEM model in Fig. 2 will be modified if the final sample size is deemed not sufficient to support the original proposed complex model.

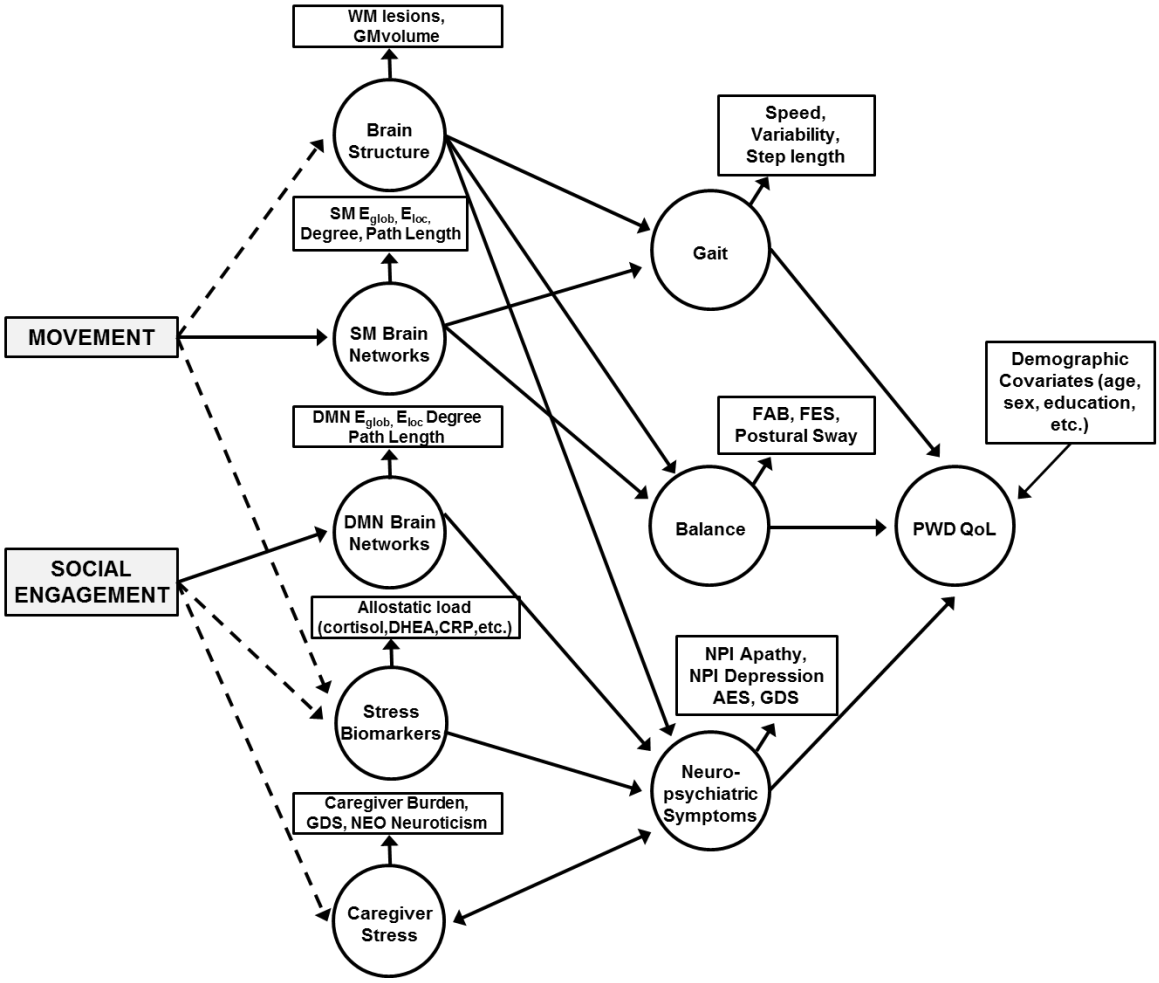

Figure 2. Path diagram for proposed SEM analysis. Grey shaded squares represent components of the intervention hypothesized to be generating an effect. Circles represent latent variables in the model. Boxes connected to circles with an arrow to represent observed variables used to create latent variables. Solid lines represent hypothesized effects. Dashed lines represent alternative hypotheses. AES=Apathy Evaulation Scale, DMN=default mode network, FAB=Fullerton Advanced Balance Scale, FES=Falls Efficacy International Scale, GDS=Geriatric Depression Scale, SM=Somatomotor.

Missing Data. Several analytic strategies will be used to treat missing values. The primary analysis will analyze the QoL-AD score at FV1. If a participant does not have FV1 data at all, we will not include the participant. If there is partially missing data (e.g., missing response to a question in a survey), we will use multiple imputation (MI) to handle the missing value. The missing-at-random principle (but not the completely-missing-at-random MCAR, a more restrictive assumption) will be followed, and MI will account for uncertainty associated with the missing values. For secondary analyses that involve both FV1 and FV2, first we will exclude participants that drop out after baseline measurement. For missing at random (MAR)

and not missing at random (NMAR), generally speaking there is no true test unless additional data are available from those that have missing values. One can use experience and judgment to determine if MAR is a reasonable assumption. It needs to be pointed out that there are tests for checking MCAR vs MAR, the most commonly used one being Little's test [149]. Because we do not assume MCAR, which is a stricter assumption than MAR, we do not plan to conduct this test.

It is not possible to tell directly from examining the data whether or not missingness is missing at random or not. If from clinical observations we suspect that data are not missing at random (e.g., sicker patients with lower cognitive measures are more likely to miss the cognitive measures), we will use statistical models such as pattern-mixture model[150] to assess the impact of missingness of data on the results. Pattern-mixture models do not assume missing at random and allow different distributions of missing values for different patterns of missing data. For example, if we are willing to assume that missing values follow some given patterns, then we will be able to evaluate the effect of intervention on different groups of patients with different missing patterns. Because of the relatively small sample size, the investigation of pattern-mixture is likely to be limited to a small number of patterns of missingness.

The current situation of a public health emergency may result in additional missing data, for example if in-person data collection visits are prohibited. If missing values occur for a dependent variable (e.g., neuroimaging, blood draw) then observations that contain valid values will be used and those with missing values will not be used. In this study, the variables most affected would be secondary and tertiary variables. If the measured variable is an independent variable, the procedures for missing values outlined above will be used.

Exploratory Analyses

The unavoidable changes in study design and sample size resulting from the COVID-19 public health emergency have the potential to impact the interpretation of outcomes. The planned analyses above are the primary analyses for the study and will be conducted as described. Additional exploratory analyses may be conducted to maximize information gained from the grant. These exploratory analyses could provide hypothesis-generating information to help guide future work and identify potential new biological mechanisms through which movement and social engagement affect PWD and their CG. Potential exploratory include 1) voxel-wise analyses of brain network data to assess whether movement or social engagement altered connectivity metrics; 2) effects of movement and social engagement on white matter integrity using NODDI data, 3) whether biomarkers of stress are affected by social engagement and movement intervention in PWD and CG, 4) whether movement and social engagement using an improvisational method can enhance divergent thinking (a measure of creativity) in PWD and CG, and 5) whether divergent thinking is associated with CG burden or neuropsychiatric symptoms in PWD. The exploratory analyses will closely follow the analytic plan for the primary outcome. The dependent variable would be the potential variables described above, and the primary predictor would be intervention condition.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Types of data collected include 1) paper forms, 2) electronic data, and 3) neuroimaging data. All data collection will be performed by trained study staff who are blinded to the participant's study arm. Every effort is made by the investigators, study staff, sponsor(s) and their agents to maintain confidentiality of protected health information collected in the study. All of the materials collected are for research purposes only and will be held in strictest confidence. All WFSM faculty and staff receive annual trainings in privacy, protection of personally identifiable information, and HIPAA regulations.

Confidentiality of data is maintained by using research identification numbers that uniquely identify each individual. Data other than demographic information will not use names as an identifier; research ID numbers will be used. Data will be used only in aggregate and no identifying characteristics of individuals will be published or presented.

Written records will be kept in locked cabinets in the Sticht Center on Aging. Files matching participants' names and demographic information with the research ID numbers are kept in a separate room and locked file with a different key from for all other files. Files may be obtained from the research unit only by authorized study personnel. After the study is completed, local data will be stored with other completed research studies in a secured storage area.

Digital records, including brain imaging data, will be stored on password protected, network drives behind the WFSM firewall. These drives are routinely backed up and access to the drives is limited to necessary personnel. Brain imaging data are stored using subject number and date of acquisition as identifiers. The study PI regulates access to the drives used for brain imaging data.

No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

10.2 Data Management

As this is a single-site study, all data will be collected by study staff at this site. The header of all data collection forms includes a unique numerical study identifier (study ID number), a unique alphabetical identifier ("acrostic"), the date the form was collected, the initials of the study staff who completed the form, the study name, and the study visit (e.g., baseline visit 1). The footer for all data collection forms includes version number and page. Paper data collection forms will be kept locked and secured at the study site. After data collection on paper forms, data will be entered into a REDCap database that is password protected and accessible only by study staff in 0-7

days after data are collected. Only the PI will have permission to download identifying information from the REDCap database and the PI will assign data access for all study staff. After data is entered by one study staff member, data entry will be checked for at least 30% of participants by a separate person.

10.3 Quality Assurance

10.3.1 Training

Training on the cognitive testing battery will be conducted using materials provided by the ADCC by a study coordinator trained through the ADCC. First, the complete cognitive battery will be reviewed verbally while showing the study staff member data collection and administration forms. The study staff member will be taught how to administer each test individually, including instruction on common mistakes and variations in response and how to code them. The study staff member will take the cognitive tests administered by a trained staff member. The study staff member will have opportunities to practice administration until they feel confident administering the testing. They will then be observed by the lead study coordinator and will be audiotaped to document appropriate testing technique. During their first study visit, they will be accompanied by a lead study coordinator. If there are any concerns about the performance of the testing, any necessary training will be repeated.

Training on administration of non-cognitive tests will occur similarly. Lead study staff have been trained in proper administration of tests by Pepper Center and Alzheimer's center staff. When a new study staff member joins the team, they will be familiarized with the CRF and the battery of tests that will be administered. They will be instructed how to administer each test individually and will be allowed to ask questions. Instruction will include common mistakes and variations in response and how to code them. The study staff will practice administration until they report being confident administering the testing. At this point, study staff will be observed administering the test to another staff member. If a lead study coordinator judges that testing technique is appropriate, the study staff will complete a study visit accompanied by a lead study coordinator. If there are any concerns about the performance of the testing, any necessary training will be repeated.

A training refresher will be conducted for all study staff on all measures annually to ensure consistency in administration. During this training, correct administration of tests will be reviewed, and all study staff will demonstrate testing. In addition, weekly laboratory meetings will include discussion of any questions study staff may have about administration, scoring, or interpretation of testing.

10.3.2 Quality Control Committee

Quality control will be completed by the study team.

10.3.3 Metrics

Quality control metrics for non-imaging data will be generated from computerized reports generated from the database after data entry. Monthly reports will identify missing data, values that are out of range, and track attendance, as well as show plots

of primary outcome measures to identify outliers that may signify data entry errors. These metrics can be generated by REDCap. A study staff member will be identified who will routinely generate these measures in REDCap approximately 24 hours prior to the monthly study meeting. The study staff member will present the data to the study team and data errors will be agreed upon by the team. During the meeting, a study staff member will be assigned an action to correct the data entry error. This will be documented in the meeting minutes as an action item and follow-up will be added to the next month's agenda. When data are corrected in REDCap, REDCap software automatically tracks the date, time, and user who modified the database.

At the end of the study, histograms of the data distribution for each variable will be generated to identify outliers that may signify errors in acquisition or data entry. Many variables in the study will be acquired at 2 or 3 time points. For these variables, histograms of differences will be generated. This additional step can identify data acquisition or entry errors through unusual amounts of change.

Quality assessment will performed on MRI data at 3 time points on all data sets and results will be recorded in a REDCap form accessible by all study team members. First, raw data will be viewed after being transferred from the scanner and converted into nifti format to ensure completeness and assess for imaging ghosting and reconstruction errors. After preprocessing, data will be viewed again to assess for errors and residual motion. Finally, data will be viewed to assess any errors during processing. All image processing steps will be verified before summary metrics are extracted for the final statistical analyses. All data quality questions will be referred to co-PI (Hugenschmidt).

10.3.4 Protocol Deviations

A computerized tracking system will be used to document participant attendance, generate quality control reports for identifying protocol deviations and to assess protocol adherence. Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate. The study team will generate Study Reports for the DSMB and will provide information on the overall status and timeline of the study including enrollment status, recruitment, subject status (i.e., number completed), safety events, and protocol deviations. Study Report tables will be generated only from aggregate (not by group assignment) baseline and safety data for the study population. Study team meetings will occur at least twice a month, and quality control metrics will be reviewed once a month.

10.3.5 Monitoring

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. The scientific PI (Hugenschmidt) will be primarily responsible for data quality and management. A computerized tracking system will be used to document participant attendance, generate quality control reports for identifying protocol deviations and to assess protocol adherence. Telephone screening and in-person assessment interviews are conducted by trained

study staff who enter data directly into desktop or laptop computers.

Questionnaire data are stored on paper forms and in electronic databases. Staff will be instructed to review all forms for completeness after each study visit. Data from hard copy forms will be entered into a web-based system with range and other cross-form validation checks to exclude erroneous values. A randomly selected subset of subject data will be double data entered to check data entry accuracy. Careful development of data collection forms is crucial (a) to ensure systematic and uniform recording of participants' data (b) to facilitate complete data collection, and (c) to minimize the possibilities for data entry error. Data entry screens are created to mimic the forms. Forms are easy to read and interpret, and designed for ease of data entry.

Video data will be stored on networked, password protected hard drives and backed up to separate password protected hard drives and/or HIPAA-compliant cloud storage. Videos of individuals will be identified using subject number. Group videos will be identified using the group name and date.

Brain imaging data are stored on dedicated drives on Wake Forest School of Medicine's secure network and are identified using subject number. Quality assessment will performed upon data acquisition and after processing. All image processing steps will be verified before summary metrics are extracted for the final statistical analyses. All data quality questions will be referred to the neuroscience PI (Hugenschmidt).

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol, the informed consent document, data collection forms, and advertising will be reviewed and approved by the WFSM IRB. Any modifications to these forms that affect participant safety or burden will also be reviewed and approved by the IRB prior to implementation.

11.2 Informed Consent Forms

Signed informed consent will be obtained from each subject. The primary outcomes for this study are QoL and biomarkers collected from the PWD. However, the CG will be an active participant. Important data will be collected through the CG about the PWD, and other important data will be collected about the CG for the purpose of testing for alternate hypotheses and controlling for factors such as caregiver personality and mood that might influence the CG's reports about the PWD. Therefore, written informed consent will be obtained from each PWD and caregiver. If public health safety concerns limit in-person study activities, consent will be administered virtually following current IRB-approved guidelines. In all cases, IRB-approved administration of consent will be obtained prior to any data collection.

The informed consent process will follow the procedures of the WFU Institutional Review Board. The study interviewers will explain the purpose, methods and extent

of the study to prospective participants. The potential participant is asked to read the informed consent form and ask questions. The form is written in simple easy to understand language. We require study staff to review all of the key aspects of the study verbally with the potential participants. Staff then question potential participants to ascertain whether they have understood the information. Potential participants who are illiterate or have impaired vision must have the consent read to them, followed by review of the checklist, opportunity for questions, and discussion. A copy of the signed and dated consent form will be given to participants, and the original document will be placed in subjects' individual study files, which will be stored in a secure location. In compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, we will access personal health information only after obtaining informed consent.

11.3 Participant Confidentiality

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

Adjudication of cognitive status will occur through the ADCC adjudication committee, a multidisciplinary panel of experts in determining cognitive status. If for any reason adjudication cannot be performed through the ADCC adjudication committee, an adjudication committee may be formed with the guidance of the ADCC that will include a comparable panel of experts.

13. PUBLICATION OF RESEARCH FINDINGS

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research.

14. REFERENCES

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