Decreasing **A**lzheimer's risk through o**N**line **C**horeographed Exercise – **D**own **S**yndrome (**DANCE-DS)** Protocol

PROTOCOL TITLE:

Decreasing **A**lzheimer's risk through o**N**line **C**horeographed Exercise – **D**own **S**yndrome (**DANCE-DS)**

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

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1.0 Study Summary

Protocol Information	Description
Study Title	Decreasing Alzheimer's Risk through Online Choreographed Exercise (DANCE) – Down Syndrome
Study Design	Single Arm Pilot Feasibility Trial
Primary Objective	To assess the feasibility of a 12 week remotely delivered group dance intervention.
Secondary Objective(s)	1. To assess changes in aerobic fitness and cognitive function in response to a 12 week remotely delivered group dance intervention. 2. To assess the intensity and total energy expenditure of remotely delivered group dance sessions
Research Intervention(s)/ Investigational Agent(s)	Adults with Down syndrome (n=20) will participate in a 12 week, remotely delivered choreographed exercise intervention. Classes will take place 2 times per week and be 35 minutes in length.
IND/IDE #	NA
Study Population	Adults (age 18-64) with Down syndrome
Sample Size	20
Study Duration for individual participants	12 Weeks
Study Specific Abbreviations/ Definitions	AD, Alzheimer's Disease; DS, Down syndrome; ID, intellectual disability; MVPA, moderate-to-vigorous physical activity

2.0 Objectives

2.1 Adults with Down syndrome (n=20) will participate in a 12 week, remotely delivered choreographed exercise intervention. Classes will take place 2 times per week and be 35 minutes in length. Prior to the start of the intervention (baseline) and at the conclusion of the intervention (week 12), aerobic fitness (6-minute walk test), cognitive function (modified cued recall), and physical activity enjoyment will be assessed. Attendance, retention, and adverse events will be collected on an ongoing basis throughout the intervention. The purpose of this pilot project is to assess the usability, feasibility, and preliminary effectiveness of a remotely delivered choreographed exercise intervention for the prevention of Alzheimer's disease in adults with Down syndrome. This project will address the following aims:

- Aim 1: Assess the feasibility of a 12 week. remotely delivered group dance intervention
- Aim 2: Assess changes in aerobic fitness and cognitive function in response to a 12 week remotely delivered group dance intervention
- Aim 3: Assess the intensity and total energy expenditure of remotely delivered group dance sessions

2.2 We hypothesize the following:

- Aim 1: Session attendance and participant retention will be ≥ 80%, and physical activity enjoyment (measured using the Physical Activity Enjoyment Disabilities Scale) will increase from baseline to week 12
- Aim 2: We expected significant improvements in aerobic fitness and cognitive function across the 12 week intervention
- Aim 3: Energy expenditure will exceed ≥3.0 METs during the exercise sessions and average heart rate will reach 65 % of age-estimated maximal heart rate

3.0 Background

Down syndrome (DS) or trisomy 21 is the most common chromosomal abnormality associated with an intellectual disability (ID) [1]. The current incidence of DS is 1 in every 650 live births [2, 3] which is ~30% higher than in 1979, largely due to women conceiving after age 35 [4]. Consequently, the prevalence of DS in the U.S. increased from an estimated 49,923 in 1950 to ~250,700 individuals in 2017 [3, 5]. The life expectancy for individuals with DS has increased dramatically in recent decades from 4 yrs. in the 1970's due to high rates of congenital heart defects, to 60 yrs. currently[6]. Alzheimer's disease (AD) is currently the leading cause of death in individuals with DS. All adults with DS will develop pathology related with Alzheimer's disease (AD)[4, 7, 8]. The median age of dementia onset is 53.8 years[9], and the lifetime incidence is 90% [8, 10].

For adults without DS, increased moderate-to-vigorous physical activity (MVPA) during mid-life [11-14] and older adulthood [15-17] may be effective in maintaining or improving components of cognition, including attention, memory, and executive function.

MVPA obtained through structured exercise appears to have the greatest benefit on cognition [18-20]. The limited research in adults with DS suggests that MVPA is closely associated with cognition[21, 22]. For example, Fleming et al. [21] reported that percent of time spent in MVPA was significantly correlated with 8/9 cognitive outcomes used the ABC-DS cognitive battery [23]. Similarly, a study by Pape et al. [22] which followed 214 participants across 12 months, observed that higher MVPA at baseline was associated with a 62% reduced risk of decline in memory and orientation at 12 months. Additionally, previous intervention studies in adults with DS have demonstrated the potential for acute or short-term (≤ 12 wks.) exercise to improve cognitive outcomes [24-28]. For example, Chen et al [29] compared the response of 3 components of executive function (choice-response time, attention shifting and inhibition) to an acute bout of moderate intensity exercise (20 min treadmill walk, n=10) with an attentional control (20 min video, n=10) in adults with DS. Compared to the control group, participants in the exercise group had non-significant improvements in choice-response time (p = 0.32) and attention shifting (p = 0.13). Participants in the exercise group had statistically significant improvement in inhibition compared with control (p = 0.03).

While MVPA might serve to benefit those with DS, it is estimated that only 9% of adults with ID, including those with DS, [30] achieve 150 minutes per week of MVPA as recommend by the Physical Activity Guidelines for Americans [31] compared with ~52% of typically developed adults [32]. Adults with DS face unique barriers to participation in MVPA including disinterest or inability to participate in typical exercise modes, e.g., walking, jogging etc., challenges with gait and/or coordination, lack of access to adapted options for MVPA, and lack of social support and low self-efficacy for exercise [33, 34]. Previous research[35]/observations by our group and others suggests that dance activities are a preferred form of exercise for adults with DS. Dance, which is characterized by rhythmic physical movements offers the potential for social engagement, and stimulation of brain functions including attention, memory, executive function, and visuospatial processing that are commonly affected by aging and cognitive decline [36, 37], particularly in individuals with DS. However, empirical evidence to support the feasibility of a remotely delivered group dance intervention and evaluation of the intensity and energy expenditure achieved by a dance intervention for adults with DS are currently unavailable and will be the focus of the proposed pilot trial.

4.0 Study Endpoints

4.1 The primary study endpoint is at the conclusion of the 12 week intervention. A secondary endpoint is upon participant withdrawal.

4.2 Participants will be removed from the study due to safety concerns if any arise.

5.0 Study Intervention/Investigational Agent

Adults with DS (n=20, age = 18 to 64 yrs.) will be asked to attend 35 min. remotely delivered (Zoom®) group dance sessions twice weekly across 12 weeks. All sessions will be directed by an instructor experienced in leading 35 min, group remote exercise sessions for individuals with intellectual disability as part of the ongoing exercise program for individuals with intellectual disability offered by the Division for Physical Activity and Weight Management. Classes will include a 5-minute warm up, 25 minutes of exercise designed to target moderate intensity activity, and a 5 minute cool down. During the 25 minutes of exercise, approximately 15 minutes of this section will be used to complete “floor progressions”. In a traditional dance class, “floor progressions” are

used to practice fundamental dance skills while traveling across the floor, such as marching across the floor to the beat of the music, side shuffle across the floor, or step-kicks across the floor. Participants will be asked to do this style of movement in place or within a radius where they can move safely in their homes and stay within range of the video camera so that exercise instructors can ensure participant safety. The final 10 minutes of the 25-minute exercise block will be used to teach dance moves as a part of a choreographed exercise routine which will be learned over the course of 12 weeks. Participants will start this section by practicing parts of the dance learned in a previous session or by learning new sections of the dance. Types of moves used in this dance routine will be similar to those used in the "floor progression" segment, including marching to the beat for an 8-count of music, stepping and clapping for an 8-count of music, swaying arms while stepping side to side for an 8-count. The choreographed dance will be designed by an individual experienced with teaching dance to adults with intellectual disabilities to ensure it is level appropriate. Each week, participants will learn 1-2 new dance moves as a part of the choreographed dance and practice these moves with the music assigned to the dance with the instructor as a part of class.

6.0 Procedures Involved

6.1 This is a 12-week pilot intervention for 20 adults with Down syndrome. The intervention will include a 2x weekly choreographed exercise intervention led by staff trained to deliver exercise interventions in this population. The structure of the class will be similar to that used in the ongoing remote exercise program for individuals with intellectual disability offered by the Division for Physical Activity and Weight Management, but substituting choreographed exercise (dance) movements to replace the aerobic component of this program. Participants will be asked to attend 2x weekly group classes remotely using Zoom® video conferencing (San Jose, CA). All outcomes will be assessed by research assistants at baseline and week 12, with the exception of the energy expenditure assessment and weekly class attendance. Outcome assessments will take place at the University of Kansas Medical Center, in Kansas City, KS. Intervention classes will take place in participant homes, using self-provided devices.

6.2 All assessments will be completed by appropriately trained staff with experience conducting assessments in adults with Down syndrome.

6.3 Anthropometrics. Research staff will measure weight, height, waist circumference, and hip circumference. Weight will be measured on a calibrated scale to the nearest 0.1 kg. Standing height will be measured with a stadiometer. BMI will be calculated as weight (kg)/height (m^2). Waist and hip circumference will be assessed using standard procedures such as those described by Lohman et al. [38]. Two measurements will be obtained with the outcome recorded as the average of the closest 2 measures. Blood Pressure and Heart Rate will also be collected following a period of seated rest (≥5 minutes).

6.4 Demographics. Basic demographic information including age, date of birth, race, ethnicity, sex, gender identity, and a brief health history will be collected at the baseline assessment.

6.5 Aerobic fitness. Aerobic fitness will be assessed using the 6-minute walk test [39-41] at baseline and week 12. Participants will be asked to

continuously walk along a pre-measured walking course for a total of six minutes. Participants are free to self-select pace of this walk and take breaks as needed. The total distance covered in the allotted time will be recorded.

6.6 Cognitive function. The Modified Cued Recall Test (mCRT)[42] will be used to assess cognitive function. The mCRT is used to assess episodic memory, and is a version specifically modified for individuals with DS. During this assessment, participants are asked to recall 12 objects previously shown to them using a set of cards following a learning phase. Participants are given one minute to freely recall these items before receiving category-based cues to retrieve remaining items. Participants are asked to complete this for a total of three trials and the total number of items across all three trials is summed.

6.7 Energy Expenditure of Remote Exercise Sessions. Energy expenditure of the remote sessions will be assessed using a previously validated portable, open-circuit indirect calorimeter (Cosmed, Italy) 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 as recommended by McMurray et al.[43]. Participants will also be provided with a FitBit device to measure heart rate achieved during the exercise sessions. Exercise instructors will remind participants to start and stop devices at the beginning and end of each exercise session. Device data will be shared with research staff.

6.8 Attendance at remote exercise sessions. After each session, the interventionist will record attendance. Overall attendance will be expressed as the percentage of possible sessions attended.

6.9 Physical Activity Enjoyment. Physical activity enjoyment will be assessed at baseline and week 12 of the intervention using the Physical Activity Enjoyment Scale [44]. Exercise self-efficacy will also be assessed at baseline and week 12. Self-efficacy will be assessed using the Self-Efficacy for Activity for Persons with Intellectual Disabilities Scale [45]. Finally, participants will complete a survey of intervention implementation success (acceptability, appropriateness, feasibility) assessed using validated 5-point Likert scales [46] at week 12 of the intervention. Participants will complete these surveys via REDCap.

7.0 Data and Specimen Banking NA

8.0 Sharing of Results with Subjects

8.1 Study results will not be shared with participants.

9.0 Study Timelines

9.1 The intervention will last for 12 weeks. Baseline testing visits will occur within two weeks of the start of the intervention and week 12 visits will occur within 2 weeks of the program ending. Based on these parameters, study enrollment will last up to 16 weeks including pre, and post intervention testing.

9.2 Participants will be recruited in two cohorts of 10 participants each. It is projected for the first cohort to begin in the Fall of 2024, with recruitment taking place in summer and early fall. The second cohort will begin in early 2025, with ongoing recruitment efforts starting during the delivery of the intervention to the first cohort.

9.3 Primary analyses will be completed in Summer 2025, following the conclusion of the second cohort. This will allow ample time for data collection and processing from both cohorts.

10.0 Inclusion and Exclusion Criteria

10.1 First, interested participants will complete a web-based initial eligibility questionnaire using REDCap, where they will provide the age, sex, race, and answer questions related to inclusion/exclusion. Those deemed potentially eligible will be contacted for a phone screen to determine final eligibility and discuss informed consent.

10.2 Remote video chat sessions (Zoom) or a phone call will be scheduled with participants and their legal guardian (if applicable) deemed to be initially eligible. During this call, the research study will be explained to participants and their legal guardian (if applicable) and eligibility criteria will be assessed.

10.3 *Inclusion criteria:* 1) Age 18-64 yrs. with a diagnosis of Down syndrome. 2) Sufficient functional ability to communicate through spoken language.3) No plans to relocate outside the study area over the next 12 weeks 4) Possession of a personal device that allows for connectivity to the internet and participate in 2x weekly group video calls. 5) Ability to participate in moderate intensity physical activity

10.4 *Exclusion criteria:* 1) Serious medical risk (e.g., cancer, recent heart attack, stroke, pregnancy, angioplasty as determined by the research staff. 2) unwilling to participate in outcomes assessments 3) uninterested

11.0 Vulnerable Populations

11.1 Study procedures will be explained in an appropriate manner by Staff familiar in working with adults with Down syndrome. Adequate time will be given for questions and consideration by both the potential participant and a caregiver.

12.0 Local Number of Subjects

12.1 A total of 20 participants will be recruited to join the study, across two cohorts of 10 participants.

13.0 Recruitment Methods

13.1 The recruitment plan was informed by our experience with completed projects where we successfully recruited adults with DS [47-49]. As in our previous trials, project staff will contact local community agencies serving adults with DS, case managers, and CDDOs by mail or email, provide presentations at CDDO meetings, and text for CDDO newsletters describing the project. Interested adults with DS or their parent/caregiver will be asked to contact the study coordinator via email or a dedicated toll-free study phone number that will be included in all recruitment materials. Participants will complete a basic eligibility survey using REDCap. The study coordinator will then contact those deemed eligible by phone to answer questions and conduct and ensure eligibility. Zoom® meetings will be scheduled with those remaining interested and potentially eligible to complete eligibility screening and to obtain informed consent or parent/guardian consent and participant assent in cases where the participant has a surrogate decision maker.

13.2 A flyer will be sent to all parties listed above and used for recruitment purposes. This flyer will include basic study information and contact information for research staff. A copy of the flyer us attached.

14.0 Withdrawal of Subjects

14.1 Participants will be withdrawn from the research without their consent if an SAE occurs which is deemed by the study team and PI and unsafe for continued participation.

14.2 Upon withdrawal from the study, all research activities will cease, and no additional data will be collected. Participants will no longer be able to attend the weekly exercise classes.

15.0 Risks to Subjects

15.1 Injury during physical activity. There is a chance for physical injury during physical activity such as muscle and joint sprains or strains, muscle cramps, and inflammation. These risks will be monitored and minimized by conducting a warmup as a part of each exercise class.

16.0 Potential Benefits to Subjects

16.1 Individual subject. Benefits to individual participants include the well-established benefits of physical activity engagement, including increased fitness and functional capacity, cognitive improvements, and mood improvements. Participants may also benefit from engaging in a group setting during the classes.

16.2 Population. The information from this study will aid in the understanding of the role of choreographed exercise in physical activity enjoyment and fitness and cognitive improvements for this population. This study may provide guidance for future interventions designed to increase physical activity for this population, with the goal of increasing cardiovascular fitness and reducing risk of Alzheimer's disease.

17.0 Data Management and Confidentiality

17.1 The primary aim of this study is to determine the preliminary feasibility and effectiveness of a 12 week remote intervention. As this is a pilot study, the sample size is not sufficient to determine true intervention effectiveness, however it will provide sufficient data to guide future studies. Other studies with similar design included between 12 and 30 participants [27, 50, 51], which is how the sample size for this pilot project was derived.

- Pre and post scores for the Physical Activity Enjoyment Scale, 6 minute walk, and cognitive assessments will be compared using paired sample t tests. Effect sizes (Cohen's d) will also be calculated.

17.2 This study will use a REDCap database for data management. Paper copies from the energy expenditure assessments will be stored in a locked file cabinet inside a locked office that is only accessible by authorized study personnel.

Data access: Only the study team at The University of Kansas Medical Center (i.e., principal investigator, co-investigators, study coordinator, and research assistant) will have access to the study folder and REDCap database.

17.3 To assure data collected are accurate and consistent, the same research assistants will complete data collection for all participants. Data entered into REDCap by the research staff will undergo data validation checks by another member of research staff not involved in data entry.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

18.1 An adverse event (AE) is any unfavorable medical occurrence in a human subject participant including any abnormal sign, symptom, or disease that is temporally associated with the participants' involvement in the research even if it is not considered related to the participation in the study. Signs and symptoms that are consistent with normal exercise including work-related dyspnea, fatigue, sweating, or light soreness of muscles 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.

AEs and SAEs will be tracked by the research assistant, study coordinator, or principal investigator for each exercise session. These events will be tracked on an adverse event form in REDCap and will include any events that occurred during or after the exercise sessions. Each reported event will be documented if it meets the criteria for an AE or SAE. Documentation will include a description of the event, when and how it happened, and any documentation to determine event severity and relatedness to the research study. Follow-up for each occurrence will be initiated by the study team and continued until the event is resolved. The principal investigator for the study will review and evaluate adverse events within 72 hours and a summary of these events can be provided to the IRB on an annual basis. Deaths will be reported within 24 hours and unanticipated SAEs will be reported within 48 hours to the IRB. All other SAEs will be reported semi-annually.

Muscular or joint-related injuries and cardiovascular events due to vigorous physical activity are the primary risks for this study, but this risk is attenuated with the warm up built into the program of each class. This risk is also minimized by the rest periods, if needed. The data safety monitoring plan will include close monitoring of each participant during the exercise testing at baseline and week 12 by the research assistants who have exercise testing experience in special populations, including those with Down syndrome. The principal investigator will be responsible for the immediate reporting of excessive or serious events to the IRB at The University of Kansas Medical Center. Safety reports will be compiled by the principal investigator throughout the study and the frequency of data review will differ based on the type and availability of the data collected and the perceived risk level. Data review will also include quarterly review of subject accrual (e.g., demographics, inclusion/exclusion) and compliance to the protocol; monthly review of adverse event rates; and semi-annual review of the stopping rules.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 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.

19.2 All research staff have training to work with adults with DS. This training includes describing research to participants, ensuring participant safety, and ensuring participant comfort. Participants and caregivers are continually reminded that their participation in any study procedure is voluntary.

20.0 Compensation for Research-Related Injury NA

21.0 Economic Burden to Subjects

21.1 Participants are responsible for providing their own transportation to and from the research center for testing visits.

22.0 Consent Process

22.1 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. Medical consent from the participant's physician will also be obtained prior to enrollment in the study. The physician will receive a description of the study, and a request for medical clearance to participate in the physical activity.

22.2 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.

22.3 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 participant assent and legal guardian/surrogate decision maker consent. We will obtain assent away from family members to make sure participants don't feel like they have to be in the study.

Cognitively Impaired Adults

The consent process for participants with known or suspected cognitive impairment includes an assessment of the capacity to provide consent for oneself. If the participant does not demonstrate capacity to consent, written consent will be obtained from the proper surrogate decision-maker, following Kansas law for DPOA and next-of-kin. In these instances, the participant's assent will be obtained and documented as well. Each team member qualified to consent has training on the ADRC SOP regarding consenting participants with impaired decision making and will follow the guidelines in the ADRC SOP Consenting Cognitively Impaired Participants to determine if subject is capable of consenting. In addition, all team members have experience consenting individuals with either DS or dementia or AD previously.

Adults Unable to Consent NA

23.0 Process to Document Consent in Writing NA

24.0 Setting

24.1 Potential research participants will be identified and recruited through contact with local community agencies serving adults with DS, case managers, and CDDOs by mail or email, provide presentations at CDDO meetings, and text for CDDO newsletters describing the project.

24.2 All research activities will be performed at the Division of Physical Activity and Weight Management or Kirmayer Fitness Center on campus of KUMC, with the exception of the energy expenditure assessment. Since classes are held remotely, research staff will travel to participant homes or wherever they engage with these classes to perform this assessment.

25.0 Resources Available

25.1 The Division of Physical Activity and Weight management currently maintains a listserve of over 230 contacts in the community that serve adults with Down syndrome. The division has been able to successfully recruit cohorts of 20 participants at a time for a previous Down syndrome physical activity study within a 1-year time frame.

25.2 KUMC Clinical Weight Management (Kirmayer Building) is a 5,000 ft^2 facility, that originally served as a Sports Medicine Clinic and has been occupied by The Division of Physical Activity and Weight Management

since the spring of 2012. This facility includes the following: an 800 ft^2 waiting room, 4 staff offices, an office suite for project coordinators, 4 exam rooms (~ 120 ft^2), a conference room, and an exercise room for conducting supervised aerobic or resistance exercise with adjacent handicap accessible locker rooms for both men and women, and extensive audio and video entertainment packages to facilitate participant compliance.

25.3 All assessments will be completed by appropriately trained staff. Baseline and 12-week outcomes will be assessed at our facilities at KUMC. Staff will receive refresher training and complete reliability assessments for all physical measures 2-3 times/yr. All dance exercise sessions will be video recorded and 20% will be reviewed by study staff. The content delivered during each session will be compared with a checklist of scheduled content. Interventionists presenting < 80% of the scheduled content for any session will receive additional training and will be dismissed if the problem recurs.

26.0 Multi-Site Research NA

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