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The Promotion of Physical Activity for the Prevention of Alzheimer's Disease in Adults with Down Syndrome (Brain Power)

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TABLE OF CONTENTS

PRÉCIS

Study Title

The Promotion of Physical Activity for the Prevention of Alzheimer's Disease in Adults with Down Syndrome

Objectives

Primary aim: Assess daily moderate-to-vigorous physical activity (MVPA, min) in the Remote Low (RL), Remote High (RH), and Usual Care (UC) arms at baseline, 3, 6, 9, and 12 mos., and obtain effect sizes for change in MVPA over 12-mos.
Secondary aim 1: Assess the impact of MVPA across the RL, RH, and UC arms on cardiovascular fitness, quality of life, cognitive function and brain parameters related to AD (whole and regional brain volume, functional connectivity, cerebral blood flow) at baseline, 6, and 12 mos.
Secondary Aim 2: Determine the feasibility (retention, session attendance, use of recorded sessions (RH/RL only) and safety of RL, RH, and UC arms.

Design and Outcomes

This is a 12-mo. trial in 80 non-demented adults with Down Syndrome. Participants will be randomized (2:2:1) to attend 40 min. remotely delivered group MVPA sessions (Zoom™ Video Conferencing Inc., San Jose, CA) at a low frequency (1 session/wk.,RL) or high frequency (3 sessions/wk., RH), or a usual care control (UC). In addition to the group MVPA sessions, participants in both the RL and RH arms will receive a step counter (Charge 3™, Fitbit, San Francisco, CA), access to resources for increasing MVPA, and two 20-min remotely delivered (Zoom™) individual support/education session/mo. Content for both the RL and RH arms will be identical with the exception of group MVPA session frequency (1 vs. 3/wk.). Participants in the UC arm will receive a step counter (Charge 3™, Fitbit, San Francisco, CA), access to resources for increasing MVPA, and bi weekly remote (Zoom™) individual support/education). Daily MVPA will be assessed by portable accelerometer (ActiGraph wGT3XBT, ActiGraph LLC, Pensacola, FL) at baseline, 3, 6, 9 and 12 mos. All secondary outcomes will be assessed at baseline, 6 and 12 mos.

Table 1: Design Overview

	Intervention Arms		
	Remote High	**Remote Low**	**Usual Care**
MVPA recommendation	150 min/wk.	150 min/wk.	150 min/wk.
Group MVPA sessions	Yes	Yes	No
Delivery format	Zoom™ video conferencing	Zoom™ video conferencing	NA
Frequency	3d/wk.	1d/wk.	NA
Intensity	≥ 3 METS	≥ 3 METS	NA
Duration	40 min	40 min	NA
Content	Stretch/aerobic activity/RE	Stretch/aerobic activity/RE	NA
Access to PA resources	Yes	Yes	Yes
MVPA Self-monitoring	Fitbit	Fitbit	Fitbit
Education/support/feedback sessions	Yes	Yes	Yes
Participants	DS adult + Study Partner	DS adult + Study Partner	DS adult + Study Partner
Frequency	2x/mo	2x/mo	2x/mo
Delivery format	Zoom™	Zoom™	Zoom™
Duration	20 min/session	20 min/session	20 min/session
	Note: NA = not applicable, RE= resistance exercise		

Interventions and Duration

Participants will be randomized to one of 3 interventions for 12 months.

1. Remote High (RH)
2. Remote Low (RL)
3. Usual Care (UC)

Sample Size and Population

80 adults (≥18 years of age) with Down syndrome will be recruited and computer randomized. Participants will be stratified by sex and then sequentially randomized by the study statistician with 2:2:1 allocation to the RL, RH, and UC arms. We expect 32 participants in the RL, 32 participants in RH, and 16 in UC.

1 STUDY OBJECTIVES

1.1 Primary Objective

Assess daily MVPA (min) in the RL, RH, and UC arms at baseline, 3, 6, 9, and 12 mos., and obtain effect sizes for change in MVPA over 12-mos.

1.2 Secondary Objectives

Secondary aim 1: Assess the impact of MVPA across the RL, RH, and UC arms on cardiovascular fitness, quality of life, cognitive function and brain parameters related to AD (whole and regional brain volume, functional connectivity, cerebral blood flow) at baseline, 6, and 12 mos.

Secondary Aim 2: Determine the feasibility (retention, session attendance, use of recorded sessions (RH/RL only) and safety of RL, RH, and UC arms.

2 BACKGROUND AND RATIONALE

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

Nearly all individuals with Down Syndrome (DS) will develop Alzheimer's Disease (AD), some beginning as early as age 30. To date, trials have failed to identify any drug that is safe or effective for the prevention of AD in adults with DS, and there is a lack of non-pharmacologic strategies for the prevention of AD in adults with DS. Previous research in typically developing adults suggests that increased MVPA may improve cognitive function and protect against age-related functional and structural brain changes; however, the potential impact of increased MVPA on the development of AD in adults with DS has not been evaluated. Despite the potential positive impact of MVPA, participation in MVPA among adults with DS is low. The limited research evaluating intervention strategies for increasing MVPA in adults with DS is not specific to adults with DS, i.e., includes all IDDs, and has been unsuccessful in increasing short-term (≤ 12 wks.) or long-term MVPA (12 mos.). Results from our 12-wk. pilot trial of a remote method which delivers real-time MVPA, led by a trained health educator, to groups of adults with DS in their homes (n=27), via video conferencing on a tablet computer demonstrated high attendance, increased MVPA during group sessions, and improvements in cognitive function. However, the sustainability, impact on total daily MVPA, optimal session frequency, and potential impacts on cognitive function and measures of brain health of remotely delivered group MVPA sessions in adults with DS are unknown. Therefore, we will conduct a 12 mo. early stage clinical trial in 80 non-demented adults with DS to determine the feasibility and potential efficacy of remotely delivered group MVPA, delivered at two different frequencies to increase daily MVPA, relative to a usual care control. This early stage clinical trial will inform and advance the design of a subsequent late stage clinical trial while providing important data regarding the effect of MVPA on cognition and measures of brain health related to development of AD in adults with DS.

3 STUDY DESIGN

This is a 12-mo. randomized control trial in 80 non-demented adults with DS. Participants will be randomized (2:2:1) to attend 40 min. remotely delivered group MVPA sessions (Zoom™ Video Conferencing Inc., San Jose, CA) at a low frequency (1 session/wk.,RL) or high frequency (3 sessions/wk., RH), or a usual care control (UC). In addition to the group MVPA sessions, participants in both the RL and RH arms will receive a step counter (Charge 3™, Fitbit, San Francisco, CA), access to resources for increasing MVPA, and one 20-min remotely delivered (Zoom™) individual support/education session/wk. Content for both the RL and RH arms will be identical with the exception of group MVPA session frequency (1 vs. 3/wk.). Participants in the UC arm will receive a step counter (Charge 3™, Fitbit, San Francisco, CA), access to resources for increasing MVPA, and monthly remote (Zoom™) individual support/education. The primary outcomes, daily MVPA will be assessed by portable accelerometer (ActiGraph wGT3XBT, ActiGraph LLC, Pensacola, FL) at baseline, 3, 6, 9 and 12 mos. The secondary outcomes, cardiovascular fitness, quality of life, cognitive function and brain parameters related to AD (whole and regional brain volume, functional connectivity, cerebral blood flow) will be assessed at baseline, 6, and 12 mos. With the exception of assessment of daily MVPA by accelerometer, all outcomes will be assessed at the University of Kansas Medical Center, in Kansas City, KS. The exercise intervention will take place in the participants home.

Table 1: Design Overview

	Intervention Arms		
	Remote High (n=32)	**Remote Low (n=32)**	**Usual Care (n=16)**
MVPA recommendation	150 min/wk.	150 min/wk.	150 min/wk.
Group MVPA sessions	Yes	Yes	No
Delivery format	Zoom™ video conferencing	Zoom™ video conferencing	NA
Frequency	3d/wk.	1d/wk.	NA
Intensity	≥ 3 METS	≥ 3 METS	NA
Duration	40 min	40 min	NA
Content	Stretch/aerobic activity/RE	Stretch/aerobic activity/RE	NA
Access to PA resources	Yes	Yes	Yes
MVPA Self-monitoring	Fitbit	Fitbit	Fitbit
Education/support/feedback sessions	Yes	Yes	Yes
Participants	DS adult + Study Partner	DS adult + Study Partner	DS adult + Study Partner
Frequency	2x/mo	2x/mo	2x/mo
Delivery format	Zoom™	Zoom™	Zoom™
Duration	20 min/session	20 min/session	20 min/session
	Note: NA = not applicable, RE= resistance exercise		

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Primary care physician (PCP) clearance will be required for all participants. To enhance generalizability, individuals on medications for common chronic diseases, i.e., depression, blood pressure, lipids, type 2 diabetes, and those with previous cognitional heart defects will not be excluded. Random assignment should distribute these characteristics equally across groups.

Inclusion criteria: *1)* Adults – age 18 and over. 2) Diagnosis of DS as determined by a Community Service Provider operating in our recruitment area under the auspices of a Community Developmental Disability Organization (CDDO). Participants will be judged competent to provide informed consent by their CDDO, or will have a guardian with power of attorney. Participants will not be enrolled without providing assent, regardless of guardian consent. 3*)* Sufficient functional ability to understand directions, communicate preferences, wants and needs through spoken language. We will exclude individuals who are unable to communicate through spoken language. These individuals may also benefit from increased MVPA; however, strategies necessary for intervention delivery are likely to differ from those used with individuals who are able to communicate through spoken language. *4)* Living at home with a parent/guardian or in a supported living environment with a caregiver who agrees to serve as a study partner. *5)* No plans to relocate outside the study area over the next 12 mos. *6)* Internet access in the home. In our previous and ongoing studies in adults with DS, 90% of the participants had wireless internet in their homes.

4.2 Exclusion Criteria

All candidates meeting any of the following exclusion criteria at baseline will be excluded from study participation: 1) Diagnosis of dementia as determine by the Dementia Screening Questionnaire for Individuals with Intellectual (DSQIID). 2) Unable to participate in MVPA. 3) Pregnancy during the previous 6 mos., currently lactating or planned pregnancy in the following 12 mos. Participants who become pregnant will be removed from the study and referred to appropriate agencies for consultation. 4) Serious medical risk, e.g., cancer, recent heart attack, stroke, angioplasty as determined by the PCP. 5) Unwilling to be randomized. 6) Participation in a regular exercise program, i.e. ≥ 20 min/d ≥ 3 d/wk. 7) Unable to walk unassisted.

4.3 Study Enrollment Procedures

Project staff will contact local community agencies serving adults with DS, case managers, and CDDOs by mail/email, provide presentations at CDDO meetings, and text for CDDO newsletters describing the project. Interested parents/guardians, caregivers, or adults with DS will be asked to contact the study coordinator via email, our website (www.ebl.ku.edu), or a dedicated toll-free study phone number that will be included in all recruitment materials. The study coordinator will contact the interested individuals by phone to answer questions and conduct an initial eligibility screen. Zoom calls will be scheduled with those remaining interested, and potentially eligible, to obtain informed consent (participants or guardian and caregivers) and assent (participant) and determine final eligibility based on the DSQIDD scores. Project staff will send a form (fax/email) to the potential participant's PCP which describes the study and requests clearance for participation. Participants found to be ineligible will be provided with written materials describing available resources for increasing physical activity. Project staff will track ineligibility and non-participants of eligible candidates using a REDCAP database. Participants will be stratified by sex and then sequentially randomized by the study statistician with 2:2:1 allocation to the RL, RH, and UC arms.

5 STUDY INTERVENTIONS

Randomization Cohorts of ~10-20 participants will be recruited and computer randomized. Participants will be stratified by sex and age (18-30 or >30) and then sequentially randomized by the study statistician with 2:2:1 allocation to the RL, RH, and UC arms. This randomization scheme was selected to include more participants in the group video conferencing arms which, if successful, will be included in a later stage trial examining the effectiveness of increased MVPA using the video conferencing approach on cognitive function and brain health in adults with DS. Intervention assignments will be concealed in envelopes and delivered to the study coordinator.

Caregiver role. We will recruit either a parent/guardian or residential support staff, to serve as a study partner for each participant. Study partners will be allowed to assist multiple adults, provided all adults are in the same intervention group. Study partners will be asked to attend all individual support/education sessions, and to support, encourage, and assist participants in complying with the study protocol, such as reminding them to attend the group exercise sessions (RL and RH only), individual support session (all groups) providing opportunities for increased MVPA, and assisting with self-monitoring of MVPA.

MVPA recommendations. We will target 150 min/wk. of MVPA (≥ 3 METs) for all groups as recommended for all adults by the American College of Sports Medicine [1] and the U.S. Department of Health and Human Services [2]. MVPA recommendations will progress from 60 min/wk. (3 d/wk., 20 min./d) to 150 min./wk. (5 d/wk., 30 min./d) at the beginning of mo. 4, and remain at 150 min./wk. through the end of the study. Accumulated MVPA in bouts ≥ 10 min will be permitted.

RL and RH Intervention.
Orientation. Each participant and their study partner will be asked to attend a group orientation session (~60 min.) conducted at the University of Kansas Medical center and led by their health educator. In addition to describing study requirements and distributing iPads, Fitbits, resistance bands, etc., this meeting is designed to establish rapport between the health educator and participants, and between participants themselves, prior to initiating the group video conference sessions. The health educator will describe and demonstrate the Zoom™ software and the Fitbit and will allow time for practice and questions. Additionally, basic stretching exercises, the use of the resistance bands, and simple dance movements will be demonstrated and practiced.

Group sessions-schedule. Group exercise sessions will be scheduled between 10 a.m. and 7 p.m., 3 days/wk. for RH and 1 day/wk. for RL. This time window was selected based on the preference of participants in our 12-wk pilot trial in individuals with DS. Prompts reminding participants of upcoming sessions will be sent via the iPad. The same health educator will conduct MVPA sessions for both the RH and RL groups in each cohort to minimize health educator effects.

*Group sessions-Delivery***.** All MVPA sessions will be conducted by a health educator experienced in working with individuals with DS and supervised by Dr. Ptomey. Group sessions will be delivered using an iPad tablet computer provided to all participants. The iPad will be pre-loaded with video-conferencing software (Zoom™) which allows participation by multiple users. Participants will be provided with an iPad/HDMI adaptor, which allows video conference sessions to be displayed on a larger TV screen, if desired. Tutorials describing trouble shooting for common technical problems, e.g., internet connectivity etc., will be loaded on the iPad. Participants with technical issues during the intervention can also contact research staff by phone or email. Access to non-study related materials, e.g., web browsing, app store, etc., will be blocked on all iPads. The iPads for both groups will also be pre-loaded with the Fitbit application.

Group MVPA session-content. Each session will include a warm-up (~5 min), moderate-to-vigorous intensity aerobic and resistance exercise (~30 min.), and cool-down/stretching (~5 min.). Resistance exercise may be especially relevant, as adults with DS have reduced muscle strength compared with their typically developing peers [3]. The aerobic/resistance exercises, accompanied by music, will include walking/jogging in place, dancing, imitating animal movements, vertical/horizontal jumps, squats, and Thera-Band exercises for major muscle groups. Activities will be modified for participants having difficulty with specific movements. The intensity of the initial sessions, as determined by Fitbit, will be light-to-moderate, with intensity increasing to moderate-to-vigorous at ~ 6 wks. All participants will be able to see, hear, and speak to each other during the group sessions. During each session, health educators will encourage interactions between participants in

support of their peer's efforts to increase MVPA and provide participant feedback relative to their level of weekly MVPA as assessed by the Fitbit. As the intervention progresses, participants will be asked to volunteer to create and lead the group in a brief (3-5 min) exercise bout. Participants will also be encouraged to interact with each other by providing verbal support to each other ("great job", "keep it up"), performing activities such as tossing an imaginary ball to other participants, or challenging other participants to complete a skill such as 10 hops on one leg etc. All group sessions will be video recorded.

Homework assignments. The group exercise sessions have the potential to provide 30 min./wk. of MVPA for the RL group and 90 min./wk. for the RH group. Thus, MVPA outside these sessions will be required to meet the 150 min weekly recommendations. Health educators will provide weekly challenges in the form of meeting a goal for increased steps, trying a new activity, or creating and performing their own exercise routine etc. Participants will be provided access to video recordings of all group sessions that can be followed on their own to help in meeting weekly MVPA goals across the 12 mo. trial, if desired. Recordings will be sent to Dropbox and will be accessible to participants on the iPad. We will also provide information regarding increasing physical activity, available from the National Center on Health, Physical Activity and Disability (NCHPAD) and the Special Olympic athletes home training guide. Participants will be asked to document MVPA outside group sessions using the Fitbit, rather than video recordings as used in our pilot due to poor compliance with the video recording protocol. Participants press a button on the Fitbit at the beginning and end of each MVPA session to differentiate planned MVPA from other daily activity. Activity monitoring using the Fitbit is being successfully implemented to monitor the MVPA component in our on-going trial of weight management in adults with IDD (DK114121, Ptomey, MPI).

Education/support sessions. Bi-Weekly (2x/mo) 20-min. education/support sessions will be delivered to participants and their study partners remotely on the iPad using Zoom™. These sessions, led by the health educator, will be designed to educate and support the participant with meeting their 150 min./wk. MVPA goal. Each session will include a review of MVPA self-monitoring data, goal setting, strategies to increase and support MVPA, and discussion of a topic relevant to MVPA including: the importance of MVPA for health and function, how to include MVPA in the daily schedule, reducing barriers to MVPA, appropriate types of activity, creating a safe environment for MVPA, alternative activities for inclement weather, importance of hydration, etc. Session outlines and materials will be preloaded on the iPad where they can be accessed by participants at any time.

UC Intervention.

Orientation. Participants and their study partner will be asked to attend an orientation session (~60 min.) conducted at the University of Kansas Medical center and led by their health educator. In addition to describing study requirements and distributing iPads, Fitbits, resistance bands, etc., this meeting is designed to establish rapport between the health educator and participants. The health educator will describe and demonstrate the Zoom™ software and the Fitbit and will allow time for practice and questions. Additionally, basic stretching exercises and the use of the resistance bands will be demonstrated and practiced.

Intervention. The UC intervention will follow the traditional approach to promote increased MVPA in individuals with DS previously used by our group [4-6] and others [7-9]. Participants will receive an iPad tablet loaded with information regarding increasing MVPA available from NCHPAD and the Special Olympic athletes home training guide, and will also receive resistance bands and a Fitbit for self-monitoring MVPA (described below). Bi-weekly 20-min. education/support sessions, identical to the education/support sessions provided in the RL and RH arms, described above, will be

delivered to participants and their study partners remotely on the iPad using Zoom[M]. Session outlines and materials will be preloaded on the iPad where they can be accessed by the participant at any time.

MVPA-self monitoring. Participants in all 3 groups will be asked to wear a Fitbit Charge 3[TM] (35.5 mm x 28 mm) activity tracker on their non-dominant wrist over the duration of the 12-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. Immediate participant feedback via a graphic display of daily steps, minutes of sedentary time, time spent in light, moderate and vigorous PA will be available on the iPad. This data, accessible to health educators, will be used to provide motivation and feedback during the education/support sessions. Participants will be reminded to wear and charge the Fitbit during the individual support/education sessions, and will receive automatic reminder messages via the iPad using the iCal app. These procedures were used successfully in our previous trials in adults with DS[4, 6, 10, 11].

Health educator training/ fidelity

*Training***.** We currently have 3 health educators with experience in delivering group exercise and individual education and support using video conferencing to groups of adults with DS. If needed, new health educators will be trained and will shadow an experienced health educator for a minimum of 3 mos. prior to delivering the intervention on their own. We will conduct weekly meetings with all health educators to discuss issues relative to intervention delivery.

*Intervention fidelity***.** A study team member will review recordings from all scheduled group MVPA and individual support sessions. The content delivered will be compared with a checklist of scheduled activities/topics. Feedback will be provided to all health educators; those covering <80% of scheduled activities/topics will receive additional training and will be dismissed if the problem recurs.

Participant Incentives. Reinforcement systems, known as positive behavioral support programs, have been successful in promoting behavioral change in individuals with DS [12]. These strategies provide modest incentives to motivate participants to meet their goals, and were successfully used in our previous trials that included adults with DS [4, 5, 10]. Participants in all groups who complete self-monitoring of MVPA on 5 of 7 d/wk. will be allowed to choose an iTunes song which will be uploaded weekly to the participant's iPad by study staff. Additionally, to compensate for time and travel, participants will receive $200 for completion of each of the 3 outcome assessment laboratory visits (baseline, 6, 12 mos.), and $50 for completion of the additional two accelerometer outcome collection periods (3 and 9 mos.). As an additional incentive, participants will be allowed to keep the iPad and Fitbit on completion of the trial (12 mos.).

Blinding. The nature of this trial precludes blinding of the health educators; however, investigators, data analysts and research assistants will be blinded to condition

ASSESSMENTS

With the exception of assessment of daily MVPA by accelerometer, all outcomes will be assessed at the University of Kansas Medical Center, in Kansas City, KS. Cognitive function, cardiovascular fitness, and quality of life will be assessed at the Center for Physical Activity and Weight Management (CPAWM) and all neuroimaging outcomes will be assessed at Hoglund Brain Imaging Center (HBIC), which is located next door to the CPAWM. Our experience with similar trials suggests these assessments, which will be completed by trained staff blinded to condition, will

require ~2.5 hrs. to complete. Some assessments will only be collected on a sub-sample of participants.

Primary Outcome- MVPA.
Schedule. MVPA will be assessed at baseline, 3, 6, 9, and, 12 mos. *Equipment.* MVPA will be assessed using an ActiGraph (ActiGraph wGT3XBT, ActiGraph LLC, Pensacola, FL) 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 physical activity in adults [13-15], and has been widely used to describe physical activity levels in adults with DS [16-18]. Our group has used the ActiGraph in previous trials in adults with IDD [4], and in typically developing adults [19, 20]. We have also developed a custom program for processing ActiGraph data, using protocols described subsequently. *Protocol*. There is a lack of consensus on the best protocols to collect, process, and score ActiGraph data [21-24]. 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, with the exception of bathing, swimming, and contact sports. A 7-day monitoring period provides a reliable estimate of MVPA [22, 25, 26].The hip rather than the wrist location will be used due to the lack of comparable data, and established protocols for assessment of MVPA using wrist-worn ActiGraphs [27-29]. *ActiGraph distribution/reminders*. Research staff will distribute and demonstrate proper placement of the ActiGraphs at laboratory visits scheduled at baseline 6, and 12 mos. ActiGraphs will be distributed by mail for the 3, 9 mo. assessments. ActiGraphs will be returned by postage paid mail following completion of all assessments. Daily reminders to comply with the ActiGraph protocol will be sent to participants' iPads each morning during the 7-day monitoring period. We have employed similar distribution and reminder protocols in previous trials [4, 6 , 20, 30, 31]. Our current supply of ActiGraphs, plus the additional units requested in this proposal, will allow 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 wGT3XBT collects raw data from 3 axes, results from studies assessing the benefit of 3 axes vs 1 axis (vertical) are conflicting [32-34]. In addition, there are currently no established algorithms for using either the raw data or the vector magnitude (square root of the sum of the squares of each of the 3 axes) to estimate MVPA [35, 36]. The widely used cut-points for determining activity intensity in adults [37] proposed for this trial use acceleration data from the ActiGraph vertical axis. 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 the course of 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 [37, 38]. 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) [37, 38]. 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 [39]. All accelerometer data processing will be completed using custom SAS/R programs developed by our team.

Cognitive Function. Working memory, processing speed, multitasking, and episodic memory will be assessed using tests selected from the widely used Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, LTD, Cambridge, UK) [40-45]. These standardized tests have been extensively evaluated, provide normative data, and allow for comparisons across trials. CANTAB® tests have acceptable construct [40, 46, 47] and concurrent validity [47]. Specifically, we will use the CANTAB®, DS Battery which has been used in previous trials in individuals with DS [48, 49] including our pilot trial [50]. The tests in this battery, which include

measures of multitasking, episodic memory, executive function, working memory, and processing speed, have demonstrated sensitivity to disease-specific cognitive deficits in DS, including those related to hippocampal dysfunction and frontal lobe dysfunction [51] and are also sensitive to the changes in cognitive function seen in AD [52, 53]. Detailed descriptions of these test are available at the CANTAB® website (http://www.cambridgecognition.com). All tests will be administered in a quiet room on an iPad in a following manufacturer's instructions. Tests will be administered in a random order and scored by Dr. Szabo- Reed who will be blinded to intervention group. Based on results from our pilot trial, we expect completion of this battery will require ~30 min. We considered the use of the National Institutes of Health Toolbox Cognitive Battery; however, the psychometric properties for use of this battery in adults with DS are unacceptable [54].

Cardiovascular fitness. In adults without DS, cardiorespiratory fitness is associated with brain volumes in the medial, temporal, and parietal cortices, suggesting that increasing cardiorespiratory fitness, by increased MVPA, may modify AD-related brain atrophy [55, 56]. A maximal treadmill test which are commonly used in adults with DS [57-59], will be completed at baseline, 6, and 12 mos. Heart rate (Polar RS 400) and expired O2 and CO2 (ParvoMedics TrueOne 2300 - calibrated prior to each test) will be measured in 20 second intervals. We will follow the protocol by Fernal et al for individuals with and without ID [60]. The protocol starts with a 2-min warm-up at a comfortable walking speed. After the warm-up, the speed will be adjusted to a brisk walking speed. After 2 min of walking at a brisk speed and 0% grade, the grade will increase every 2 mins by 2.5% until a 12.5% grade is reached. From that point on, grade will be held constant, whereas speed will be increased by 1.6 or 0.8 km·h−1 every minute until exhaustion. The test will be ended when the participant hits two or more of the following four criteria of peak effort:1) test ended because of volitional exhaustion, 2)VO2 or HR plateau with an increase in work rate (VO2 plateau defined as an increase less than 150 mL·min−1 ; HR plateau defined as an increase less than a 2 bpm), 3) HRpeak within 5 beats of predicted HRpeak according to the formulas of Fernhall et al. [60], and 4) an RER >1.10. The exercise test will be terminated early if the participant can no longer keep up with the treadmill speed or ask to stop. A cardiologist will be on-site for all treadmill tests per American College of Sports Medicine recommendations for testing individuals with DS [61].

Quality of Life. Quality of life will be assessed at baseline, 6, and 12 mos. with the Personal Well-Being Index-Intellectual Disability(PWI-ID) [62, 63]. This instrument contains 7 items, each corresponding to a quality of life domain: standard of living, health, life achievement, personal relationships, personal safety, community-connectedness, and future security. Cronbach alpha of 0.76, and 1- to 2-wk. test–retest reliability of 0.58 have been reported in adults with IDD [62]. The PWI-ID scale differs from the original Personal Well-Being Index (PWI-A) in that it incorporates a pre-testing protocol to determine whether, and to what level of complexity, respondents are able to use the scale. The ID version also uses more simple and concrete wording. An additional question which asks how happy or sad the respondent is with life as a whole is included. A reduced choice format, illustrated as a series of outline faces, from very sad to happy, is provided to enhance comprehension and substitutes for the Likert scale used in the PWI-A version [63].

Neuroimaging (Sub-sample).. Neuroimaging measures of brain volume i.e. structural MRI, functional connectivity, i.e. resting state MRI (rsMRI), blood flow, i.e. arterial spin labeling (ASL), and spectroscopy (MRS) will be assessed at baseline, 6, and 12 mos. utilizing the scan parameters currently implemented by the NIAD and ABC-DS Structural MRI imaging has elucidated the specific brain regions impacted by dementia in DS. These grey matter changes are detectable prior to the development of signs of clinical dementia [64, 65] and have been impacted by cardiovascular fitness/MVPA[56]. Structural MRI is a feasible test in adults with DS. In a recent review of 9 trials that used rsMRI in adults with DS [66], 4 reported no scanning issues, and in the remaining 5, ~17% of participants were excluded due to motion artifact with those who have more severe intellectual

disabilities being more likely to move during the scan. However, only individuals with mild to moderate intellectual disabilities will be included in this study, which will decrease the likelihood of motion during the scan. To further reduce motion during the scan and to minimize attrition, participants will have the option to partake in a practice session before the scheduled baseline scan. For the practice session, participants will be introduced to Hoglund study team members, lie in the scanner with the appropriate head coil while 3 minutes of a study sequence runs. The practice session will last ~15 minutes and a safety screener will be completed at the beginning of the practice session. Volumetric analyses of overall and regional, e.g. hippocampus, brain volumes will be performed using FreeSurfer segmentation using the longitudinal processing stream [67], which is currently being implemented for the Alzheimer's Disease Center registry data at KUMC. rsMRI examines functional connectivity within and between brain networks. Individuals with DS show increased connectivity between networks compared to typically developing adults which has been hypothesized to reflect increased compensatory brain activation [68]. Pre-processing of rsMRI data will be performed for each participant using Analysis of Functional NeuroImages (AFNI, Medical College of Wisconsin). The rsMRI images will be realigned to the first slice collected in each scanning session to correct for motion. The images will be spatially smoothed with a 4 mm Full Width Half Maximum (FWHM) Gaussian blur. Functional and anatomic images obtained in each session will be aligned and normalized to a DS brain template [68]. An ASL sequence will be collected to measure changes in blood flow that may be related to increased fitness associated with physical activity. ASL analyses will be performed using the ASL Toolbox [69] with Statistical Parametric Mapping version 12 software (SPM12) [70] and applying methods that are currently implemented for the Alzheimer's Disease Center registry at KUMC.

Energy expenditure of Exercise Sessions (Sub-sample).. Energy expenditure of the remote sessions will be assessed in a volunteer sample using a previously validated portable, open-circuit indirect calorimeter (Pnoe, Greece) which measures breath-by-breath ventilation, expired oxygen, and carbon dioxide. 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. During exercise sessions, participants will breathe into a facemask that directs air into the unit housing the O_2 and CO_2 analyzers. Data will be retrieved for analysis via a serial port interface and software provided with the calorimeter, and aggregated over 20-second epochs for the calculation of 1-min averages. MET levels will be age corrected using the Schofield equation [71] as recommended by McMurray et al [72].

Physical Function (Sub-sample). Functional lower extremity strength will be assessed using the Five Times Sit to Stand test (5XSTS)[73, 74].Participants are asked to sit with arms folded across their chest and with their back against a free-standing chair. They are instructed to stand up and sit down five times in a row as quickly as they can. The score is the amount of time it takes to complete the task (seconds). Functional mobility will be assessed using the Timed Up and Go (TUG) test [69,70]. From a sitting postion in a standard arm chair participants are ask to stand up, walk to a line 10 feet away, turn around, return to the chair and sit down. The score is the time (seconds) it take to complete the task. Grip strength for both the dominant and non-dominant hands will be assessed using a Jamar hand grip dynamometer (JWL Instruments, Chicago, IL). Participants are asked to hold their arm with their elbow bent at a 90-degree angle and to squeeze the dynamometer as hard as possible using a smooth motion. The procedure is repeated three times with the average of the three readings used in the analysis. I/ADL will be assessed using the 17-item Waisman Activities of Daily Living survey (W-ADL)[75].

Caregiver Outcomes (Sub-sample).. Caregiver burden will be assessed using the Center for Epidemiological Studies Depression Scale (CES-D)[76] which captures multiple aspects of caregiver

burden (physical, emotional, financial). Caregiver stress will be assessed using the Caregiver Self-Assessment Questionnaire (CSAQ), which is a caregiving-specific measure of psychosocial stress and is an appropriate measure for depression screening[77]. Caregiver quality of life will be assessed using the Adult Carer Quality of Life Questionnaire (AC-QoL)[78], which covers eight different domains for caregivers: support for caring; caring choice; caring stress; money matters; personal growth; sense of value; ability to care; and caregiver satisfaction.

Feasibility. *Retention.* Retention will be measured as the percentage of participants who complete the 12 mo. intervention, defined as completing the 12 mo. outcome assessments. *Session attendance*. Session attendance for both group MVPA and individual education/support sessions from baseline to 12 mos. will be obtained from records maintained by the health educator, and expressed as the percent of possible sessions. Attendance at group MVPA sessions will be defined as being logged in to the video conference and remaining on the screen for the entire 30-min session. Attendance at individual support/education sessions, for the both exercise and UC conditions, will be defined as answering the Zoom call, and being present on screen for the entire session. *Use of recorded exercise sessions (RL and RH only)* will be tracked using Dropbox which provides information on how many times each user watched a video. *Safety*. Safety will be measured by number of participants reporting a serious adverse event, i.e., any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or results in persistent or significant disability/incapacity.

Descriptive outcomes. To characterize our study sample, we will measure weight, height and waist circumference in participants at baseline, 6, and 12 mos. Weight will be measured in light clothing on a calibrated scale (Model #PS6600, Belfour, Saukville, WI) to the nearest 0.1 kg. Standing height will be measured with a portable stadiometer (Model #IP0955, Invicta Plastics Limited, Leicester, UK). BMI will be calculated as weight (kg)/height (m^2). Waist circumference will be assessed using the procedures described by Lohman et al.[79].

Exit interview. At the end of the intervention**,** Dr. Gorczyca will conduct structured interviews by phone with a 20% random sample of participants and study partners from each intervention arm to gather information that might be useful for improving the intervention. Topics will include preference for the RH, RL, or UC arms, reasons for missing scheduled sessions, intervention length, difficulties with compliance, suggestions for improvements and overall satisfaction with the intervention, enjoyment of the MVPA and educational sessions, health educators, MVPA recommendations, satisfaction with the MRI scan protocol, and willingness to take part in outcome procedures that could be used in future studies (collection of spinal fluid, PET scan). Additionally, we will interview all caregivers to explore caregiver perspectives on the role and potential impact of increased MVPA for healthy aging in adults with DS and how improved physical function in adults with DS in their care may impact their caregiving

5.1 Adherence Assessment

Retention. Retention will be measured as the percentage of participants who complete the 12 mo. intervention, defined as completing the 12 mo. outcome assessments. *Session attendance*. Session attendance for both group MVPA and individual education/support sessions from baseline to 12 mos. will be obtained from records maintained by the health educator, and expressed as the percent of possible sessions. Attendance at group MVPA sessions will be defined as being logged in to the video conference and remaining on the screen for the entire 30-min session. Attendance at individual support/education sessions, for the both exercise and UC conditions, will be defined as answering the Zoom call, and being present on screen for the entire session. *Use of recorded*

exercise sessions (RL and RH only) will be tracked using Dropbox which provides information on how many times each user watched a video.

6 STUDY PROCEDURES

6.1 Schedule of Evaluations

				KUMC Visits				At- Home Activities		
Assessment	**Home Screening: Visit-1 (Day-30 to Day -1)**	**Enrollment, Randomization: KUMC Visit 1 (Day -14 to Day -1)**	**Start of Exercise Intervention (Day 0)**	**Accelerometer Mailed to Home (Month 3)**	**KUMC Visit 2 (Month 6)**	**Accelerometer Mailed to Home (Month 9)**	**KUMC Visit 3 (Month 12)**	**Weekly**	**Bi- Monthly**	**Daily**
Informed Consent Form	X									
Demographics	X									
Medical History	X									
DSQIDD	X									
Enrollment/Randomization		X								
Current Medications		X			X		X			
MVPA		X		X	X	X	X			
Cardiovascular Fitness		X			X		X			
Cognitive Function Test		X			X		X			
Quality of Life Questionnaire		X			X		X			
Anthropometrics		X			X		X			
Physical Function		X			X		X			
Caregiver Outcomes		X			X		X			
Optional practice session and MRI		X			X		X			
Exercise Session Attendance								X		
Individual Education Session Attendance									X	
Fitbit										X
Adverse Events		X			X			X	X	X

6.2 Description of Evaluations

6.2.1 Screening Evaluation

These evaluations occur to determine if the candidate is eligible for the study.

Consenting Procedure
Remote video chat sessions (Zoom) or in person consent meetings depending on participant preference, will be scheduled with participants, caregivers, and their legal guardian (if applicable) deemed to be initially eligible to describe the project in detail, answer questions, verify eligibility, and to obtain participant consent or, if the participant is not their own legal guardian, guardian consent and participant assent.

For remote video chat sessions (Zoom): 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. Study staff will set up a virtual Zoom meeting that allows for remote video chat. Study staff will "share screen" the consent document and walk through each section, noting questions that arise, and answer these questions fully. The signed and dated consent form will be submitted online through REDCap.

For in person consent meetings: study staff will meet at a mutually chosen location to meet with the potential participant, study partner, and legal guardian (if applicable). They will review the study with them, read the informed consent to them, and answer any questions. The participant will be allowed to keep the consent form and read over on their own and join at a later time. We will collect informed consent from participants, or if a participant is not their own legal guardian, we will collect particpant assessnt and legal guardian/suggoarte dicssion maker consent. We will obtain assesnt away from family members to make sure particpiants don't feel like they have to be in the study.

Screening
After consent, participant will be asked to complete the DSQIDD to verify eligibility. This will take place at the consenting appointment within 1 month of starting the study.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment
Enrollment is defined as the date in which a participant has signed a consent form, passes the DSQIDD turned in a physician consent form.

Baseline Assessments.
Baseline Assessments will take place within two weeks of starting the intervention and will include

- Medication review
- MVPA using accelerometer
- Cognitive Function
- Cardiovascular Fitness
- Quality of Life Questionnaire
- Anthropometrics
- Physical Function (Sub-sample).

- Caregiver Outcomes (Sub-sample).
- Optional practice MRI
- MRI (Sub-sample).
- Adverse Events Review

Randomization
Randomization will take place within 2 weeks before the start the intervention.

6.2.3 Follow-up Visits

- Accelerometer (3 months): Within 1 week of participants hitting 3 months (13 weeks) a CSA accelerometer will be mailed to their home for them to wear for 1 week and mail back.
- *Visit 2 (6 months):* Visit 2 will occur within 2 weeks of participant hitting 6 months (26 weeks) of the intervention and will include.
    - Medication review
    - MVPA using accelerometer
    - Cognitive Function
    - Cardiovascular Fitness
    - Quality of Life Questionnaire
    - Anthropometrics
    - Physical Function (Sub-sample).
    - Caregiver Outcomes (Sub-sample).
    - MRI (Sub-sample).
    - Adverse Events Review

- Accelerometer (9 months): Within 1 week of participants hitting 9 months (39 weeks) a CSA accelerometer will be mailed to their home for them to wear for 1 week and mail back.

6.2.4 At-Home Data Collection

- Attendance
    - Session attendance for both group MVPA and individual education/support sessions from baseline to 12 mos. will be obtained from records maintained by the health educator, and expressed as the percent of possible sessions. Attendance at group MVPA sessions will be defined as being logged in to the video conference and remaining on the screen for the entire 30-min session. Attendance at individual support/education sessions, for the both exercise and UC conditions, will be defined as answering the Zoom call, and being present on screen for the entire session.
- Fitbit
    - Daily MVPA will be tracked from the Fitbit device. It will be used by the Health Coaches to provide feedback.
- Exercise Video Recordings:
    - Use of recorded exercise sessions (RL and RH only) will be tracked using Dropbox which provides information on how many times each user watched a video
- Adverse Events
    - As described below, we will ask participants for any adverse events at group exercise sessions and individual education sessions.

6.2.5 Completion/Final Evaluation

- *Visit 3 (12 months):* Visit 3 will occur within 2 weeks of participant hitting 12 months (52 weeks) of the intervention and will include.
  - Medication review
  - MVPA using accelerometer
  - Cognitive Function
  - Cardiovascular Fitness
  - Quality of Life Questionnaire
  - Anthropometrics
  - Physical Function (Sub-sample).
  - Caregiver Outcomes (Sub-sample).
  - MRI (Sub-sample).
  - Adverse Events Review
  - Interview

7 SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

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 in adults with DS. 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.

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

Staff involved in performance of the protocol will continually monitor participants for adverse events throughout all outcome's assessments, exercise sessions, and individual education session. All AEs and SAEs will be recorded in the studies REDCap database.

7.3 Adverse Events and Serious Adverse Events

An adverse event (AE) is 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. Reported signs and symptoms consistent with normal exercise such as transient work-related dyspnea, flushing, fatigue, sweating, or light soreness of muscles or joints will not be considered AEs.

A serious adverse event (SAE) is defined as any adverse event that results in death, a life-threatening event, inpatient hospitalization, or a permanent disability.

7.4 Reporting Procedures

The MPIs will review and evaluate adverse events within 72 hours. AEs are reported to the DSMB bi-annualy for review, and immediately if unexpected. 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, DSMB, 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, DSMB, 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 DSMB semi-annually.

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 sessions, or individual education sessions reports adverse events or complaints, relevant information will be collected and documented using REDCap.

7.5 Follow-up for Adverse Events

Study team members will follow-up with adverse events at the next exercise session or individual education session until event is resolved.

7.6 Safety Monitoring

This study will use a DSMB. The DSMB consists of three members. Membership consists of individuals who have no financial, scientific, or other conflict of interest with the trial. Written documentation attesting to absence of conflict of interest will not be required as the experimental intervention/manipulation is standard of care. The DSMB includes experts with relevant clinical expertise and understanding of clinical trial methodology, and biostatistics.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size and Randomization

Eighty participants will be randomized in a 2:2:1 manner to RH (n=32), RL (n=32) and UC (n=16), respectively. We except a standard deviation in daily MVPA of ~ 10 min. for our primary endpoint (12 mos.) based on 12 mo. data from adults with DS who participated in our weight management trial in adults with IDD (DK83538, PI Donnelly). We will be able to estimate the mean MVPA at each time point (baseline, 3, 6, 9 and 12 mos.) with 99% confidence within ± 5 min. for the RH and RL groups with 32 participants, and with 98% confidence with 24 participants, i.e. allowing for a 25% loss to follow-up. We will be able to estimate the mean MVPA at each time point with 94% confidence within ± 5 min. for the UC group with 16 participants, and with 89% confidence with 12 participants, i.e. allowing for 25% loss to follow-up). Thus, we will have precision to estimate the intervention effects even with a 25% loss to follow-up.

8.1.1 Treatment Assignment Procedures

Cohorts of ~10-20 participants will be recruited and computer randomized. Participants will be stratified by sex and age (18-30 or >30) and then sequentially randomized by the study statistician with 2:2:1 allocation to the RL, RH, and UC arms.
This randomization scheme was selected to include more participants in the group video conferencing arms which, if successful, will be included in a later stage trial examining the effectiveness of increased MVPA using the video conferencing approach on cognitive function and brain health in adults with DS.
Intervention assignments will be concealed in envelopes and delivered to the study coordinator.
Participant randomization will be stored on the study Redcap Database.
The study team and the participants will not be blinded to group assignment.

8.2 Interim analyses and Stopping Rules

No interim analysis of outcomes is planned. We believe this trial conveys minimal risk. Indeed, increased physical activity is desirable and may convey health benefits compared to sedentary behavior. The most likely scenario indicating the need to stop the investigation would be a failure to recruit or deliver the intervention as planned. Another issue relating to stopping rules for this trial could include new information that might become available that would warrant stopping the trial, although this is a remote possibility.

8.3 Data Analyses

Our primary aim is to assess daily MVPA (min.) among the RL, RH, and UC arms at baseline, 3, 6, 9, and 12 mos. and obtain effect sizes for change in MVPA over 12-mos. We will calculate the mean and standard deviation and 95% confidence intervals of daily MVPA at each time point for all 3 groups, as well as for the change from baseline to each time point. This descriptive information will be summarized graphically which will aid in determining if, and when, differences in MVPA arise among and across the 3 groups. The corresponding effect sizes at each time point will be calculated as the differences in the mean divided by the common standard deviation. We will also estimate the correlation of MVPA over time within individuals. This information will be critical to identifying whether single point in time or longitudinal assessments will be utilized to identify the sample size needed for future large-scale confirmatory trials. We will subsequently run a repeated measures ANOVA comparing the change in baseline at each time point across the three groups using a linear mixed model approach with an autoregressive correlation structure over time. The model will include a main effect of group and time and a group by time interaction which will provide an estimate of the treatment effect when modeling longitudinally. The data from this trial will provide solid preliminary data to determine the potential for an effect and inform the best design to employ in subsequent trials.

Our first secondary aim will assess the impact of MVPA across the RL, RH, and UC arms on cardiovascular fitness, quality of life, cognitive function, and brain parameters (whole and regional brain volume, functional connectivity, cerebral blood flow) at baseline, 6, and 12 mos. We will estimate the correlation of change in MVPA on changes in cardiovascular fitness, qualify of life, cognitive function, whole and regional brain volume, functional connectivity and cerebral blood flow at 6 and 12 mos. This analysis will be completed with the total sample, irrespective of study arm. Thus 80 participants will provide at least 80% power to detect correlation of 0.31 or higher or -0.31 or lower with a type I error rate of 5%. Sixty subjects (25% loss to follow-up) will still allow us to detect a correlation of 0.36 or higher or -0.36 or lower with 80% power and type I error rate of 5%.

Our second secondary aim will determine the feasibility (retention, session attendance, use of recorded sessions (RH/RL only), and safety) of RL, RH, and UC arms. We will estimate the proportion of participants retained, session attendance, use of recorded sessions and safety, i.e. significant adverse events across the 12 mo. trial, the proportion that adhere to treatment within each arm. Within the RL and RH arms, 32 participants allow us to estimate these proportions with a margin of error no greater than 0.09. Within the UC group, 16 participants will allow us to estimate these proportions with a margin of error no greater than 0.125.

For all analysis we will explore the impact of demographic characteristics such as gender, and racial/ethnic subgroups.

9 DATA COLLECTION AND QUALITY ASSURANCE

9.1 Data Management

This study will use a REDCAP database for data management.

9.2 Quality Assurance

9.2.1 Training

We currently have 3 health educators with experience in delivering group exercise and individual education and support using video conferencing to groups of adults with DS. If needed, new health educators will be trained by Dr. Ptomey and Ms. Danon, OT, and will shadow an experienced health educator for a minimum of 3 mos. prior to delivering the intervention on their own. Dr. Ptomey and/or Ms. Danon will conduct monthly meetings with all health educators to discuss issues relative to intervention delivery.

9.2.2 Fidelity

A study team member will review recordings from all scheduled group MVPA and individual support sessions. The content delivered will be compared with a checklist of scheduled activities/topics. Feedback will be provided to all health educators; those covering <80% of scheduled activities/topics will receive additional training and will be dismissed if the problem recurs.

9.2.3 Protocol Deviations

Protocol Deviations will be logged by health educators, research assistants, and study staff in the Redcap database.

9.2.4 Monitoring

Informed consents will be reviewed by study staff quarterly to assure they were completed correctly. 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. Feasibility data (retention, attendance, use of recorded sessions) will be reviewed monthly by the MPIs. KUMC IRB may conduct an audit during the study period.

10 PARTICIPANT RIGHTS AND CONFIDENTIALITY

10.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (Appendix 1) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The consent form should be separate from the protocol document.

10.2 Informed Consent Forms

A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g. person with power of attorney), this individual must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's

record.

10.3 Participant Confidentiality

Any data, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

10.4 Study Discontinuation

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

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