Study Protocol and Statistical Analysis Plan

A Dyadic Approach for a Remote Physical Activity Intervention in Adults with AD and their Caregivers

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I. Purpose, Background and Rationale

A. Aim and Hypotheses

Approximately 5.3 million adults age 65+ in the U.S. have Alzheimer's dementia (AD), a number that is projected to increase to 13.8 million by 2050. Most adults with AD live in the community and receive support from a caregiver. Participation in moderate intensity physical activity (MPA) improves activities of daily living and mobility, and may improve general cognition and balance in adults with AD, as well as reducing the risk of AD, improving depression, sleep, sense of burden and level of fatigue in caregivers. However, MPA in community dwelling adults with AD and their caregiver is lower than in healthy older adults and non-caregivers, respectively. Usual care strategies for increasing MPA have shown minimal effectiveness in this population. For example, our group completed an 8-wk. trial in 21 adults with AD designed to increase their daily steps. Participants were given a pedometer to wear daily and asked to double number of steps taken. Baseline step counts were low (27,059 steps/wk.) and only increased by 5% (1,284 steps/wk.) across the 8-wk trial. Trials evaluating innovative, scalable strategies for increasing and maintaining MPA in community dwelling dyads of adults with AD and their caregivers are currently unavailable. Our group recently completed a single arm pilot trial in 9 adults with AD/caregiver dyads which demonstrated the feasibility of delivering group-based MPA via video conferencing (Zoom® software) on a tablet computer (iPad®) to participants in their homes. A health coach delivered three, 30 min interactive exercise sessions/wk. to 4-6 dyads over 12 wks. Each session included a warm-up (5 min), aerobic and resistance exercise (20 min), and cool down (5 min). Session attendance was ~77% for adults with AD and ~79% for their caregiver. Total PA assessed by (Fitbit) increased by 60 min/wk. with an increase in MPA of 24 min/wk. (49%) in adults with AD and 35 mins/wk. with an increase in MPA of 23 min/wk. (13%) in caregivers across 12 wks. This approach may be effective for increasing MPA in adults with AD and their caregiver as it allows participants to engage in group-based activity in their home, thus eliminating the need to travel to an exercise facility, provides an opportunity for interaction and social support from both the health coach and their peers, and decreases caregiver burden associated with caregiver directed exercise, e.g., finding time, providing adequate support, motivation. Although the group video approach appears promising, the effectiveness of this approach to increase and maintain MPA over a longer time frame in adults with AD and their caregiver is unknown. Thus, we propose to compare the effectiveness of two delivery strategies for increasing MPA, real-time group video conferencing (RGV) vs. usual care enhanced with caregiver support and participation (EUC), in 100 community dwelling adults with mild to moderate AD and their caregiver (dyads) over 18 mos. (6 mos. active, 6 mos. maintenance, 6 mos. no contact). All participants will be provided with an iPad® for intervention delivery, Fitbit for self-monitoring MPA, and will be asked to complete 150 min of MPA/wk. Dyads in the RGV arm will be asked to complete three 45 min sessions that will include aerobic, resistance, and balance/coordination exercises delivered by a trained health coach via Zoom® software on an iPad® during mos. 0-6, and 1 session/wk. during mos. 7-12 to groups of 5-8 dyads in their home. Dyads in the EUC arm, will be provided with structured exercise plan to complete on their own. Dyads in both arms will be provided with written materials regarding exercise and physical activity from the National Institute on Aging and will be asked to complete brief (15-20 min) FaceTime® meetings (0-6 mos.= 2/mo.; 7-12 mos.= 1/mo.) with the heath coach to discuss progress, provide support and receive additional guidance on how to increase MPA. Our primary outcome, MPA, will be assessed by accelerometer across the 6-mo. active intervention and total 18 mo. trial.

Primary aim. To compare total MPA (min/wk.) across the 6-mo. active intervention in adults with AD and their caregiver randomized to RGV and EUC. We expect greater MPA in the RGV compared to EUC arm.

Secondary aims: To compare the following across 18 mos. between RGV and EUC. *Adults with AD:* MPA (min/wk.), sedentary time (min/wk.), percentage meeting 150 min/wk. goal, functional fitness, activities of daily living (basic/instrumental), quality of life, residential transitions, neuropsychiatric symptoms, cognitive function. *Caregivers:* Total MPA (min/wk.), sedentary time (min/wk.), functional fitness, quality of life, caregiver burden. We expect more favorable changes for all secondary outcomes for both adults with AD and caregivers in the RGV compared with the EUC arm.

Exploratory aim. To evaluate the influence of process variables/ characteristics on MPA in adults with AD and their caregiver across 18 mos.: age, sex, BMI, attendance (exercise/support sessions), use of recorded sessions, PA self-monitoring, peer interactions during group sessions, caregiver support, level of dementia.

B. Background and Significance

Alzheimer's Dementia. Approximately 5.3 million adults in the U.S. age 65+ (3.3 million women, 2 million men) have Alzheimer's dementia (AD). AD is a progressive, irreversible brain disease that is characterized by amyloid plaques and neurofibrillary tangles in the brain which are associated with the deterioration of brain function resulting in cognitive decline, behavioral and psychiatric symptoms and reductions in functional status including the ability to complete activities of daily living (ADL) and self-care (1). A series of recently published systematic reviews concluded there is insufficient evidence for interventions employing physical activity (2), pharmacologic treatments (3), over the counter supplements (4) or cognitive training (5) for the prevention of cognitive decline or dementia in healthy older adults. Aging is the prominent risk factor for the development of AD. Thus, the prevalence of AD is expected to increase to 13.8 million by 2050 as the number of adults age 65 and over increases (6). Individuals who survive with AD will eventually become completely dependent on others for assistance with basic ADLs, including eating (1). The long duration of illness spent in a state of disability and dependence prior to death contributes to the public health impact of AD. Between 1990 and 2010 the burden of AD, measured by disability-adjusted life years, has increased from 25th to 10th, more than any other disease or condition (7). Adults with AD and their family members, who provide the majority of unpaid care for adults with AD living in the community, suffer significant emotional, financial and physical stress (8). In addition, caring for adults with AD burdens both the health and long-term care systems as the rates of hospitalization in this group are 2 to 3 times that of same age adults without AD, and ~70% of residents of assisted living facilities have some form of cognitive impairment (9, 10). Thus, interventions targeting both the prevention of residential transitions to long-term care systems in adults with AD and improvements in the quality of life and level of burden of caregivers are warranted.

Role of physical activity in AD. Drugs approved for the treatment of AD may temporarily improve disease symptoms; however, none of these drugs modify the underlying neuropathology of the disease or its progression, and are associated with side effects that may limit long-term use (11, 12). Physical activity may provide an accessible, practical and economical non-pharmacologic approach for the management of AD. Participation in moderate intensity physical activity (MPA) may allow patients with AD to maintain cognitive and physical function and quality of life to the extent possible as the disease progresses, without the side effects associated with currently available medications. Physical activity in adults with dementia, assessed by both accelerometer (13-16) and questionnaire (17, 18) is lower than healthy older adults. For example Van Alpen et al (14) reported that physical activity assessed by accelerometer over 6 consecutive days was ~22% lower and sedentary time was ~9% greater in community dwelling adults with dementia (n = 37, age = 77 yrs.) compared with community dwelling healthy older adults (n = 26, age=79 yrs.). A recent Lancet Commission report

on prevention, intervention and care for dementia concluded that exercise programs for adults with mild-to-moderate dementia are feasible and well tolerated, and offer small positive effects on physical function; however, the impact on cognition is unclear (12). Martin-Ginis et al (19) recently developed an evidence based public health messaging statement for the use of physical activity for the prevention of AD and the management of symptoms and complications of AD based on a systematic review of 20 systematic reviews (121 unique studies) on this topic. Management outcomes considered included cognition, depression/mood, challenging behaviors (aggression, restlessness, wandering, rummaging), physical performance/function (cardiovascular fitness, gait speed, lower extremity strength, mobility) balance and fall prevention, ADLs, and quality of life. The messaging statement resulting from this review reads *"Regular participation in physical activity is associated with a reduced risk of developing Alzheimer's disease. Among older adults with Alzheimer's disease and other dementias, regular physical activity can improve performance of activities of daily living and mobility, and may improve general cognition and balance*" (19). Insufficient or inadequate evidence was available to address the other management outcomes. Physical activity in adults with dementia has been associated with low risk of adverse events (20) with no evidence of increased physical activity being associated with disease progression (19). Thus, increased physical activity may play an important role in the management of AD; however, effective, cost-efficient, scalable strategies for increasing physical activity in community dwelling adults with AD are not currently available.

Caregivers. Over 15 million people in the U.S. provide unpaid care for adults with AD or other dementias (1). Approximately 80% of adults with AD in the U.S. live in the community (21); 66% of caregivers live with the care recipient (22). More than 90% of those with AD living in the community rely on family or unpaid caregivers for their care (22). Caregiving typically includes assistance with ADLs, including bathing and dressing, and with instrumental activities of daily living including (IADL) such as bill paying, transportation and shopping. Approximately 50% of caregivers for individuals with dementia are in a high-burden situation based on the Burden of Care Index which is a composite of the number of hours of care provided, and the number of ADLs and IADLs performed (21). Care for dementia patients tends to be of longer duration than care for other conditions. More than half (57%) of family caregivers for adults with AD or other dementias living in the community provide care for 4 or more yrs. (1). High burden of care over an extended time frame places significant mental and physical strain on caregivers, and may have a negative impact on caregiver health (21, 23). Thirty-five percent of dementia caregivers report declines in their health status as a result of caregiving responsibilities compared with 20% of caregivers of non-dementia adults (21). Caregivers of adults with AD have reduced health related quality of life (24, 25), are often socially isolated (8, 26) and are at increased risk for depression and anxiety (8, 27), musculoskeletal discomfort (28), and stroke (29), and show elevated biomarkers for cardiovascular disease (30, 31). Caregiving has also been associated with reduced physical activity (32-36). Caregiver health problems are frequently superseded by those of the care recipient although poor caregiver health may negatively impact the quality of care provided and hasten nursing home placement for the adult with AD. Data from a limited number of home-based physical activity interventions directed to family members providing care for adults with dementia have shown reduced stress, caregiver burden, depression, and improved sleep quality and positive affect (37-43).

Promotion of MPA. As previously described, increased MPA in both adults with AD and their caregiver is associated with important health and functional benefits. Usual care strategies to promote MPA typically include providing recommendations for MPA, handouts on how to achieve this recommendations, and provision of a pedometer for self-monitoring. However, usual care strategies have shown minimal improvements in MPA. For example, members of our research team completed an 8-wk. trial designed to evaluate a usual care approach to increase the number of steps/wk., assessed by a Fitbit, in a sample of 21 adults with cognitive impairment (age=72 yrs., 43% female)(44). Participants were provided written recommendations to increase their steps by

20% each wk. over the first 5 wks. and to maintain this level for the remainder of the 8- week trial. Health coaches made individual phone calls to each participant (2 calls/mo.) to encourage exercise, problem-solve barriers to exercise, and provide technical support. Health coaches also monitored participants daily step data obtained from the Fitbit and made additional phone calls to remind participants to wear or upload Fitbit data if no activity was recorded for 3 consecutive days. Baseline steps were low, 27,058 ± 21,661 steps/wk., and increased by 1,284 ±12,976 steps/wk. (4.7%) across the 8-wk intervention (44). Caregiver support, which was not included in this trial, may have improved the effectiveness of this minimal intervention.

Intervention delivery. Usual care strategies have not been shown to provide significant improvement in MPA in adults with AD across time and there are no trials designed specifically to evaluate alternative strategies to increase long-term (≥12 mos.) daily MPA in this group. Most trials in community dwelling adults with AD and/or caregivers have been designed primarily to assess the impact of exercise on cognitive and physical function, neuropsychiatric symptoms, quality of life etc., and did not include assessments of changes in daily MPA. Participants in these trials were generally required to travel to a medical clinic or community site for supervised exercise (45-50); however, home visits by exercise specialists, (43, 46, 51-53), and trained caregivers have also been used to deliver exercise interventions (54, 55). The significant barriers associated with these approaches, including the time and cost associated with travel to clinic or community site, expense associated with individual home visits and additional burden associated with caregiver directed exercise greatly reduce the potential of these approaches to result in sustained improvements in MPA. Limited information is available regarding alternative strategies to increase MPA in community dwelling adults/caregivers that eliminate or reduced barriers including telephone (37, 39) ,and telehealth (56). For example, Farran et al (39) completed a 12 mo. telephone delivered behavioral intervention designed to increase MPA (goal ≥ 150 min/wk., assessed by self-report) in family caregivers (n=211, age= 61 yrs.) for adults with dementia living in the community. Brief intervention calls (15-20 min) using social cognitive approaches were conducted with participants weekly over the first 2 mos., bi-weekly during mos. 3-4, and monthly during mos. 5-12. Control participants completed a 12-mo. skill building intervention, delivered by phone on the same schedule as the MPA intervention. The skill building intervention was designed to provide information and support for caregivers but did not include any information or discussion regarding physical activity. At 12 mos., MPA (min/wk.) doubled in the intervention group and decreased by 5% in controls. From mos. 3-12, 63% of the intervention compared with 37% of controls achieved the 150 min/wk. goal (p<0.0001). The assessment of MPA by self-report and high and differential drop-out between groups (intervention = 37%, control = 16%, p=0.001) limit the validity of these findings. A small (n=2 patient/caregiver dyads), short-term (4 wk.) pilot trial demonstrated the feasibility of telehealth (video link) delivery of an exercise intervention; however, this approach does not remove the transportation burden as participants need to travel to a telehealth site which are limited and often located some distance from participants (56).

Potential for video conferencing. An intervention delivered via video conferencing to adults with AD and their caregivers in their homes, represents a potentially effective approach for increasing MPA in this group. This approach requires no travel, since the need for transportation to a medical clinic or other community facility is eliminated, and offers the potential for peer support and socialization, which may be important for initiation and maintenance of MPA. To assess the feasibility of the video conferencing approach, we recently completed a 12-wk. single arm pilot trial in 9 adults with AD (age = 74 ± 16 yrs., 56% female) and their family caregiver (dyads) (age = 67 ± 13 yrs., 67% female) funded by the University of Kansas Alzheimer's Disease Center (KU-ADC). Three, 30-min. group exercise sessions/wk. were delivered by trained health coaches via video conferencing (Zoom® software) on a tablet computer (iPad®) to 4-6 dyads in their homes. Each session included a warm-up (5 min), aerobic (10-15 mins) and resistance exercise (5-10 mins), and cool down (5 min). Participants wore a Fitbit activity tracker over the 12 wk. intervention to assess

the duration and intensity of the physical activity sessions and total weekly MPA (min./wk.). Participants received brief monthly phone calls (<5 min) from the health coach to provide strategies for encouraging and supporting MPA, and as a reminder of the upcoming video session. Session attendance was ~77% for adults with AD and ~79% for caregivers. MPA per group session averaged 20.4 ± 8.5 (at ~ 57% of estimated HR_{max}) and 27.0 ± 8.2 min/session (at ~61% of estimated $HR_{max)}$ in adults with AD, and their caregiver, respectively. Attendance at the monthly individual support session was 87% for both the adults with AD and the caregivers. At baseline, total weekly MPA was 53.9 ± 34.5 min/wk.in adults with AD and 166.4 ± 54.7 min/wk. in caregivers, and increased by 24 min/wk (45%) and 49 min./wk. (30%), in adults with AD and caregivers, respectively. Compliance with the Fitbit protocol was acceptable as adults with AD and caregivers wore the Fitbit on 82.5 ± 27.7% and 79.9 ± 25.7% of the total study days, respectively. Exit surveys indicated that participants generally enjoyed the program, preferred a home-based program vs. traveling to an exercise facility, preferred group over individual exercise sessions, and were interested in participating in longer sessions.

C. Rationale

Adults with AD and their caregivers represent a sizeable and underserved segment of the population with low levels of MPA and diminished physical, functional, and psychological outcomes. Available evidence suggests that regular MPA can improve performance of ADLs, IADLs, and mobility, and may improve general cognition and balance in adults with AD, as well as reduce the risk of development of AD and improve health and well-being in caregivers. However, the options for increased MPA in community dwelling adults and their caregivers are limited, e.g., medical clinics, community sites, home visits, caregiver delivered, and are associated with significant barriers including the time and cost associated with travel to clinic or community site, expense associated with individual home visits and additional burden for caregiver directed exercise that greatly reduces the potential of these approaches to result in sustained improvements in MPA. Trials specifically designed to evaluate strategies to increase long-term daily MPA in adults with AD and their caregivers are currently unavailable. Results from our single arm, short-term (12-wk.) pilot trial suggest the feasibility and potential effectiveness of video conferencing to deliver an intervention to increase MPA in this group. Video conferencing allows participants to engage in group-based activity, led by a health coach, in their home, and provides an opportunity for interaction and social support from both the health coach and their peers. However, the effectiveness of the group video approach to increase and maintain MPA over a longer time frame (12-18 mos.) in adults with AD and their caregiver is unknown. Thus, we propose to compare 2 strategies for the delivery of an intervention to increase MPA in adults with AD and their caregiver; real-time group video conferencing (RGV) vs. enhanced usual care (EUC). If effective, RGV may provide a scalable and sustainable format, which could be used by community agencies, or others to efficiently deliver MPA to adults with AD and caregivers in their homes.

A. Study Objectives

We will compare 2 strategies for the delivery of an intervention to increase MPA in community dwelling adults with AD and their caregiver (dyads); real-time group video conferencing (RGV) vs. enhanced usual care (EUC- caregiver participation plus support).

B. Study Type and Design:

We will study older adults (age ≥ 55 yrs.) with mild to moderate AD (n=100) and their caregiver (n=100) randomized (1:1) to one of two intervention delivery strategies for increasing MPA; real-time group video conferencing (RGV) vs. enhanced usual care (EUC). All participants will be provided with an iPad® for intervention delivery, Fitbit for self-monitoring MPA, and will be asked to complete 150 min of MPA/wk. Dyads in the RGV arm will be asked to complete three 45 min sessions that include aerobic, resistance, and balance/coordination exercises delivered by a trained

health coach via Zoom® software on an iPad® during mos. 0-6, and 1 session/wk. during mos. 7-12 to groups of 5-8 dyads in their home. Dyads in the EUC arm, will be given an exercise plan to do own their own. Dyads in both arms will be provided with written materials regarding exercise and physical activity from the National Institute on Aging and will be asked to complete brief (15-20 min) FaceTime™ meetings (0-6 mos.= 2/mo.; 7-12 mos.= 1/mo.) with the heath coach to discuss progress, provide support and receive additional guidance on how to increase MPA. Our primary outcome, MPA, will be assessed by accelerometer across the 6 mo. active intervention and total 18 mo. study (secondary outcome).

C. Sample size, statistical methods, and power calculation

We will recruit 100 adults with AD and their caregiver (100 dyads) at baseline to achieve adequate power to test both short-term (0-6 mos.) and long-term (0-18 mos.) effects of the intervention. Our power calculation, based on 21 measurements of MPA, 35 measurements of secondary and exploratory outcomes, a previously observed correlation of 0.22 between repeated measures, and a high attrition rate of ~20%, indicated that this sample size (≥42/arm after attrition) would produce ≥80% power to detect an anticipated difference of 10-min/d in MPA (*SD*=30 min/d; *f*=0.17) between adults with AD randomized to RGV and EUC during the active intervention (0-6 mos.). This sample size would also yield ≥81% power to test a between-arm difference as small as *f*=0.15, e.g., 6 ± 30 min/d in MPA, during maintenance (7-12 mos.) and no contact (13-18 mos.).

D. Subject Criteria (See Vulnerable Populations appendix, if applicable):

Primary care physician (PCP) clearance will be required of participants with AD and their caregiver. To enhance generalizability, individuals taking AD or other medications, or receiving treatment for other chronic diseases, or with risk factors such as hypertension, tobacco use, lipid abnormalities, T2DM, etc., will be allowed to participate with PCP clearance. *Inclusion criteria (Adults with AD): Inclusion: 1)* Very mild to moderate dementia (MMSE or STMS ≥ 11; Telephone Interview for Cognitive Status (TICS) ≥ 6). *2)* Age ≥ 55 yrs. *3)* Low-risk of falls, assessed by PCP consent *4*) Ability to participate in MPA, e.g., walk including with an assistive device, as verified PCP clearance. *5)* Ability to communicate verbally. *6)* Vision and hearing sufficient to safely comply with the intervention program as verified by PCP clearance. *7)* Reside at home and receive support from a caregiver. *8)* Internet access in the home. *Exclusion criteria (Adults with AD):1)* Current exercise, i.e., > 3, 30-min bouts of planned exercise/wk. *2)* Clinically significant psychiatric disorder; systemic illness or infection likely to affect safety; clinically-evident stroke; myocardial infarction or coronary artery disease in the last 2 yrs.; cancer in the last 5 yrs.; or significant pain or musculoskeletal symptoms that would prohibit exercise. *4)* Unwilling to be randomized. *Inclusion criteria (caregivers): 1)* Age ≥18 yrs. *2)* Spends at least 20 hrs./wk. with the adult with AD. *Exclusion criteria (Caregiver): 1)* Unable to participate in MPA, i.e., brisk walking. *2)* Unwilling to be randomized. *3)* Serious medical risk, such as cancer within the last 5 yrs. or cardiac event, i.e., heart attack, stroke, angioplasty within the last 2 yrs.

E. Specific methods and techniques used throughout the study

Randomization. Cohorts of ~20 dyads will be stratified by sex and computer randomized by the study statistician with equal allocation to the RGV or EUC arms. Intervention assignments will be concealed in envelopes and delivered to the study coordinator. Assignments will be revealed to adult/caregiver dyads at the orientation session described below.

Consumer advisory panel. Prior to initiating the intervention, we will convene a group of 4-5 adults with AD and their caregivers, who will not participate in this trial, and representatives from 4-5 community agencies providing services to adults with AD. This group will review the intervention protocols, materials, etc., and offer suggestions for modification, and will reconvene annually to offer input on issues that may arise during the intervention, discuss results, and provide insight

regarding logical next steps. If our intervention is successful, community agencies will be provided with information and guidance on implementing the intervention within their agency and individuals they serve, if desired.

Intervention components common to both arms

Orientation. One week prior to initiating the intervention, health coaches will conduct a home visit (~ 60 min) with each adult with AD/caregiver dyad in both intervention arms. Health coaches will deliver all necessary equipment and orient participants to the use of all equipment/software, answer questions regarding the general requirements of the trial, and demonstrate/practice the basic aerobic and resistance exercises with participants. Each dyad will be provided with the following: iPad®, iPod® touch, 2- Fitbit Versa Lites ® and resistance bands (TheraBand, Akron, OH). The iPad® will be used to deliver either the real time exercise sessions (RGV only), individual support sessions, and for syncing the Fitbit of adults with AD. The iPod® will be used to sync the Fitbit of caregivers, as the iPad® is capable of syncing only one Fitbit. The iPod® will also allow for communication between the caregiver and the health coach via iMessage. Dyads in the RGV arm will be provided with an iPad®/HDMI adaptor, which allows video conference sessions to be displayed on a larger TV screen, if desired. All software/apps appropriate for each intervention arm will be loaded on the iPad®/ iPod®, i.e., Zoom®, Dropbox® (to provide access to recorded videos and written materials) and Fitbit app. Reminders regarding upcoming group video and/or health educator/dyad support sessions will be programed using the iCalendar app on the iPad®. Access to non-study related materials, e.g., web browsing, app store etc. will be blocked on all iPads®/ iPods® until completion of the maintenance intervention (12 mos.). *Individual support sessions.* Dyads will be asked to attend 15-20-min education/support sessions (2 sessions/mo. during the active intervention (0-6 mos.) and 1 session/mo. during maintenance (7-12 mos.) delivered remotely on the iPad® using FaceTime®. No individual support sessions will be scheduled during the no-contact period (13-18 mos.). Sessions will be designed to educate and support the adult with AD and caregivers with meeting their 150 min/wk. goal for MPA. Each session will include a review of physical activity self-monitoring data, goal setting, strategies to increase and support MPA, and discussion of a topic relevant to MPA. During the active intervention (0-6 mos.) topics will include the importance of MPA for health and function, how to include MPA in the daily schedule, reduce barriers to physical activity, appropriate types of activity, creating a safe environment for physical activity, alternative activities for inclement weather, importance of hydration, etc. During maintenance (7-12 mos.) the discussion will focus on strategies to ensure continued participation in MPA, opportunities for physical activity in the community, and continued encouragement of dyadic activity. Topic outlines and information relative to support sessions will be pre-loaded on the iPad® where they can be assessed at any time across the 18-mo. trial. *Self-monitoring-physical activity***.** Adults with AD and caregivers in both arms will be asked to wear a Fitbit Versa Lite activity tracker on their non-dominant wrist over the duration of the 18-mo. trial. This request may appear onerous; however, wearing the Fitbit is akin to wearing a wristwatch. Real-time data from the Fitbit is automatically transferred, via the web, to cloud storage (Fitabase, Small Steps Labs LLC, San Diego, CA), thus, participant burden is minimal. Fitbit data is available to both participants and the health coach via the Fitbit app. Immediate participant feedback of daily steps, minutes of sedentary time, and time spent in light, moderate and vigorous physical activity will be available via a graphic display on the device and the Fitbit app. The health coach will log into each participant account once per week to verify they are wearing and charging the device and to monitor participant activity solely for use in providing motivation and feedback during the individual support sessions. Outcome data for MPA and sedentary time will be assessed by accelerometer as described subsequently. Dyads will be reminded to wear and charge the Fitbit during group exercise (RGV only) and individual support sessions, and will receive automatic reminder messages every 3 days via the iPad® using the iCal app. We successfully used the Fitbit and these reminder procedures in our pilot trails in adults with AD (44) and similar procedures have been used by others (60).

RGV arm

Schedule. Group exercise sessions will be scheduled on 3 non-consecutive days/wk.(M,W,F) during the active intervention (0 to 6 mos.) and 1 day/wk. during maintenance (mos. 7-12). Group sessions will not be scheduled during the no-contact period (13-18 mos.). During orientation sessions, dyads will be asked to provide times of the day, between 10 a.m. and 7 p.m., that would be most convenient to complete the group sessions. Based on this information we will offer dyads in each cohort the choice between 2 potential session times each day. Prompts reminding adults with AD/caregivers of upcoming sessions will be sent using iMessage on the iPad® (adult with AD)/iPod® (caregiver) and iCalendar. *Session delivery***.** Real-time exercise sessions will be delivered to adults with AD/caregiver dyads in their home by a trained health coach experienced in working with adults with AD using Zoom® video conferencing software. This software allows multiple users to see and interact with each other and the health coach via the iPad®. The health coach will conduct exercise sessions from our remote-delivery exercise studio (see facilities) which we used for remote delivery of exercise in our AD pilot (61) and in trials with adolescents with intellectual and developmental disabilities (IDD) (62), and adults with Down Syndrome (63). Tutorials describing trouble shooting for common technical problems with the Zoom® software, e.g., internet connectivity etc., will be loaded on the iPad®. Dyads with technical issues during the intervention may also contact research staff by phone or email. An alternative caregiver (other family member, staff etc.) may participate in the event that the caregiver enrolled in the trial is unable to attend an exercise session. These procedures were used in our AD pilot trial where alternative caregivers attended 8% of sessions (61). *MPA session content.* Dr. Vidoni, a physical therapist, will develop the exercise program for this trial. He developed the exercise content for our pilot trial in adults with AD and has been involved in other exercise trials for adults with AD (R01AG034614, R01AG033673) (64-66). Each session will include a warm-up (~5 min), moderate intensity aerobic activity (3-5 METs) (~30 min), resistance and balance/coordination exercise (~5 min.), and cool-down/stretching (~5 min.). The MPA portion will ramp from 10 min/session at wk. 1 to the goal of 30 min/session at wk. 8. Each session will include aerobic activity, e.g., walking/jogging standing in place or sitting in a chair, sit to stand, dance movements); resistance exercise, e.g., TheraBand®-arm curls, leg extensions, side leg raises, and seated rows; and balance exercise, e.g. heel to toe walks, balance walk, and standing on one foot with/without support of a chair). Dr. Vidoni will provide modifications for participants having difficulty with any specific exercises. Health coaches will encourage interactions between participants during group sessions and ensure interactions between participants do not focus on dementia (67), but rather on issues relative to supporting their peer's efforts to increase MPA. Additionally, the Zoom app used for the sessions allows for messaging between participants during and after the group exercise sessions. Caregivers will be allowed to message the research staff and other caregivers for help and support both during the sessions and outside of the group sessions. We will keep copies of the messages sent to research staff on the KUMC P-Drive. *Outside session MPA*. Group exercise sessions will provide the potential to accumulate 90 min/wk. (3 sessions x 30 min/session) during the active intervention (0-6 mos.) and 30 min/wk. (1 session) during maintenance (7-12 mos.). Thus, MPA in addition to that accumulated in group sessions will be required to meet the MPA goal of 150 min/wk. To provide a transition from a sedentary to a more physically active lifestyle we will recommend goal of 45 min of MPA/wk. at wk. 1 and increase the goal by 15 min/wk.to reach the 150 min/wk. goal at wk. 8. We successfully used this MPA progression in previous trials in adults with AD (57). At the completion of each group session health coaches will provide a "weekly challenge" for participants to try a new activity or create and perform a new exercise routine etc. in order to reach the 150 min./wk. goal. Additionally, the NIA pamphlet "Exercise and Physical Activity: Your Everyday Guide" will be loaded on the iPad to assist participants in meeting the 150 min./wk. goal. *Video recordings*. Video recordings of all group exercise sessions will be uploaded to Dropbox®. Participants/caregivers will be encouraged to access video recordings using their iPads®/iPods® to assist with meeting the 150 min./wk. goal. Frequency and duration of participant/caregiver video access will be tracked using Dropbox® analytics. *No contact follow up (13-18 mos.).* Group video and individual support sessions will be discontinued. Participants will be

asked to continue to obtain 150 min/wk. of MPA and self-monitor their MPA via Fitbit. Access to the video recorded sessions will be maintained; however, new content will not be added.

EUC arm

Intervention. Individuals with AD and caregivers will be provided information regarding increasing MPA, available from the "Exercise and Physical Activity: Your Everyday Guide from the National Institute on Aging (NIA)", provided with a Fitbit for self-monitoring, and encouraged to achieve 150 min/wk. of MPA. The NIA guide reviews the importance of endurance, strength, balance and flexibility exercise, provides suggestions for incorporating physical activity into daily life, describes how to properly perform different types of exercises, and includes examples of daily exercise schedules. Protocols for individual support sessions and self-monitoring have been described previously (*see Intervention components common to both arms)*. Caregivers will be allowed to message research staff through the Zoom app for additional support or questions as needed. *No contact follow up (13-18 mos.).* Individual support sessions will be discontinued. Participants will be asked to continue to obtain 150 min/wk. of MPA and self-monitor their MPA via Fitbit. To provide a transition from a sedentary to a more physically active lifestyle we will recommend goal of 45 min of MPA/wk. at wk. 1 and increase the goal by 15 min/wk.to reach the 150 min/wk. goal at wk. 8.

Health coach training/blinding/fidelity. *Training.* We currently have 3 health coaches with experience in delivering group exercise using video conferencing to adults with AD. If needed, new health coaches will be trained by Drs. Vidoni and Ptomey, and will shadow an experienced health coach for a minimum of 3 mos. prior to delivering the intervention on their own. Dr. Vidoni will train health coaches on how to perform each exercise, the order of presentation of the exercises, and provide guidance on how to recognize and correct common mistakes in performing specific exercises. Dr. Ptomey will provide training regarding strategies for effective communication with adults with AD, i.e., speaking clearly and slowly, providing/repeating simple specific instructions (68), focusing on reassurance and empathy for each participant (69), and fostering interaction between participants with strategies to ensure the focus of the interactions is not on dementia (67). *Blinding*. The nature of this trial precludes blinding of the health coaches; however, investigators, data analysts and research assistants will be blinded to condition. *Intervention fidelity*. Recordings from all group exercise sessions (RGV only) and individual support sessions will be reviewed. Dr. Gorczyca will compare recordings of both group exercise and support sessions with a check list of exercises/topics scheduled to be included in each session. Health educators covering <80% of scheduled content, or failing to deliver physical activity as prescribed, will receive additional training from Dr. Ptomey, and will be dismissed if the problem recurs.

ASSESSMENTS

MPA. Primary outcome (Baseline (0 mos.)- 6 mos.)/Secondary outcomes (0-18 mos.)

Schedule. MPA in adults with AD and their caregiver will be assessed at baseline (1 wk. prior to starting the intervention), 3, 6, 12, and 18 mos. *Equipment.* MPA/sedentary time will be assessed using an ActiGraph model wGT3x-BT tri-axial accelerometer (3.3 x 4.6 x 3.5 cm, wt. = 19 g., dynamic range ± 8 g). The ActiGraph provides valid and reliable assessments of MPA/sedentary time in adults (70-73). Our group has used the ActiGraph in several trials in a variety of populations including adolescents (74) and adults with IDD (75), and in typically developing children (76, 77) and adults (78, 79). *Protocol*. There is a lack of consensus on the best protocols to collect, process, and score ActiGraph data (80-82). Thus, our decisions regarding ActiGraph location, monitoring period, data processing etc. were based on current practice, as described below. Participants will be asked to wear the ActiGraph on a belt over the non-dominant hip at the anterior axillary line during waking hours for 7 consecutive days, except for bathing and swimming. A 7-day monitoring period provides a reliable estimate of MPA (81, 83-85). The hip, rather than the wrist location, will be used due to the lack of comparable data and established protocols for assessment of MPA using wrist-worn ActiGraphs (86-88). *ActiGraph distribution/reminders*. Research staff will distribute and

demonstrate proper placement of the ActiGraphs at home visits scheduled at 0, 6, 12 and 18 mos. ActiGraphs will be distributed by mail for the 3-mo. assessment. Daily reminders to comply with the ActiGraph protocol will be sent to participant's iPad® each morning during the 7-day monitoring period. We have employed similar distribution and reminder protocols in previous trials (74 , 75-77, 79). Our current supply of ActiGraphs, plus the additional units requested in this proposal, will allow physical activity assessments to be completed on all participants in the proposed timeframe. *Data collection*. ActiGraphs will be initialized and downloaded using ActiLife Software version 6.13.3 or higher (ActiGraph Corp, Pensacola, FL) and set to collect in the raw data mode from all 3 axes at 60 Hz. Although the wGT3x-BT collects raw data from 3 axes, the widely used cut-points for determining activity intensity in adults proposed for this trial use acceleration data from the ActiGraph vertical axis (89). However, raw data from all 3 axes will be downloaded and stored, and will be available should algorithms for processing this data become available during this trial. *Data processing* Accelerometer data will be processed using the protocol for adults used in the 2003-2004 and 2005-2006 cycles of NHANES (89, 90). Data will be aggregated over 60-sec epochs. The following intensity cut-points will be used: sedentary (< 1.0 MET; ≤ 100 counts/min), light (1.1-2.99 METs; 101-2019 counts/min.), moderate (3.0-5.99 METs; 2020-5988 counts/min) and vigorous ≥ 6 METs; ≥ 5999 counts/min) (89, 90). Non-wear time will be defined as at least 60 consecutive minutes of zero counts, with allowance for 1-2 min of counts between 0 and 100. Counts ≥ 20,000/min will be considered spurious (91). All accelerometer data processing will be completed using custom SAS/-R programs developed by Drs. Little and Lee, the project statisticians, in collaboration with our research group. *Missing accelerometer data*. Recent advances in both statistical methods and computing power have made it possible to impute missing data with large data sets, such as will be collected in the proposed trial, i.e., 7 wk.-long assessments across 18 mos. A detailed description of the methods and procedures for handling missing ActiGraph data (non-wear and device malfunction time) is included in the analysis plan. MPA data for both adults with AD and caregivers will be analyzed including and excluding video conference exercise sessions (RGV arm).

Secondary outcomes. Secondary/exploratory outcomes will be assessed at baseline (1-2 wks. before starting the intervention), 6, 12 and 18 mos. in the adult with AD or caregiver's home. Our experience with similar trials suggests these assessments, which will be completed by trained staff blinded to condition, will require ~75 min to complete. Staff will receive refresher training and complete reliability assessments for all physical measures 2-3 times/yr.

Secondary outcomes-Adult with AD. *Sedentary time* will be assessed using data collected from the ActiGraph as described above. *Functional fitness* will be measured using Functional Fitness Test (FFT) previously called the Senior Fitness Test (92). The individual fitness test items involve common activities such as getting up from a chair, walking, lifting, bending, and stretching. Reliability of the FFT in older adults with cognitive impairment is high in all of the test items (ICC ≥ 0.93) (93). *Activities of daily living* will be assessed using the Disabilities Assessment for Dementia (DAD)(94). The DAD includes 40 items: 17 related to basic self-care and 23 to instrumental activities of daily living. DAD demonstrated a high degree of internal consistency (Cronbach's alpha = .96) and excellent inter-rater (n = 31, ICC = .95) and test-retest (n = 45, ICC = .96) reliability. In addition, it has been shown to have no gender bias. *Quality of life* will be assessed using the QOL-AD(95), a brief, 13-item self-report and 15-item caregiver-report. The QOL-AD has shown acceptable validity and reliability when completed by adults with AD or a caregiver proxy (ICC= .76 and .92 respectively) (95). *Residential transitions*, i.e., from home to institutional care, will be tracked by health coaches. We will also assess caregiver desire to institutionalize the adult with AD using the 6-item Morycz's Desire-to-Institutionalize Scale (96). This scale demonstrated moderate reliability with KR-20 alpha of .694 for Whites, .742 for African Americans, and .767 for Hispanics (97). *Neuropsychiatric symptoms* will be assessed using the Neuropsychiatric Inventory (NPI) (98). The NPI evaluates 12 neuropsychiatric disturbances common in dementia and the amount of caregiver distress engendered by each of the neuropsychiatric disorders. Validity

(ICC=0.53-0.97) and reliability (inter-rater agreement=94-100%) of the NPI are acceptable (99). *Cognitive function* will be assessed using the Symbol Digit Modalities Test (SDMT) (100) which has previously been used in adults with AD (101, 102). Test-retest correlations for the SDMT, as well as the correlation between its written and oral administrations, are both 0.80 (103, 104). *Quality of the dyadic relationship* will be assessed using the dyadic relationship scale (DRS) which measures negative and positive dyadic interactions from the perspective of both the patient and the caregiver. The DRS has acceptable construct, discriminant, and concurrent validity, as well as reliability for both patients and family caregivers (105)

Secondary outcomes-Caregiver. *Sedentary time* will be assessed using data collected from the ActiGraph as described above. *Functional fitness* will be measured using the FFT described above. Reliability of the FFT for community-dwelling older adults without cognitive impairment is acceptable (ICC = 0.80–0.98)(92). *Quality of Life* will be assessed using the SF-36(106) which has acceptable reliability and validity in the general population (107). *Caregiver Burden* will be assessed using the Zarit Burden Interview-short version, a 12-item self-report questionnaire in which the caregiver is asked to answer using a 5-point scale. The short version (108) has shown acceptable correlations (0.92 to 0.97) with the full 22-item version in caregivers of adults with AD.(109). *Quality of the dyadic relationship* will be assessed using the dyadic relationship scale (DRS) described above.

Exploratory outcomes

BMI. Weight will be measured in duplicate in light clothing on a calibrated scale (Model #PS6600, Belfour, Saukville, WI) to the nearest 0.1 kg. Standing height will be measured in duplicate with a portable stadiometer (Model #IP0955, Invicta Plastics Limited, Leicester, UK). BMI will be calculated as weight (kg)/height (m^2). *Session attendance* for group exercise (RGV only) and support sessions will be obtained from records maintained by the health coach, and expressed as the percent of possible sessions from 0-6 mos. and 7-12 mos. Attendance for adults with AD, enrolled caregivers, and alternative caregivers will be recorded separately. *Use of recorded videos* (frequency and duration of access, RGV only) will be assessed using Dropbox® analytics. *Self-monitoring of physical activity* will be assessed as the percentage of days with Fitbit data over a minimum of 8 hrs., between 6 am and midnight (0-6, 7-12, 13-18 mos.). *Peer interactions (RGV only).* Staff will review video recordings of a random sample of 33% of group exercise sessions to identify and classify both peer to peer, and health coach to participant interactions. Interactions will be quantified and coded as verbal/non-verbal (waving, pointing, shaking head in agreement/disagreement), and as positive, neutral or negative, relative to support, using a modification of a checklist we previously developed for a group video exercise intervention for adolescents with IDD (62).*Caregiver support* will be assessed using the percentage of group exercise sessions (RGV) and/ or individual support sessions completed by both the person with AD and their caregiver. *Quality of the dyadic relationship* will be assessed at baseline, 6, 12, and 18 mos. using the dyadic relationship scale (DRS) which measures negative and positive dyadic interactions from the perspective of both the patient and the caregiver. The DRS has acceptable construct, discriminant, and concurrent validity, as well as reliability for both patients and caregivers(105). We will evaluate the impact of the DRS on our primary and secondary outcomes as well as examine changes across time in both groups. *Type of dyadic relationship*. We will document the type of caregiver, e.g., spouse, adults child, paid staff, and evaluate the impact of caregiver on our primary and secondary outcomes. *Number of caregivers*. We will document the number of different caregivers for adults with AD and evaluate the impact of the number of caregivers on our primary and secondary outcomes. *Level of dementia* will be assessed at baseline using the CDR(110) which has shown acceptable validity(111) and reliability(112). *Energy Expenditure of Remote Sessions* Energy expenditure of the remote sessions will be assessed in a volunteer sample of both patient and caregiver using a previously validated portable, open-circuit indirect calorimeter (Cosmed, Italy) which measures breath-by-breath ventilation, expired oxygen, and carbon dioxide. Study staff will schedule the assessment with participants which will involve an

additional visit to participants' homes in which study staff will administer the assessment. The flow turbine will be calibrated using a 3.0-L syringe. The lightweight (~1.5 kg) portable system will be attached by a harness around the waist and shoulders of the participant before each assessment. The device will be programmed utilizing study ID numbers, with no other identifying information. During exercise sessions, participants will breathe into a facemask that directs air into the unit housing the O2 and CO2 analyzers. Data will be retrieved for analysis via a serial port interface and downloaded to a university monitored, HIPPA compliant computer once staff returns to campus. Software provided with the calorimeter will be used to analyze data by aggregating over 20-second epochs for the calculation of 1-min averages. MET levels will be age corrected using the Schofield equation (117) as recommended by McMurray et al (118). Participants will be asked to wear both hip and wrist ActiGraphs during the assessment for comparison of physical activity levels between devices.

Exit interview. We will conduct structured interviews by phone with a 20% random sample of adults with AD and caregivers from both intervention arms to gather information that might be useful for improving the intervention and/or implementing the intervention in settings serving adults with AD. Topics will include preference for the RGV or EUC interventions, reasons for missing scheduled sessions for both the adult with AD and caregiver, enjoyment of the live video sessions, intervention length, difficulties with compliance, suggestions for improvements and overall satisfaction with the intervention, caregivers enjoyment of the exercise and educational sessions, performance of health coaches, physical activity recommendations etc. Qualitative content analysis (Atlas, ti 6.2) will be conducted to search for broad themes across interviews (113).

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F. Risk/benefit assessment:

Potential Risks. Risks to the individual with AD and caregiver in this study are minimal. There have been no serious adverse events with PA interventions in any of our completed trials, including trials with older adults and individuals with AD. Increased PA may be associated with minor injuries such as strains and sprains, and the potential for muscle soreness, particularly in the early stages of the PA protocol, may exist. These risks will be minimized by gradually increasing the MVPA recommendation and providing instruction on proper exercise technique.

Protection Against Risk. Risks for injury related to participation in PA will be minimized by discussions with health coaches and the individual with AD and caregiver regarding gradual progression of PA, warm up, cool down, etc. and modification of activities, if necessary, by Dr. Vidoni. There are some potential health risks for individuals who are using medications during exercise interventions; however, we have appropriate inclusion/exclusion criteria and physician consent will be necessary for participation. We also have over 30 years' experience with physical activity studies that provide services to individuals with a wide variety of health risks without any serious adverse events or deaths. We will use a data safety and monitoring plan to assure participant safety during the intervention. Participant's data will be identified only by an assigned study ID number. Participant's identifiable information will not be shared unless required by law or with written permission. All iPads will be set up by the IT team at KUMC and additional security software, Casper, will be installed. On top of encrypting all data on the iPad, Casper will prevent participants from downloading and using non-study related apps. Additionally, if the iPad is lost or stolen Casper will allow the IT team to wipe it clean remotely. Individual accounts for all apps (Fitbit, Zoom, Dropbox) will be created by the study team and will contain no identifiable information. While the videos that will be distributed by cloud-storage (Dropbox) will have identifiable information (videos of participants) we will use a HIPPA compliant cloud storage program (Dropbox business) to ensure the safety of these video recordings.

Removal from the Study. If the study present greater then minimal risk to a participant they will be censored from the study and referred to the University of Kansas Alzheimer's Disease Center for recommendations for other resources for PA. All participants and caregivers will be informed that they may be censored from the study due to safety risk during the consent procedure. We believe the following scenarios would present a greater than minimal risk to participants. *Lack of caregiver*. A caregiver will be asked to participate in the intervention with the adult with AD. Many caregivers will be older adults and it is possible some may become deceased, become ill or hospitalized and unable to provide care to the AD individual. If this happens, the adult with AD will be asked to identify another individual to serve as the official study caregiver. if an alternative caregiver cannot be identified the individual with AD will be censored from the study from that time forward. *Transition to a residential facility*. Some adults with AD may be placed in a residential care facility during the 18-mo. intervention. If this occurs the adult with AD will be censored from the study. *Change in severity of AD*. If dementia progresses to the point that either the caregiver or research staff feel the intervention is no longer safe for the individual, they will be censored from the study. If an individual with AD is removed from the study for one of the aforementioned reasons (transition to residential facility or change in severity of AD), decides to no longer participate in the intervention, or dies during the intervention, the caregiver will be allowed to continue in the intervention, if they choose. If a caregiver stays enrolled in the intervention without the person with AD we will no longer collect outcomes regarding Caregiver Burden or Quality of the dyadic relationship.

Potential Benefits of the Proposed Research to the Subjects and Others. The benefits to the participants are the well-established benefits of PA including improvements in activities of daily living and mobility and may improve general cognition and balance in adults with AD. Additionally, caregivers may benefit from reduced caregiver burden and increased quality of life. Individuals with AD and caregivers may benefit from an increased understanding regarding how to develop PA routines, the benefits of regular PA, and ways to encourage PA in the household. The information obtained from this study will increase our understanding regarding strategies for the delivery of PA interventions to individuals with AD and caregivers. The risks to participants in this study are minimal while the benefits to individuals with AD and caregivers in need of increased MVPA are potentially large.

Importance of the Knowledge to be Gained. Individuals with AD and caregivers have low rates of PA and may benefit greatly from participation in a PA program. The development of an effective strategy for increasing PA would be important for improving physical function, mobility, and quality of life in adults with AD and their caregivers, resulting in allowing individuals with AD to stay in their homes longer and reducing caregiver burden. Thus, we believe adults with AD and their caregivers deserve to be included in the development of state-of–the-art interventions to improve their mobility and quality of life and believe this proposal offers a potentially viable strategy for increasing MVPA in this population.

G. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

Adverse Event and Serious Adverse Event Collection and Reporting. Staff involved in performance of the protocol are expected continually monitor participants for adverse events throughout all outcome's assessment, exercise sessions, and individual education session. Expected side effects of exercise such as mild soreness that resolve in a reasonable short amount of time (less than 48 hours) will not be considered an AE.

Adverse Event Grading. This study uses the definition of adverse events (AE) from the "NIA Adverse Event and Serious Adverse Event Guidelines, Version 3 December 2013". AE are defined as any untoward or unfavorable medical occurrence in a human subject participant, including any

abnormal sign, symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.
The MPIs will determine the severity and relatedness of the AE to the intervention and be responsible for reporting to the National Institute on Aging (NIA), and Safety Officer (SO) in the appropriate time frames. Severity of the adverse event will be determined using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0. The intervention and measurement protocols proposed for this study pose minimal risk to participants. Because of this low risk status, the data safety monitoring plan (DSMP) for this trial focuses on close monitoring by the multiple principal investigators (MPI) and the safety officer along with prompt reporting of excessive or serious adverse events to the NIH and to the Human Subjects Committee (HSC) at The University of Kansas Medical Center.

Adverse Event Reporting The MPIs will review and evaluate adverse events within 72 hours. All adverse events, regardless of their seriousness, severity or relatedness to the intervention are reportable to NIA PO and the Safety Officer (SO) semi-annually. A summary of these reports is provided to the IRB on an annual basis. Deaths and SAEs are handled in an expedited fashion as follows:

- Deaths: All deaths will be reported within 24 hours to the NIA Program Officer, SO, and the IRB.
- Unanticipated SAEs: When SAEs occur that are unanticipated and related to the intervention, they will be reported to the NIA Program Officer, ISO, and the IRB within 48 hours of study team's knowledge of the SAE.
- Other SAEs: The summary of all other SAEs will be reported to the NIA Program Officer and SO quarterly.

All potential Adverse Events will be collected on an Adverse Event Form. If study staff, tester, participant, or other individual interacting with the participant during the testing visits, group exercise session, or individual education sessions reports adverse events or complaints, relevant information will be collected and documented using REDCap.

Stopping Rules. We believe this trial conveys minimal risk. Both intervention groups in this trial will have the potential to increase their level of physical activity, a desirable behavior change that conveys health benefits when contrasted with sedentary behavior. We expect greater physical activity in the RGV compared with the EUC arm; however, the magnitude of this difference is irrelevant in regards to decisions to stop the trial. Physical activity in participants in both groups will likely be increased. Even if this is not the case there will be no increase in health risk above baseline in either intervention group. The most likely scenario indicating the need to stop the investigation would be a failure to recruit or deliver the intervention as planned.

Data and Safety Monitoring
The Principal Investigators (MPIs) and co-investigators will be responsible for ensuring study staff are appropriately trained in good clinical research practice and human subjects protections to minimize risk and maximize the value of the participants' contributions. The PI and co-investigators will be responsible for ensuring the collection of all the information necessary for SO to evaluate the quality and safety of the study. The MPIs will be responsive to the questions, inquiries, and concerns of the SO, IRB, and NIA regarding these data and procedures.

Frequency of Data and Safety Monitoring. The frequency of data review for this study differs according to the type of data, the availability of data collected, and the perceived level of risk. Safety reports are sent to the SO at least twice a year and will include a detailed analysis of study progress, data and safety issues.

Data type	Frequency of review

Subject accrual (adherence to protocol regarding demographics, inclusion/exclusion)	Quarterly
Adverse events (injuries/illness)	As they occur
Compliance to treatment	Monthly
Out of range laboratory data	Semi-annually

Data Analysis and Coordination. Data will be checked for outliers and normalcy at logical time points but at least at 4-month intervals. Questionable data (e.g., >3 SD from the mean) will be re-checked and re-entered, if necessary.

Measurement and Reporting of Subject Accrual, Adherence to Inclusion/Exclusion Criteria. The study statisticians Dr. Lee and Little will review of the rate of subject accrual and adherence to inclusion/exclusion criteria will occur quarterly to assure that participants meet eligibility criteria and ethnic diversity goals outlined in the grant proposal.

Measurement and Reporting of Participant Compliance to the Treatment Protocol. Compliance to the intervention will be reported monthly by the study statisticians. To monitor compliance, they will report the group attendance at group exercise sessions (RGV) and/or individual health education sessions (EUC). Compliance to the intervention protocol will be reviewed monthly by the MPIs. We are using an intent-to-treat design; thus, participants will not be dismissed for non-compliance, but will be counseled on strategies to improve compliance during scheduled FTF or RD sessions.

Safety Officer. The safety officer for this trial will be Ryan Townley, MD. Dr. Townley is a Neurologist at the University of Kansas Alzheimer's Disease Center and is not affiliated with the study in any other fashion and is not in the MPI's chain of command. zhe will review the reports sent by the study coordinator semi-annually and adverse events as they occur and will use the checklists attached to this document to determine whether there is any action, such as an ad hoc review or stopping rule violation that should be communicated to the study investigators, The University of Kansas Human Subjects Committee, or NIH. In addition, the safety officer may comment on whether the study investigator needs to report any specific out of range laboratory data to the participant, and/or their physician.

II. Subject Participation

A. Recruitment: The KU-ADC will contact individuals in their database who appear to be eligible based on patient records by phone and by a letter sent to their homes. Names and contact information of interested patients will be forwarded to the study, who will contact the patient/caregiver to describe the study, answer questions and to assess initial patient and caregiver eligibility. Additionally, we will recruit individuals in the community through flyers that will be distributed though social media advertisement, the city bus system, and email. Flyers will have a link to our study website (www.ebl.ku.edu/m2g) which contains a link to the eligibility questionnaire that can be filled out by individuals who are interested in the study. Participants who fill out the eligibility questionnaire and appear to qualify will be contacted by a member of the study team who will describe the study, answer questions and complete the dementia screening questionnaire. Informed consent will be obtained from each subject prior to entry into the study. Visits, video conference calls (Zoom® software), or phone calls will be scheduled with individuals deemed to be initially eligible to describe the project in detail, answer questions, verify eligibility, and to obtain subject consent. Prior to the consenting session, the participant will be sent the consent form and cover letter through Kansas University Medical Center's (KUMC) secure email system. Each participant will be given the option to consent with staff in-person, remotely using video conferencing (Zoom® software) or telephone, or online through REDCap.

For participants choosing to consent remotely, the signed and dated consent form will be sent to the project staff's secure KUMC email or submitted online through REDCap. Separate informed consent will be obtained for the patient and caregiver. If the patient with AD is not their own legal guardian, we will obtain consent from their legal guardian and assent from the patient. Project staff will fax/email a form to the primary care provider of both the patient and caregiver, which describes the eligibility criteria, study requirements, and requests clearance for participation. Those found to be ineligible will be provided with written materials describing available resources for increasing their MPA.

B. Alternatives to Participation: Participants may join other physical activity programs.

C. How new information will be conveyed to the study subject and how it will be documented: New information will be told to the subjects during their health educator visits as well as by emails sent to all participants and their legal guardians.

D. Payment, including a prorated plan for payment: Gift cards valued at $50 for both adults with AD and caregivers will be provided for data collection at baseline, 6,12, and 18 mos. to compensate for time required to complete testing. Adults with AD and caregivers will receive $50 gift cards to compensate for time and travel associated with completing the consent process and the CDR at KU-ADC at baseline, and $25 gift cards for the assessment of MPA via ActiGraph at 3 mos. As an additional incentive, adults with AD and caregivers will be allowed to keep the iPad®/iPod® and the Fitbit on completion of the active intervention (12 mos.).

IV. Data Collection and Protection

Data will be entered into a KUMC Redcap database. Only de-identified data will available to study personnel, e.g., statisticians. Data will be checked for outliers and normalcy at logical time points. Questionable data (e.g., >3 SD from the mean) will be re-checked and re-entered, if necessary. Checked data will be archived weekly. Data entry will be completed by research assistants blinded to group assignment. All personnel have current Human Subjects/HIPAA certificates. Study materials, and copies of the group exercise videos will be stored on our secure sever through KU-L.

iPads will be set up by KUMC's IT department. All iPads will be set up with a study iCloud account, and all Zoom accounts, Fitbit accounts, and Dropbox accounts will be created by the study team, and will not have identifiable information on them.

V.Data Analysis and Reporting

A. Statistical and Data Analysis:

Statistical design. *Baseline equivalence.* The distributional properties of baseline demographic characteristics (MPA, BMI, age, sex, race/ethnicity, etc.) and dyadic relationship between adults with AD and their caregiver (quality, type, number of caregivers) will be inspected within the sample and between the RGV and EUC arms. Variables that demonstrate a significant nonequivalence between RGV and EUC arms will be statistically controlled in the hypothesis testing to improve accuracy of our inferences on intervention effects. Additionally, variables that significantly differ between dyads that dropped out and those that did not will be controlled to minimize any systematic bias stemming from attrition.

Primary aim: To compare MPA (min/wk.) across the 6-mo. active intervention in adults with AD randomized to RGV and EUC. Our analysis will account for/evaluate the clustering of observations (repeated measurements; level 1) within participants (level 2) and dyads (level 3; if multiple caregivers) by estimating intra-class correlations and variances/covariances of regression

coefficients at, and across, different levels in random-effects multilevel models (mixed models). To address the aim, models will examine overall between-arm difference in MPV across time (group effect), linear/non-linear change in MPV over time (time effect), and, if appropriate, between-arm difference in this change (group-by-time interaction), while controlling for (i) the number of contacts with research staff and (ii) the baseline characteristics imbalances between participant subgroups (RGV vs. EUC, dropouts vs. completers). For example, a significant interaction would indicate that adults with AD in the RGV arm achieve more minutes of MPA compared to those in the EUC arm and this difference becomes greater as intervention participation increases, i.e., in the later mos.

Secondary aim: To compare adults with AD and their caregivers randomized to RGV or ECU on the following outcomes across 18 mos. Adults with AD: MPA (min/wk.), sedentary time (min/wk.), percentage meeting 150 min/wk. goal, functional fitness, activities of daily living (basic/instrumental), quality of life, residential transitions, neuropsychiatric symptoms, and cognitive function. *Caregivers*: MPA (min/wk.), sedentary time (min/wk.), functional fitness, quality of life, and caregiver burden. Similar mixed models will be fitted separately for these outcome variables to examine group effect, time effect, and group-by-time interaction while controlling for the number of contacts with research staff and the baseline characteristics imbalanced between participant subgroups.

Exploratory aim: To evaluate the influence of process variables/participant characteristics on MPA in adults with AD and their caregiver across 18 mos.: age, sex, BMI, attendance (exercise/support sessions), use of recorded sessions, PA self-monitoring, peer interactions during group sessions, caregiver support, type and quality of the dyadic relationship, number of caregivers, and level of dementia. If MPA is not significantly different between RGV and EUC across 18 mos., i.e., no significant group effect or group-by-time interaction, we will combine the two arms and examine associations of the process variables/characteristics with MPA in mixed modeling. However, if a significant between-arm difference in MPA is identified, we will determine whether the process variables/characteristics enhance or attenuate the treatment effects, i.e., moderation, by testing a 2-way interaction with the group effect and/or a 3-way interaction with the group-by-time interaction term. In addition, we will examine how caregiver MPA influences the MPA of adults with AD over the 6-mo. active intervention, 6 mos. maintenance, and 6 mos. no contact. Some variables will be measured only at baseline, some will be summarized across the trial, while others will be assessed at specific time points. Thus, we will carefully design our models to assure the appropriateness of the analysis.

Missing data. Missing data is anticipated due to either attrition, e.g., participant dropout, or nonresponse, e.g., ActiGraph non-wear or malfunction. Our intent-to-treat approach will employ full information maximum likelihood (FIML) estimation in the modeling, which does not discard participants who dropped out but utilizes all available data from their partial measurements, thereby producing unbiased parameter estimates and smallest possible standard errors. Missing observations due to nonresponse will be handled by Monte Carlo Markov Chain (MCMC) multiple imputation (MI) (114). A sufficient number of imputed datasets will be created to ensure accurate recovery of missing data and analysis results from each imputed dataset will be combined to make valid statistical inferences. Our imputation process will incorporate a number of auxiliary variables, thereby satisfying the missing at random (MAR) assumption (115). The state-of-the-science on missing data indicates that FIML and MI are extremely robust and leads to unbiased generalizability (116).

V. Bibliography / References / Literature Cited

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