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SYNchronizing Exercises, Remedies in GaIt and Cognition at Home (SYNERGIC@Home): Feasibility of a home-based double-blind randomized controlled trial to improve gait and cognition in individuals at risk for dementia

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ABSTRACT

Introduction: Physical exercise and cognitive training are emerging interventions with the potential to enhance cognitive function and mobility in older adults at risk of Alzheimer's disease and related dementia (ADRD), but little is known about the feasibility of delivering multi-domain interventions in home settings of older adults at risk of ADRD. This study aims to assess the feasibility of home-based delivery of exercise and cognitive interventions, and to evaluate the relationship between participants' intervention preferences and their subsequent adherence. Secondary objectives include the effect of the interventions on ADRD risk factors including frailty, mobility, sleep, diet and psychological health.

Methods and analysis: The SYNERGIC@Home feasibility trial is a randomized control trial that follows a 2x2 factorial design, with a 16-week home-based intervention program of physical exercises combined with cognitive training. Participants will be randomized in blocks of four to one of the following four arms: 1) combined exercise (aerobic and resistance) + cognitive training (NEUROPEAK™); 2) combined exercise + control cognitive training (web searching); 3) control exercise (balance and toning) + cognitive training; and 4) control exercise + control cognitive training. SYNERGIC@Home will be implemented through videoconferencing. Baseline and post-intervention assessments at 4 months and 10 months follow-up will include measures of cognition, frailty, mobility, sleep, diet, and psychological health. Primary feasibility outcome is adherence to the interventions. Primary analytic outcome is the relationship between pre-allocation preference for a given intervention and subsequent adherence to the allocated intervention. A series of secondary analytic outcomes examining the potential effect of the individual and combined interventions on cognitive, mobility, and general well-being will be measured at baseline and follow-up.

Ethics and dissemination: Ethics approval was granted by the Research Ethics Boards of the University of New Brunswick (#2020-168), Horizon Health Network (#2020-2954), Vitalité Health Network (#2020-35), and Université de Moncton (#2021-049).

Keywords: Exercise, cognitive training, intervention preference, cognition, gait, dementia, home-based intervention program.

Strengths and limitations of this study

- This study is one of the first randomized control trials (RCTs) in Canada to establish the feasibility of fully remote recruitment, consent, assessment and delivery of bilingual, multi-domain, contactless interventions in the home for preventing dementia in at-risk older adults.
- This study will also quantify the relationship between participants' preferences for intervention type and their subsequent adherence to the interventions they were allocated to, which will provide evidence on whether alternate experimental designs that account for preference are scientifically justified.
- Consistent with a feasibility study, the sample is powered for feasibility outcomes rather than cognitive and health outcomes.
- The study intervention duration of 16-weeks is short but sufficient for evaluating feasibility and estimating effect sizes of cognitive and mobility outcomes using remote assessments.
- Elements of the study design are consistent with a full-scale double-blind RCT, including robust screening, randomization and allocation, comprehensive pre- and post-assessments with long-term follow-up assessment and semi-structured exit interview.

1 INTRODUCTION

In 2015, over 46 million people lived with Alzheimer's disease and related dementias (ADRD) worldwide, with 1 new case appearing every 4.1 seconds[1]. The cost associated with these cases is over a trillion Canadian dollars[1-3]. There is no cure for dementia[4]. Recently, there has been a shift in interventional studies on ADRD to targeting pre-dementia states, such as mild cognitive impairment (MCI)[5,6]. The SYNERGIC Trial (SYNchronizing Exercises, Remedies in GaIt and Cognition) implemented a multi-domain intervention study for individuals with MCI at sites across Canada[7] in both English and in French. The positive results of multidomain trials like SYNERGIC,[8-10] and the ensuing COVID-19 pandemic, have warranted investigation of a home-based version of the protocol that can reach a wider population of older adults.

The primary goal of the SYNERGIC@Home feasibility trial is to assess the feasibility of in-home delivery of exercise and cognitive training interventions for improving cognitive and physical functioning in older adults at risk for ADRD. Remote delivery of physical exercise interventions has been of significant interest for decades[11,12] but randomised controlled trials (RCT) almost always happen in clinical or academic environments. Building capacity for conducting assessments and interventions in the home of older adults is now critical for ensuring safety and accessibility, with the added benefit of reaching a wider and more diverse population of at-risk older adults[13] while reducing costs of program delivery[14].

The analytic aim of this feasibility trial is to assess if participant's pre-allocation preference for different types of interventions is related to their subsequent adherence to the interventions allocated to them. The landmark Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)[10] supports the efficacy of multidomain interventions, but to date no studies have examined if preference plays a role in adherence to those interventions. This study will inform whether a future preference trial design is warranted.[15]

1.1 Rationale for the SYNERGIC@HOME Interventions

Aerobic exercise (AE) and progressive resistance training (RT) have been shown to improve cognition, physical capacity and mobility in older adults.[16-19] Both AE[20] and RT[21] trials have reported positive results in improving cognitive performance, with effects lasting more than 3 months.[16,22] Given the potential benefits of combining both types of exercise, we will deliver a combined (AE+RT) progressive exercise program as our active exercise intervention. The control exercise will include balance and toning (BAT) exercises with equivalent time exposure but no progression. While evidence exists that BAT exercises can improve gait stability[23] and strength[24], their effect on cognition is not demonstrated[25].

The rationale for adding cognitive training stems from a plethora of recent research suggesting that improvements in brain plasticity occur after cognitive training,[26-28] and from the potential synergistic effect of combining it with physical exercise. Active cognitive training will be delivered using the NEUROPEAK™ program which consists of a dual-task cognitive training regimen designed by our group. NEUROPEAK™ has been shown to improve balance[29], mobility[27], and cognition[30,31] in healthy older adults. The control cognitive training will involve

basic web searching and watching videos (WS+V), which is expected to have a minimal effect on cognition or mobility.

Finally, sixteen-week interventions of exercise and cognitive training has been conducted in previous studies in a clinical environment which has been shown to give significant and promising results[32,33], however has not been tested virtually in a home setting.

1.2 Primary objectives and research questions

Our **primary feasibility objective** will measure **adherence to interventions** to answer the question: Will community-dwelling older adults adhere to a 16-week in-home, multidomain, supervised intervention program to improve their health and reduce their risk of ADRD?

To determine if affinity for any one intervention is an important factor in participants' adherence to the study interventions, we designed the Intervention Preference Questionnaire (see Appendix A) that will be used to answer the following questions:

- **Relation to adherence**: Is adherence correlated with receiving the active treatment they prefer as indicated by their pre-allocation preference ratings?
- **Preference attitudes**: Which intervention type (physical exercise or cognitive training) do most participants prefer over the other? What proportion of participants have no particular preference for either intervention?

Our **secondary feasibility objectives** will measure **recruitment rate, retention rate**, **trial experience**, **adverse events**, and **data loss** to answer the questions, respectively: How efficient is recruitment? Do participants stay in the trial for its duration? How satisfied are participants with the interventions? What adverse events are related to the intervention(s)? What is the rate of data loss when doing remote assessments?

2 METHODS AND ANALYSIS

2.1 Study design

SYNERGIC@Home is a home-based, double-blind, randomized controlled trial, with a four-arm full-factorial (2x2) design. It will be administered virtually through a secure online video conferencing platform. Block randomization by four will be used to allocate enrolled participants into one of four arms, with 16 participants in each arm (experimental conditions are in bold):

- Arm 1: **Combined exercise (AE+RT)** + **Cognitive training (NEUROPEAK™)**
- Arm 2: **Combined exercise (AE+RT)** + Control cognitive training (WS+V)
- Arm 3: Control exercise (BAT) + **Cognitive training (NEUROPEAK™)**
- Arm 4: Control exercise (BAT) + Control cognitive training (WS+V)

The experimental design is shown in Figure 1.

<Figure 1>

Assessments will occur at baseline (T0), 4mo (T4), and at 10mo follow-up (T10). The SPIRIT schedule of enrollment, interventions, and assessments is shown in Figure 2.

<Figure 2>

2.2 Participants and setting

Sixty-four older adults (age 60-90 years) at risk of developing ADRD, who live in the province of New Brunswick, Canada, and meet the inclusion and exclusion criteria will be recruited by study staff not involved in the participant's ongoing care. Participants will include francophone and anglophone and geographical recruitment areas will be both rural and urban. All intervention activity will take place in the participant's home.

2.3 Inclusion criteria

- Age 60 to 90 years
- Has a Family Physician/Nurse Practitioner
- Has internet access and basic technology ability (able to send and receive emails)
- Resides in their own home/apartment
- Has access to a home computer and/or a laptop computer device
- Self-reported levels of proficiency in English and/or French for reading, speaking and writing
- Able to comply with scheduled home-based assessments and interventions
- Able to ambulate at least 10 m independently with or without a walking aid
- At risk of developing dementia (see Table 1 and Appendix B):

    a) Mild Cognitive Impairment (MCI)
    b) Subjective Cognitive Impairment (SCI)
    c) Cognitively Intact (CI) with 2 or more of the following risk factors: obesity, hypertension, diabetes, cardiovascular disease, physical inactivity, first-degree family history of dementia, dyslipidemia, poor sleep, and poor diet

- Deemed safe by the study physician to participate in exercise[31]
- Preserved activities of daily living (score of > 14/23 on the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale[34]).

<Table 1>

2.4 Exclusion criteria

- Diagnosis of dementia
- Living in Nursing Homes or Adult Residential Facilities.

- Serious underlying disease, which, in the opinion of the study physician would compromise the participant's safety
- Surgery within the last two months or in the coming 12 months
- History of intracranial surgery
- Regularly takes benzodiazepines that would interfere with participation
- Presence of major depression, schizophrenia, severe anxiety or drug/alcohol abuse or other medical illness that would prohibit safe participation
- Current Parkinsonism or any neurological disorder, active musculoskeletal disorders or history of knee/hip replacement that affects gait
- Severe visual and/or auditory impairment
- Intention to enroll in other clinical trials during the same period
- Active participation in an organized and planned exercise program involving aerobic and/or resistance training regimen in previous 6 months

2.5 Recruitment and screening

2.5.1 Recruitment procedures

Recruitment will include posters and posts on community and healthcare provider websites, public and social media, physician offices, and paid newspaper advertisements.

2.5.2 Screening and consenting procedures

Consent will be obtained (see Appendix C) before any screening activities occur. The screening visit will be done virtually using a secure online platform. Following the screening visit, a virtual meeting with the study physician will occur for diagnostic validation and determination of inclusion and exclusion criteria. Participants will then be enrolled and randomized. Participants will indicate on the consent form if acquisition and retention of their saliva sample is permitted for the Polygenic Hazard Score analysis.[35,36]

2.5.3 Study Care Partners

Each participant will be asked to identify a care partner (someone who knows them well) who can assist with some of the cognitive tests and assessments as needed. A care partner is not mandatory unless the participant has MCI or SCI. The care partner will be asked to provide informed consent as well (see Appendix D).

2.6 Randomization and allocation

Randomization will be conducted by research personnel not involved in screening, assessments or interventions using a simple excel formula that generates a random number within a sequence. A block randomization by four will be applied to ensure an appropriate balance between treatment arms. Permuted blocks will be employed to ensure balance over time.

2.7 Blinding and debriefing

To minimize bias, the study will be double-blinded. Research personnel performing the outcome assessments will be blinded to group allocation. Participants will also be blinded to which intervention they received and to study hypotheses. Only the designated research personnel delivering the interventions will know the treatment group that participants belong to and will not reveal the participants' allocation (unless it is medically necessary to do so) until the end of the trial.

2.8 Early withdrawals

Participants will be withdrawn from the study if they: 1) no longer wish to continue their participation in the study (voluntary withdrawal), or 2) in the opinion of one of the study physicians, it is medically necessary to withdraw the participant (medically necessary withdrawal).

2.8.1 Voluntary withdrawal

Participants who inform their Intervention Research Assistant (RA) that they wish to voluntarily withdraw will be asked by the Intervention Coordinator (to protect blinding) if they would be willing to continue their participation in either intervention on its own and return for their follow-up assessments. In this scenario, they will not be withdrawn from the study provided they agreed to at least the T4 assessment. Voluntary non-compliance will be captured by entering 0 values in their intervention logs for the remainder of the weekly session(s) they withdrew from.

If the participant wishes to completely withdraw from the study, s/he will be asked to complete the Exit Survey and will subsequently be withdrawn from the study.

2.8.2 Medically necessary withdrawal

Medically necessary withdrawals may be required if participants experience unanticipated adverse events or changes in medication or health status, that in the judgement of a study physician, places the participant at risk of harm.

If it is deemed medically necessary to withdraw the participant, the Clinical Research Coordinator and/or Study Physician will meet with the participant to explain the reason(s) for being withdrawn from the study, and to inquire about the elements of the study that may have led to their change in health status (if applicable). If willing, the participant will be asked to complete the Exit Survey and will subsequently be withdrawn from the study.

2.9 Interventions

All participants will receive home-based intervention sessions of 90 minutes each three times per week for 16 weeks (48 sessions). Intervention research assistants (RA) trained and certified by the Canadian Society for Exercise Physiology (CSEP) will remotely supervise all sessions via a secure online video conferencing platform. Each participant will be assigned an RA that remains

with them throughout the trial. Each session will consist of 20-25 minutes of cognitive training (NEUROPEAK™) or the control cognitive training (WS+V), followed by 50-60 minutes of exercise intervention (AE+RT) or control exercise (BAT). RAs will maintain an intervention log for each participant, documenting start and end times for each activity.

2.9.1 Active Exercise Intervention: Aerobic Exercise + Resistance Training (AE+RT)

Participants receiving the AE+RT intervention will have home-based aerobic and resistance exercise (Table 2). The RA trainers will coach participants throughout the entire session and document their progress. The level of difficulty and progression for the AE+RT exercise will be tailored to their individual level with constant monitoring.

2.9.2 Control Exercise Intervention: Balance and Toning (BAT)

Participants receiving the BAT control exercise will have home-based balance and toning exercises (Table 3). The format of the BAT session including the duration of activities and the amount of coaching will mirror that of the AE+RT session except the exercises will be devoted to improving muscle tone, balance and flexibility. Resistant load and number of repetitions will *not* progress during the trial.

2.9.3 Cognitive Training Intervention: NEUROPEAK™

Participants assigned to the active cognitive intervention will first receive training on how to use NEUROPEAK™ on a tablet computer provided by the study (for uniformity). For this study a custom-written program consisting of a dual-task training program will be used[37-39] that requires participants to maintain and prepare for many response alternatives (working memory) and to share attention between two concurrent tasks (divided attention). Difficulty and progression of cognitive training is tailored to their individual functioning level and performance.

2.9.4 Control Cognitive Intervention: Web Search and Video (WS+V)

Participants assigned to the control cognitive training will received home-based sessions that alternate between two different tasks: web searching for tourist sites and video watching. For the touristic web searching, participants will be required to find hotels, touristic places, and restaurants of their own preference in a city assigned by the RA (a new city will be selected each session). For the video watching, participants will view an educational video about nature and will be asked several questions about it.

2.10 Assessment Outcomes

All feasibility objectives are consistent with current recommendations on conducting feasibility trials.[40]

2.10.1 Primary Feasibility Outcome

- **Intervention Adherence:** Defined as the percent of all intervention sessions attended of the total planned sessions per participant (48-2=46 allowing for 2 missed sessions). To account for partial sessions each intervention session will be treated as a fractional measure: number of minutes training/scheduled session minutes, where scheduled minutes are 50min for exercise interventions and 20min for cognitive interventions.

2.10.2 Secondary Feasibility Outcomes

- **Recruitment Rate**: Defined as the total percent of enrolled participants relative to number of people screened for eligibility.
- **Retention Rate:** Defined as the total percent of enrolled participants who continue throughout the trial and participate in outcomes assessments. Enrollment retention is the % of enrolled participants who complete T4 assessment, and follow-up retention is the % of those who complete the follow-up T10 assessment.
- **Trial Experience:** A mixed methods approach will be used to explore participant experience after the trial using one-on-one interviews with a sub-sample (3 per arm=12). All participants will be invited to complete an Exit Survey about their experience.
- **Adverse Events (AEs):** Relationship between AEs severity and relation to trial.
- **Data Loss:** Defined as data lost due to technical failures resulting in data loss include problems with electronic equipment or internet communications, personnel errors such as issuing improperly configured equipment, scheduling errors, and omitting assessments, and participant non-compliance such as omitting responses on surveys or declining assessments.

2.10.3 Primary Analytic Outcomes

Intervention Preference: The primary analytic goal of SYNERGIC@Home is to assess the relationship between participants' adherence to the interventions and their affinity for each intervention going into the trial, as well as other questions about preference. All participants will be given the IPQ at T0, prior to randomization.

The IPQ asks about their affinity for the offered interventions by quantifying interest level and preferences for the interventions. We will explain to participants that their responses on the questionnaire will not in any way influence the intervention group they will be randomly assigned to.

2.10.4 Secondary Analytic Outcomes

Various cognitive and psychological tests will be administered as part of a neuropsychological test battery, as well as gait, mobility, sleep, diet and biological markers (please see Figure 2 for a fuller list).

2.11 Safety evaluation

All adverse events (AEs) and serious AEs (SAEs) that occur between consent and completion of the study will be reported. All AEs and SAEs will be monitored to determine the outcome or

until the study physician and/or appropriate research personnel considers it justifiable to terminate follow-up. AEs will be classified as mild, moderate, or severe. The relationship of the AEs to study procedure will be determined and classified as not related, unlikely, possible, probable, or definite. All AEs and SAEs will be reported to the Safety and Data Monitoring Committee and REBs as required.

2.12 Sample size

Power analysis was conducted using G*Power 3.1 based on our primary analytic goal of assessing the relationship between intervention preference and subsequent adherence to the interventions. Specifically (see 2.13.2 below), we plan on examining correlations among continuous variables with one-tailed analyses at $\alpha = .05$ for two pairs of variables (equivalent to a two-tailed test at $\alpha = .1$, to account for both intervention types). To achieve a power of .8 we would require 48 participants. Assuming a 25% loss, a total of sixty-four participants will be enrolled.

2.13 Statistical analysis

All calculations will be made using the Statistical Package for the Social Sciences (SPSS version 23.0, IBM Inc., Chicago, IL) and Stata (Stata Statistical Software: Release 14, StataCorp LP, College Station, TX).

Descriptive statistics for demographic and baseline characteristics will be provided with means and standard deviations, or medians and the interquartile range where appropriate, for continuous characteristics and frequencies and percentages for categorical variables.

2.13.1 Feasibility outcomes

Adherence to the interventions will be analyzed using a one-sample t-test that will test the null hypothesis that participants complete 50% of their scheduled intervention time. This test will be used to determine if the adherence is superior to that hypothesized (feasibility target is 75%) or inferior to that hypothesized (questionable feasibility is significantly <50%).

Secondary feasibility outcomes will be analyzed using non-parametric Chi-square tests. Target enrollment retention (75%) and follow-up retention (56%) will be tested against observed frequencies using a Chi-square goodness-of-fit test. This test will be used to determine if the achieved distribution of eligible participants is similar to that hypothesized, superior to that hypothesized or inferior to that hypothesized. Adverse events will be analyzed using a Chi-square cross-tabulation analysis between AEs severity and AEs relation-to-trial. We will use this analysis to test the hypothesis that there is a relationship between AEs severity and being in the trial. Furthermore, we will stratify the sample by treatment arm and use a Chi-square goodness-of-fit test to determine if AEs are distributed differently across treatment arms against the null hypothesis of an even distribution (no relation to treatment arm).

2.13.2 Analytic outcomes

Intervention preference will be analyzed by transforming a set of variables:

- **Interest in the Interventions:** Question 1 in the IPQ rates participant's interest in each intervention independently: exercise (**INT_EX**) and cognitive training (**INT_CT**), on a 0-10 scale.
- **Intervention Preference:** The second question rates their relative preference for either intervention. This will generate a single variable that gives the relative preference (-2 to 2 scale), **PR**, where negative scores and positive scores indicate a preference for exercise or cognitive training, respectively.
- **Intervention Allocated:** The treatment arms can be represented by two dummy (0,1) variables for exercise (**EX_ARM)** and cognitive (**CT_ARM)** where 1=active treatment and 0=control treatment.
- **Adherence to Interventions:** Adherence to the interventions at the end of the trial, for exercise (**AD_EX**) and cognitive training (**AD_CT**), as well as overall **AD**, are continuous scale variables.

What is the relationship between adherence and intervention interest? We will correlate interest level for each intervention with adherence rates calculated from trial logs, using Pearson correlation coefficient ($\rho_{X,Y}$) with a one-tailed alpha of .05. The intervention is powered for testing this hypothesis (see 2.12).

H0: $\rho_{X,Y} = 0$, H1: $\rho_{X,Y} > 0$, where X=**INT_EX** and Y=**AD_EX**

H0: $\rho_{X,Y} = 0$, H1: $\rho_{X,Y} > 0$, where X=**INT_CT** and Y=**AD_CT**

Rejection of the null hypothesis for either test will allow us to conclude that interest level in the intervention type prior to the trial explains a significant amount of variance in adherence to the trial.

Do participants adhere better if they receive the active treatments they prefer? Because some participants will be randomly assigned to the active intervention that matches their preference and others will not, we will transform the **PR** score into a signed logical **PR_MET** (-1=preference not met, 0=no preference, +1=preference met) according to what intervention (**EX_ARM** and/or **CT_ARM**) they were allocated to. We will test the hypothesis that

H0: $\rho_{X,Y} = 0$, H1: $\rho_{X,Y} \neq 0$, where X=**PR_MET** and Y=**AD**

Rejection of the null hypothesis ($p<.05$) will allow us to conclude that adherence to the interventions is significantly influenced by receiving the active intervention they prefer.

How do cognitive and mobility outcomes change as a result of the interventions? Finally, intention-to-treat (ITT) analysis of cognitive and mobility outcomes with a general linear model or linear mixed model approach will be used to measure intervention effects, and we will estimate effect size based on Cohen's descriptors 0.2 = small; 0.5 = moderate; 0.8 = large for cognitive and mobility outcomes listed in Figure 2.

2.14 Data management and monitoring

All electronic data will be stored on a secure platform at the lead university site. Paper copies of assessment forms will be stored in locked cabinets located at the workplaces of remote study research staff, and then transferred to the participating hospital site. Deidentified copies of the data will also be stored on a secure server called LORIS (Longitudinal Online Research and Imaging System) at the McGill Centre for Integrative Neuroscience, McGill University, Montreal, Quebec. All data will be double entered for data quality monitoring. Assessments at T0, T4, and T10 will be video and audio recorded. In addition, a subset of three intervention sessions will be selected to be video recorded per participant for quality control. The video and audio recordings will be deleted once the data have been validated and released by LORIS.

There will be a Data Safety and Monitoring Committee chaired by an independent person not related to the study and will be comprised of the principal investigators, key research staff and researchers, an independent physician and two community representatives (anglophone and francophone). They will review all AEs, SAEs, protocol deviations, progress of the research, and audit study procedures if needed. Protocol amendments will be reported to this committee. All information related to adverse events, protocol amendments, and protocol deviations will be reported to the appropriate Research Ethics Boards.

2.15. Access to data

Access to and analyses of study data stored in LORIS may be granted to qualified persons 12 months after the principal paper answering primary research questions are published. Such requests will be made via email to the Canadian Consortium for Neurodegeneration and Aging [ccna.admin@ladydavis.ca] or via the LORIS Data Access Module.

2.16 Participant and public involvement

The SYNERGIC@Home feasibility study offers older adults and their families a unique opportunity to participate in a fully remote bilingual (French and English) RCT from their home. Participants will be invited to share their experience through questionnaires upon completion of the study as well as through individual semi-structured interviews. Participants will be able to provide direct feedback on trial improvement strategies, which could be implemented in future studies.

2.17 Ethics and dissemination

This study is conducted in compliance with International Conference on Harmonization of Good Clinical Practice (ICH-GCP) and all applicable regulatory requirements. SYNERGIC@Home has undergone review and approval from the Research Ethics Committees/Boards of: Horizon Health Network (#2020-2954); Vitalité Health Network (#2020-35), University of New Brunswick (#2020-168), and Université de Moncton (#2021-049).

3 DISCUSSION

Older adults at risk for ADRD have incident rates of related risk factors several times higher than their cognitively healthy counterparts.[41] Additionally, these individuals at risk for ADRD have an increased risk of falling and mobility decline.[42,43] Physical exercise and cognitive training are emerging as promising non-pharmacological interventions to enhance mobility and cognitive functioning in older adults, especially in pre-dementia states. These interventions have been tested separately, with positive results for physical exercise and cognitive training in improving cognitive function.[9,16,18,21,44] The preliminary success of the original SYNERGIC program and similar combined interventions have illustrated the promising nature of non-pharmacological exercise interventions and cognitive training to enhance cognition for older adults at risk of developing ADRD [7,45-47].

To our knowledge, this is the first study investigating the feasibility of conducting an entirely virtual, home-based, combined exercise and cognitive training intervention program for older adults at risk for ADRD.

3.1 Significance of establishing feasibility

Establishing the feasibility of conducting a virtual, home-based, multidomain intervention has the potential to inform other researchers on the logistics of designing remote intervention programs. If successful, the methodology and procedures tested in this feasibility trial could set the standard for a new platform in which participants are no longer restricted to intervention studies conducted in a common physical space.

3.2 Significance of examining intervention preference

Establishing if preference bias plays a role in which interventions older adults at risk of ADRD will adhere to is expected to provide unique insights into multidomain trial adherence, and will inform the design of future larger RCTs if it is found warranted to control for such bias using a preference design.[15]

3.3 Significance of secondary outcomes

We expect that the combined active exercise and cognitive training arms will have the greatest improvement (or least decline) of cognitive and mobility outcomes, followed by those who receive one active treatment, and finally those receiving both control treatments having the least improvement (or greatest decline). If successful, the combined interventions will further demonstrate a delay in their progression to dementia, warranting a larger RCT.

3.4 Benefits of interventions

Mechanistically, AE and RT exercises can provoke a cascade of biochemical, physiological, and structural changes in the brain including increases in blood flow, neurotrophic factor release, neurogenesis, immune system efficacy and metabolism. These effects of exercise could combat inflammatory processes and the atrophy of brain structures often associated with aging and

ADRD[32,34]. Mechanisms suggested involve modulation of insulin-like growth factor-1 and insulin sensitivity, decreasing inflammation, enhancing release of brain-derived neurotrophic factor pathways, and even a decrease in brain amyloid.[21,48,49] Combined exercise interventions have also shown increased brain volume and muscle mass in older adults.[50] Furthermore, cognitive training has also been shown to improve overall cognition.[30,31] Individuals who practiced monitoring of two tasks at the same time on computer devices have presented with improved connectivity between prefrontal and temporal cortices, areas known to be important for executive functioning and memory, when compared to control participants.[40]

3.5 Strengths and concluding remarks

To our knowledge, this fully remote RCT is the first to test the feasibility of implementing, in two official languages, a combined physical exercise program with cognitive training to improve cognition and mobility in community-dwelling older adults at risk for ADRD. We will also establish the extent to which measuring participant preference for a given intervention is related to subsequent adherence. We believe that this will inform other researchers and scholars on whether the costs and efforts associated with tailoring interventions in future studies to match participant preferences are worthwhile.

In conclusion, SYNERGIC@Home will build capacity for future research RCT designs using home-based interventions in older adults at risk for ADRD.

<end of main body>

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Table 1. Canadian Consortium on Neurodegeneration in Aging (CCNA) Criteria for Cognitively Intact with risk factors, and Subjective and Mild Cognitive Impairment from COMPASS-ND[51]

Group	Core Diagnostic Criteria	Operationalized as
Cognitively Intact (CI) with risk factors	Absence of SCI and/or MCI based on below definitions, with two or more known risk factors for dementia.	Not having SCI or MCI, and having at least two (2) of the following risk factors: • Obesity • Hypertension • Diabetes • Cardiovascular disease • Physical inactivity • First-degree family history of dementia • Dyslipidemia • Poor sleep • Poor diet
Subjective Cognitive Impairment (SCI)[52]	Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.	Answer "yes" to both of the following questions: "Do you feel like your memory or thinking is becoming worse?" and "Does this concern you?"
	Normal age-, sex-, and education-adjusted performance on standardized cognitive tests, which are used to classify mild cognitive impairment (MCI) or prodromal Alzheimer's Disease (AD).	Global Clinical Dementia Rating (CDR) scale = 0, Logical Memory II above Alzheimer's Disease Neuroimaging Initiative (ADNI) education-adjusted cutoffs (≥ 9 for 16+ years of education; ≥ 5 for 8-15 years of education; ≥ 3 for 0-7 years of education); Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) word list recall score > 5; Montreal Cognitive Assessment (MoCA) total score ≥ 25.
Mild Cognitive Impairment (MCI)[5]	Concern regarding a change in cognition.	Report from patient and/or informant of such.
	Impairment in one or more cognitive domains.	One or more of the following: • Logical memory below ADNI cutoffs ((≥ 9 for 16+ years of education; ≥ 5 for 8-15 years of education; ≥ 3 for 0-7 years of education). • ADAS-Cog word list recall < 6. • MoCA score 13-24 inclusive. • Global CDR > 0.
	Preservation of independence in functional abilities.	Score > 14/23 on the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale.

	Not demented.	Global CDR ≤ 0.5.

Table 2. General overview of active intervention exercise regimen structure.

Section	**Type of Exercise**	**Duration (min)**
Warm Up	Marching in one place with arm swings for 1 minute	1
	Dynamic Hamstring Stretching: 15 per side	1
	Shoulder Circles: 15 per direction	1
	15 Arm Reaches	0.5
	Torso Twists: 15 per direction	1
	Ankle Circles: 15 per direction per side	2
	Side Stepping for 1 minute	1
	15 Quarter Squats	1
	Total Warm Up Duration	8
Break		1
7 Strength Training Exercises	Chest	5
	Upper Back	5
	Bicep Curls	2.5
	Abdominals	2.5
	Mid/Lower Back	5
	Quadriceps	5
	Hamstrings	5
	Total Strength Training Duration	30
Break		3
Aerobic Exercise	Alternating Video for Participants	15
	Total Aerobic Exercise Duration	15
Break		3
Cool Down	Quadriceps Stretch	0.5
	Hamstring Stretch	0.5
	Calf Stretch	0.5
	2 Hip Stretches	0.5
	Static Torso Rotation	0.5
	Seated Side Bend	0.5
	Back and Shoulder Stretch	0.5
	Chest Stretch	0.5
	Triceps Stretch	0.5
	Neck Stretch	0.5
	Total Cool Down Duration	5
Total Time		**Approx. 65**

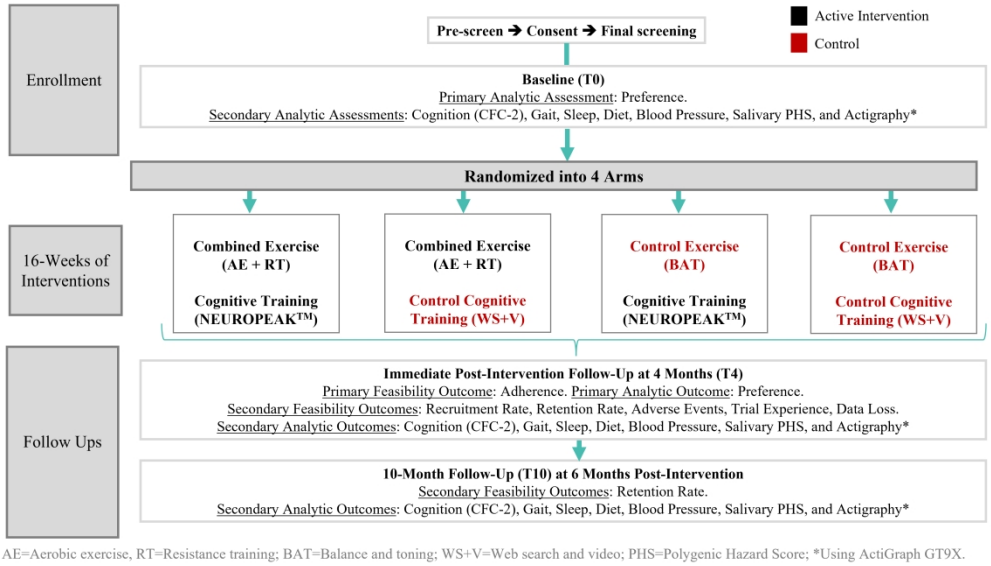
Table 3. General overview of control BAT regimen structure.

Section	Type of Exercise	Duration (min)
Warm Up	Marching in one place with arm swings for 1 minute	1
	Dynamic Hamstring Stretching: 15 per side	1
	Shoulder Circles: 15 per direction	1
	15 Arm Reaches	0.5
	Torso Twists: 15 per direction	1
	Ankle Circles: 15 per direction per side	2
	Side Stepping for 1 minute	1
	15 Quarter Squats	1
	Total Warm Up Duration	8
Break		1
7 Balance and Toning Activities	Standing with Feet Together + Tandem + Single Leg Stand	10
	Core Contractions + Core & Arm Raises	8
	Shoulder Retractions	3
	Isometric Quadriceps Strength	3
	Seated Hamstring Curls	3
	Seated Arm Shake	3
	Total Balance and Toning Duration	30
Break		3
Stretching Exercise	Alternating Video for Participants	15
	Total Stretching Duration	15
Break		3
Cool Down	Quadriceps Stretch	0.5
	Hamstring Stretch	0.5
	Calf Stretch	0.5
	2 Hip Stretches	0.5
	Static Torso Rotation	0.5
	Seated Side Bend	0.5
	Back and Shoulder Stretch	0.5
	Chest Stretch	0.5
	Triceps Stretch	0.5
	Neck Stretch	0.5
	Total Cool Down Duration	5
Total Time		**Approx 65**

Figure Captions

Figure 1. Design of the SYNERGIC@Home feasibility trial.

Figure 2. SPIRIT schedule of enrollment, interventions and assessments. Time points are: $-t_2$ = 4 weeks prior to allocation; $-t_1$ = 2 weeks prior to allocation; t_0 = Baseline testing and allocation (T0); t_1 = first week of interventions; t_2 = last week of interventions; t_3 = 4mo follow-up assessment (T4); t_4 = 2 weeks prior to 10mo follow-up; t_5 = 10mo follow-up assessment (T10). Interventions are 3x per week for 16 weeks (t_1-t_2). [a] Pre-screening at $-t_2$ consists of exclusion screening and inclusion screening not requiring assessment, such as clinical dementia status and risk. [b] Final screening at $-t_1$ consist cognitive battery #1, diet, sleep and functional risk factors used to designate participants as not demented but having mild cognitive impairment, subjective cognitive impairment, or cognitively intact with 2 or more risk factors. [c] Cognitive battery #1 ($-t_1$, t_3, t_5) consists of: Telephone Cognitivie Screen (TCogS); Full MoCA via Audio-Visual Conference; Lawton-Brody IADL; Cognitive Functional Composite (CFC-2) consisting of ADAS-Cog 3 Immediate Word Recall, Delayed Word Recall, and Orientation, Logical Memory I & II; Clinical Dementia Rating Scale (CDR), and Cognitive Functional Activities Questionnaire. [d] Cognitive battery #2 (t_0, t_3, t_5) consists of: Oral Trail Making Test (Part A & B); Boston Naming Test; ADAS-Cog Word Recognition; DKEFS Phonemic Fluency Test and Semantic Fluency Test; WAIS III Digit Span Test; Digit Symbol Modalities Test-Oral Version. [e] Sleep and activity monitoring for 10 days prior to assessment time points ($-t_1$-t_0, t_2-t_3 and t_4-t_5) using wrist worn Actigraph (GT9X) monitor. [f] Dual task gait battery ($-t_1$, t_3, t_5) consists of: Usual Gait; Seated Dual Task; Dual Task Gait counting backwards by ones, naming animals, and counting backwards by sevens. [g]Exit survey completed at end of study or upon early withdrawal when possible. [h] Polygenic Hazard Score biomarkers assessed via saliva sample at any time point during study.



Design of the SYNERGIC@Home feasibility trial.

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	STUDY PERIOD								
	Enrollment		Alloc.	Post-Allocation					End
TIMEPOINT	$-t_2$	$-t_1$	t_0	t_1	t_2	t_3	t_4	t_5	t_6
ENROLLMENT:									
[a]Pre-screen	X								
Informed consent	X								
[b]Final screening		X							
Allocation			X						
INTERVENTIONS:									
Arm 1: AE+RT + NEUROPEAK™				◆—	—◆				
Arm 2: AE+RT + WS+V (control)				◆—	—◆				
Arm 3: BAT (con.) + NEUROPEAK™				◆—	—◆				
Arm 4: BAT (con.) + WS+V (con.)				◆—	—◆				
ASSESSMENTS:									
Primary feasibility outcomes									
Intervention adherence						X		X	
Secondary feasibility outcomes									
Recruitment rate									X
Retention rate									X
Trial experience (1:1 interview)								X	
Adverse events				◆—	—	—	—	—◆	
Data loss									X
Primary analytic outcomes									
Preference Questionnaire			X			X			
Secondary analytic outcomes									
[c]Cognitive battery #1		X				X		X	
[d]Cognitive battery #2			X			X		X	
Mediterranean Diet Assessment		X				X		X	
Eating Pattern Self-Assessment			X			X		X	
Vitamin D Intake Questionnaire			X			X		X	
[e]Sleep monitoring (Actigraphy)		◆—	—◆		◆—	—◆	◆—	—◆	
Pittsburgh Sleep Quality Index		X				X		X	
Work and Sleep Diary		◆—	—◆						
[e]Activity monitoring (Actigraphy)		◆—	—◆		◆—	—◆	◆—	—◆	
Clinical Frailty Scale		X				X		X	
Generalized Anxiety Disorder		X				X		X	
Geriatric Depression Scale		X				X		X	
Falls Calendar		◆—	—	—	—	—	—	—◆	
Physical Activity Scale for the Elderly			X			X		X	
Life Space Questionnaire			X			X		X	
[f]Dual task gait battery			X			X		X	
One Minute Sit to Stand Test			X			X		X	
Short Form 36			X			X		X	
Get Active Questionnaire		X							
COVID-19 Questionnaire			X						
Technology Ability and Use			X						
STOFHLA Test		X							
[g]Exit survey or early withdrawal debrief				*At end or early withdrawal*				X	
[h]Polygenic Hazard Score		*Any time during study*							

SPIRIT schedule of enrollment, interventions and assessments. Time points are: -t2 = 4 weeks prior to allocation; -t1 = 2 weeks prior to allocation; t0 = Baseline testing and allocation (T0); t1 = first week of interventions; t2 = last week of interventions; t3 = 4mo follow-up assessment (T4); t4 = 2 weeks prior to 10mo follow-up; t5 = 10mo follow-up assessment (T10). Interventions are 3x per week for 16 weeks (t1-t2). [a] Pre-screening at –t2 consists of exclusion screening and inclusion screening not requiring assessment, such as clinical dementia status and risk. [b] Final screening at –t1 consist cognitive battery #1, diet, sleep and functional risk factors used to designate participants as not demented but having mild cognitive impairment, subjective cognitive impairment, or cognitively intact with 2 or more risk factors. [c] Cognitive battery #1 (–t1, t3, t5) consists of: Telephone Cognitivie Screen (TCogS); Full MoCA via Audio-Visual Conference; Lawton-Brody IADL; Cognitive Functional Composite (CFC-2) consisting of ADAS-Cog 3 Immediate Word Recall, Delayed Word Recall, and Orientation, Logical Memory I & II; Clinical Dementia Rating Scale (CDR), and Cognitive Functional Activities Questionnaire. [d] Cognitive battery #2 (t0, t3, t5) consists of: Oral Trail Making Test (Part A & B); Boston Naming Test; ADAS-Cog Word Recognition; DKEFS Phonemic Fluency Test and Semantic Fluency Test; WAIS III Digit Span Test; Digit Symbol Modalities Test-

Oral Version. [e] Sleep and activity monitoring for 10 days prior to assessment time points (-t1-t0, t2-t3 and t4-t5) using wrist worn Actigraph (GT9X) monitor. [f] Dual task gait battery (–t1, t3, t5) consists of: Usual Gait; Seated Dual Task; Dual Task Gait counting backwards by ones, naming animals, and counting backwards by sevens. gExit survey completed at end of study or upon early withdrawal when possible. [h] Polygenic Hazard Score biomarkers assessed via saliva sample at any time point during study.

Appendix A:

Intervention Preference Questionnaire

Page 1 of 1

1. Given what you know *at this point in time*, please indicate how interested you are in each of the following interventions, by placing a mark along the line between no interest and strong interest.

   Rate your level of interest in **physical exercise** as a way to improve your brain health

   None Some Strong

   

   Rate your level of interest in **brain exercise** as a way to improve your brain health

   None Some Strong

   

2. Please rate your preference between physical exercise and brain exercise training. Select the response below that best describes your preference at this point in time.

   - ☐ Strong preference for **physical exercise**
   - ☐ Slight preference for **physical exercise**
   - ☐ No preference
   - ☐ Slight preference for **brain exercise**
   - ☐ Strong preference for **brain exercise**

3. If you have selected that you prefer one of the interventions over the other, please indicate *why* you prefer it. If you have an equal preference, then you may skip this question.

4. Are there other interventions (besides physical exercise and cognitive training) that you would prefer? If so, please describe them below:

5. Please indicate if you have any additional comments pertaining to the interventions in this study below:

Appendix B:

GENERAL INCLUSION CRITERIA

Dementia Risk Factors

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The following is a list of the dementia risk factors for cognitively intact older adults included for this study and their definitions. Please review with the candidate and indicate the presence of each.

RISK FACTOR:	DEFINITION	PRESENCE
Obesity	Body Mass Index > 30 kg/m^2 (derived from NIH Metric BMI Calculator) Weight (kg): _____ Height (m): _____ BMI: _____	YES ☐ NO ☐
Hypertension	Hypertension (documented Systolic Blood Pressure > 140 mm Hg), OR Physician diagnosis of hypertension, OR Treatment for hypertension, OR Other approaches to treatment (e.g. diet, exercise))	YES ☐ NO ☐
Diabetes	Physician diagnosis of diabetes, OR Medications used for the treatment of diabetes, OR Other approaches to treatment (diet or exercise)	YES ☐ NO ☐
Cardiovascular Disease	Physician diagnosis of: Angina, Myocardial infarction, Coronary revascularization or other arterial revascularization, Stoke, Transient Ischemic Attack (TIA), and/or peripheral vascular disease.	YES ☐ NO ☐
Dyslipidemia	Dyslipidemia (documented total cholesterol > 6.5 mmol/L), OR Physician diagnosis of hypercholesterolemia, OR Treatment for hypercholesterolemia, OR Other approaches to treatment (e.g. diet, exercise))	YES ☐ NO ☐
Poor Sleep	PSQI score of 6 or more = YES. PSQI score: _____	YES ☐ NO ☐
Poor Diet	MDA-14 score of 7 or less on a scale of 14 =YES. MDA-14 score: ____	YES ☐ NO ☐
Abnormal Dual Task Gait	A reduction in gait speed by 20% or more on the Dual Task Gait Test compared to the Non Dual Task gait speed = YES. Non Dual Task Gait Speed (m/sec): _____ Dual Task Gait Speed (m/sec): _____ Reduction (%): _____	YES ☐ NO ☐
Physical Inactivity	Defined as inactive, whereby active is defined as engaging in a minimum of 20-30 minutes of physical activity causing sweating and breathlessness, at least two times per week	YES ☐ NO ☐
First-degree family history of dementia	First-degree family history of dementia (parents, siblings, or children)	YES ☐ NO ☐
	TOTAL YES =	**SCORE _____**

Appendix C:

CONSENT TO PARTICIPATE AS A PARTICIPANT IN A CLINCIAL RESEARCH TRIAL

Study Title

SYNchronizing Exercises, Remedies in Galt and Cognition at Home: Feasibility of a home-based double-blind randomized controlled trial to improve gait and cognition in individuals at riskfor dementia

Principal Investigators

Dr. Chris A. McGibbon, PhD
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Université de Moncton, New Brunswick, Canada

Dr. Ludivine Chamard-Witkowski, MD
Department of Neuroscience, Dr. Georges-L.-Dumont University Hospital Centre, Moncton, New Brunswick, Canada

Dr. Manuel Montero-Odasso, MD, PhD, FRCPC
Schulich School of Medicine & Dentistry, London, Ontario, Canada; Departments of Medicine (Geriatrics) and of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario, Canada

LETTER OF INFORMATION AND PARTICIPANT INFORMED CONSENT FORM

You are invited to participate in a research project assessing the feasibility of administering various interventions such as exercise and cognitive training (e.g. puzzles) at home through video conferencing. We hope that in addition to learning how feasible it is to do a research study entirely at home, we can help improve memory in older adults with our interventions.

This consent form contains information that will help you to decide whether you wish to participate in this study. The decision to take part in this study is voluntary. It is important that you understand why this study is being conducted and what it will involve. Please read this form carefully and ask any questions you may have. You may choose to discuss this study with your family, friends, family doctor, and any of the research team members.

INTRODUCTION AND BACKGROUND

There is currently an ongoing study (the SYNERGIC trial) taking place across Canada, in which various interventions are being tested with individuals who are at risk for dementia. This ongoing study has been funded by the Canadian Consortium on Neurodegeneration and Aging (CCNA) which is a pan–Canadian research initiative aimed to better understand cognitive decline in aging and dementia syndromes. The goal is to develop a clear understanding of how to best prevent the progression of memory problems leading to dementia in older adults. To date, the results are very promising.

This study that you are being asked to participate in—SYNERGIC@Home— is an extension of the SYNERGIC trial that will allow you to participate in a home-based program that will use an online virtual platform called *Zoom for Healthcare***.** This study is part of the *New Brunswick Brain Health Initiative: Preventing Alzheimer's through Lifestyle Modification* (NB-PALM), funded by the Healthy Seniors Pilot Projects, Public Health Agency of Canada and the Province of New Brunswick.

POPULATION UNDER STUDY

We are interested in studying older adults living in the community in New Brunswick who are at risk for developing dementia. Individuals between 60 and 90 years of age who have two or more risk factors for dementia, **OR** Subjective Cognitive Impairment (SCI) **OR** Mild Cognitive Impairment (MCI) are eligible to be enrolled in this study. Currently, there are no medications approved that will reduce the risk of developing dementia for persons with risk factors, SCI or MCI. Evidence suggests that some types of physical exercise and cognitive training activities (e.g. games, puzzles) may slow memory decline. The SYNERGIC@Home study will examine specifically whether physical exercise coupled with cognitive training is effective in slowing the rate of memory decline in the study group.

DESCRIPTION OF STUDY

This study, which will take place over a 10-month timeframe, is to learn about the role of certain types of exercises paired with cognitive training in delaying or preventing decline in memory. Initially, there will be assessments to evaluate your current level of cognition, mobility and overall function. If you are eligible to participate, you will be randomly assigned (by chance) to one of four groups. This will be followed by sixteen weeks of exercise and cognitive training sessions done in your home three times a week. The time required to complete each intervention session will be approximately 90 minutes.

CRITERIA FOR PARTICIPATION

Inclusion Criteria

To participate in this study, you must:

- Be between 60 - 90 years of age.
- Live in your own home/apartment in the community.
- Have Internet access; a home computer and / or a laptop; access to and able to send and receive emails
- Able to speak, write and understand English or French
- Able to complete the scheduled home-based sessions: assessments with research staff, physical and cognitive training exercises and other study procedures.
- Able to walk at least 10 m (or about 32 feet) independently with or without a walking aid.
- Have eyesight and hearing abilities with or without aids to participate in the required exercises and procedures.
- Have a diagnosis of Mild Cognitive Impairment (MCI) OR Subjective Cognitive Impairment (SCI).
- Have no problems with cognition AND have a history of two or more of the following risk factors:
    - ☐ Obesity
    - ☐ Hypertension/High blood pressure
    - ☐ Diabetes
    - ☐ Cardiovascular disease
    - ☐ Physical inactivity
    - ☐ First-degree family history of dementia (parents, children, siblings)
    - ☐ High cholesterol
    - ☐ Poor sleep
    - ☐ Poor diet

Exclusion Criteria

There are certain conditions that will ***exclude*** you from participating in the study, including the presence of one or more of the following:

- A diagnosis of Dementia.
- Living in Nursing Homes or Adult Residential Facilities (Special Care Homes).
- Serious underlying disease, which in the opinion of the study physician, may prevent you from safely participating in the interventions required for the study.
- Have had surgery within the last two months or have planned surgery in the upcoming 12 months that could interfere with vision, hearing or mobility or any other ability to participate.
- Have a history of intracranial surgery.
- Regularly taking benzodiazepines.
- Presence of ongoing significant mental health issues.
- Presence of ongoing drug/alcohol dependency.
- Parkinsonism or any neurological disorder with residual motor deficits (e.g. stroke with motor deficit)
- Active musculoskeletal disorders (e.g. severe osteoarthritis of lower limbs) or history of knee/hip replacement affecting walking.
- Severe visual and/or auditory impairment, which according to the study physician, prevents participation in the study.
- Intention to enroll in other similar clinical trials during the same time period.
- Current and ongoing participation in an exercise program involving aerobic exercise and / or resistance training two or more times per week in the previous 6 months.

PARTICIPATION REQUIREMENTS

The following is a list of what you will be doing as a participant in our study. Detailed explanations are provided later in this consent form.

SCREENING AND CLINICAL CASE CONFERENCE SESSIONS

You will complete screening and clinical case conference sessions over a four-week period. You will meet with research staff who will administer initial tests and gather information. The purpose of this screening assessment is to determine your eligibility to participate and ensure that it is safe and in the best interest of your health and well-being to do so.

Screening includes:

1. A **clinical screening** session. One of our research staff will connect with you through *Zoom for Healthcare* and go through some questionnaires assessing your medical history, your memory and thinking. One of these memory assessments must be completed by a study partner (i.e., spouse, a close friend or family member explained later in the consent) if you can provide one.

2. **Clinical Case Conference.** The study physician and members of the research team who you have met during the screening sessions will meet with you to review your medical history, results of the assessments and confirm your eligibility to participate in the study.

DETAILS OF STUDY PROCEDURES

Participating in this home-based study will require home WIFI / Internet access as well as a laptop or desktop computer. For the entire study, you will have one-on-one contact with our trained research staff members. We recognize that others you know may also be study participants. We ask that you not discuss the details of your participation or "compare notes" about the particular exercises and cognitive training that you are completing if you know other participants.

The following assistance will be provided:

- **Technical Support for Connecting to Zoom for Healthcare.** Prior to initiating the study, we will call you and work with you step by step in getting *Zoom for Healthcare* set up on your computer.
- **Cognitive Training.** We will connect with you through phone or Zoom for Healthcare to set up this training.
- **Exercise Training.** During the exercise training, a certified exercise physiologist will connect with you through Zoom for Healthcare to assist and monitor you to make sure you are supported and safe.

Intervention Sessions

You will be randomly assigned (by chance) to one of four groups within the study. Each will include some type of exercise paired with cognitive training. You will be asked to participate in this portion of the study three times a week for four months (16 weeks). It is important you know that we will provide you with any equipment (explained later in this consent) you may need to perform both the cognitive and exercise training.

- **Cognitive Training.** At each session, you will complete 30 minutes of cognitive training,

which will include doing tasks on the computer or tablet to develop skills that are cognitively stimulating.

- **Exercise Training.** After each cognitive training portion, you will complete 60 minutes of exercise training which will be fully supervised by a trained and certified exercise physiologist who will supervise your exercise training by watching and guiding you through *Zoom for Healthcare*.

As we will be testing the effect of a combination of exercises and cognitive training on slowing memory decline or improving memory, we ask that you do not engage in any additional physical or cognitive exercises that you do not typically do daily. For example, if you walk every day you will continue to do so. However, participating in a structured, routine program such as Zumba® or a program that is trainer-led and occurs two to three days of the week, will exclude you from the study. Additionally, you should not engage in any cognitive training exercises outside of your daily activities. If you do crossword puzzles, or activities such as Sudoku™, you may continue to do so.

Assessment Sessions

In order to test whether the interventions help improve your memory, we will conduct assessment sessions at three separate time points: 1) Baseline 2) Immediate post-intervention follow-up and 3) Six-month post-intervention.

These assessments include some tests of memory, attention, executive functioning (your ability to think and reason) and some assessments of how you walk (your gait) as well as measuring how well you perform simple tasks (such as saying words or doing calculations) while walking a short distance in your home. The time required to complete both types of assessments is approximately 3 hours, scheduled on a date / time that is convenient for you. (Each session is approximately 1 ½ hours.) You will have the opportunity to take breaks between the testing as required. Our research team members will help with you throughout the entire process.

<u>Baseline</u>

- A **clinical assessment** (your first testing session) testing. Health history, family medical history, memory and thinking, diet and mood.

- An **activity assessment** testing your mobility, overall functional ability.

<u>Immediate post-intervention follow-up (after you complete the 16-week intervention)</u>

- A **clinical assessment** (within one week after completing the 4-month intervention) testing your memory and thinking.

- An **activity assessment** testing your mobility, overall functional ability.

<u>Six-month post-intervention follow-up</u>

- A **clinical assessment** (to ensure that the effects of the intervention have been sustained) testing your memory and thinking.

- An **activity assessment** testing your mobility, overall activity.

Activity Monitoring

After your screening assessment, we will ask you to wear an activity monitor (provided to you) to monitor your usual physical activity level and sleep patterns. The activity monitor will attach to your wrist like a watch and it can be worn at all times except when bathing. These activity monitors are very ordinary looking, no different than a wristwatch. You will be asked to wear this for 10 days, prior to each of the three assessment session time points (baseline, immediate post-intervention follow-up and six-month post-intervention follow-up). We will ask you to maintain your usual daily activities and to please not do anything physically out of the ordinary that is not required of you. After completing each of the 10 days of wearing the activity monitor, you will return it to the study site using stamped, addressed packages we will provide to you.

Falls Calendar

At the beginning of the study you will be given a calendar for you to record every day whether you experienced a fall. If you do have a fall, there is a space at the back of the sheet where you can provide more details about the fall (where you were, what you were doing, whether you were injured). This is one way that we can monitor your health and safety during this study. You will complete this calendar for the duration of the study; completing this calendar should take no more than 5 minutes on any given day.

Study Care Partner

We encourage you to include a study care partner such as a spouse, close friend, or a relative. Your study care partner's role will be to answer some questions about your memory and to assist you to complete some questionnaires. This will occur at three assessment sessions (baseline, immediate post-intervention follow-up and six-month post-intervention follow-up). The study partner will sign their own consent form for participation in the study as your study care partner. If you do not have a study care partner, you will not be excluded from the study unless the study physician determines that a care partner is necessary.

Participant Questionnaire and Interview

Following completion of your 4-month (16 week) study intervention, we will send you a short questionnaire to better understand your experience as a participant in this home-based study. Once you complete it, you will either scan and return it by email or mail it to a research team member using a self-addressed, stamped envelope we will provide you.

After your six-month post-intervention follow-up assessment, we will contact you to arrange a time for you to participate in a one on one interview with a research team member. The purpose is to collect information about your ideas and opinions regarding your experience as a participant in this study. This information will provide us with important feedback about improvements we can make in conducting future home-based research studies involving exercise and cognitive training.

Saliva Sample

Your saliva contains genetic content known as DNA, or deoxyribonucleic acid which is an identifiable biomarker or biological element that can be specifically linked to normal or abnormal biological processes (i.e. dementia). Being able to identify these biomarkers in individuals could be greatly advantageous, since it would allow the early detection of disease by using relatively non-invasive methods (detection by saliva). The test that will be conducted on your saliva sample is currently not a standard medical diagnostic test that is used in clinical care today. This test is currently being done for research purposes only.

To obtain your saliva, we will send you a saliva sample collection kit. During the sample collection process, you will be assisted by a research team member on how to properly collect, store, and returnyour sample to the laboratory. Using a stamped, addressed container your sample will be sent the Clinical Genomics Centre, Mount Sinai Hospital, 600 University Ave, Toronto, Ontario and be processed under the guidance of Dr. Kathy Siminovitch. The return address on this sample will be University of New Brunswick Synergic@Home to maintain your confidentiality. Once the laboratory receives your sample, it will be properly stored in the research laboratory with labels that contain only the date and time of collection and your study identification number to avoid having any personal or identifying information linked with your sample. Providing a saliva sample is optional. You may decline to provide a sample and continue to participate in the study.

Saliva samples are sometimes kept for future research through a process called biobanking. Sample biobanking is important for creating new knowledge through future research that will use existing genetic material that has been collected from participants in numerous research studies who have given consent to have their genetic material stored. However, only participants who consent to biobanking their sample for future studies will have their sample analyzed for other purposes. Access to these samples will be regulated by the Biological Sample Access Committee which is made up of members of Canadian Consortium on Neurodegeneration in Aging.

At this time, the processes required for biobanking saliva are not determined. When they become available, if you agreed, we will discuss this further with you to see if you are interested. If you are interested, you will need to sign a separate consent for biobanking at that time and that specific research activity will be explained to you.

Study Equipment and Materials

Once your eligibility has been decided, research staff will provide you with all the necessary items for this home-based program. We will properly and thoroughly sanitize all items prior to delivery through a secure courier or postal delivery service. Please note that some items are yours to keep, while others are to be returned to the study site using self-addressed, stamped packages we will provide to you.

Items that you will receive include the following:

- **Basic Exercise Equipment**. These items are specifically for the exercise training portion of the study and they are yours to keep.
- **Measuring Tape**. This is a simple measuring tape that you may use to take measurements such as your waist circumference as well as the distance of space available in your home to walk for the gait assessments (described below).
- **An Activity Monitor**. This is a small simple device that looks like a watch, is very comfortable to wear, and can be worn on your wrist or hip. You will be asked to wear it on your wrist or hip for the first 10 days prior to each of your three assessments. The activity monitor will measure your walking speed, your steps, and your sleep cycle. This will help us monitor your progress throughout the study. After you complete each of the 10 - day cycles of wearing the activity monitor, you will return it using the self-addressed, stamped package we will provide. Returns will be made through a secure courier or postal delivery service.
- **A Blood Pressure Device.** We will provide you with a simple device that will measure your blood pressure and heart rate during study assessment and intervention sessions. At the end of the study, you will return the blood pressure device using the self-addressed, stamped package we will provide.
- **A Saliva Kit**. This kit will be given to you at the outset of the study and includes a small

plastic tube in which you will provide a small amount of your saliva.

- **A Tablet Device.** Depending on which study group you are a member of we may need to loan you a tablet device to complete the study interventions. Upon completion of the study, the tablet will be returned to the research site, using the self-addressed, stamped package we will provide to you.

COVID-19 Precautions

Considering the COVID-19 pandemic of 2020, many closures have taken place, forcing some participation in research studies to take place remotely. Part of the motivation for implementing a home-based program is because we are committed to ensuring that you are safe. All materials will be thoroughly sanitized using disinfectant sprays and wipes. At all times we will continue to adhere to proper sanitization practices when transporting and delivering the study materials to your home. In particular, the activity monitor will be thoroughly sanitized.

Delivery of Study Materials to Your Home

Any required study documents, materials, devices / equipment you need will be delivered to your home by a secure courier or postal delivery service (such as FedEx) If we cannot arrange for delivery this way, a drop-off will be arranged to occur at an agreed-upon location.

Return of Study Materials from Your Home

We will arrange for the return of the equipment and materials to our research site. It is important to note that the activity monitor will be returned after each of the three activity monitoring sessions. If you are unable to return the equipment by mail, arrangements will be made by a member of the research team for it be picked up at an agreed upon location.

Setting Up Video Calls from Home

To help set you up *Zoom for Healthcare*, a member of the research team will schedule a call with you once you have received all your study materials and equipment. We will go through the process step by step with you to ensure that *Zoom for Healthcare* works properly.

POTENTIAL BENEFITS OF PARTICIPATION

While there is no guarantee that you will personally benefit from participating in this study, exercises have been demonstrated to benefit memory and cognitive function. Being a part of a research study such as the one described here where you will be monitored has also been associated with cognitive improvement in participants. Your participation will help researchers advance knowledge in the area of memory and mobility in older adults. Beyond this, there are no direct benefits to you from participating in this study.

POTENTIAL RISKS OF PARTICIPATION

The risks associated with participation in the SYNERGIC@Home study are minimal. Below, we have outlined the risks associated with each procedure in the study.

Exercise Training. Your participation in this research should not pose any additional medical risk to you. The study physician and certified exercise physiologist will do their best to ensure that the risks to you are minimized. If you experience any adverse symptoms while exercising, there will be a certified exercise physiologist monitoring you remotely and all appropriate measures will be followed

to maximize your safety. A Participant's Manual that details your exercise training, safety and what to do in the event of any adverse symptoms will be shared and reviewed with you prior to engaging in exercise. We do not expect major adverse symptoms, but in case this situation occurs while exercising and requires immediate medical attention, be informed that the Research Assistant may have to call 911 for your safety. It is very important that you follow the directions for the exercises and heed the advice of the research team.

Cognitive Training. There are no known risks associated with participation in cognitive training. However, you may experience some frustration, which is normal, as you complete some cognitive training tasks.

Risks of Memory Testing and Mood Assessments: Repeated testing and questions about your mental status may be slightly frustrating or produce fatigue and boredom. Some questions may start distressing feelings or memories. If you feel distressed while completing the questions or testing, the research staff are there to assist to you and if you need a break, that will be accommodated.

Risks of Physical Activity and Sleep Recordings: There are no known medical risks to you from using the activity monitor to record your sleep and daily activity. However, one possible side effect is minor discomfort from wearing the activity monitoring device, which would be like wearing a wristwatch. It is very important not to wear the activity monitor while bathing, swimming or near water such as washing dishes.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Participation in this research is voluntary. You have the right to refuse to participate. You may withdraw from the study at any time without having to justify your reason Your withdrawal will have no impact on your future health care. If you choose to withdraw, we will ask you for consent to retain your saliva samples and information conducted during the study, if you provided one up to this point. If you choose to withdraw your information that has been collected for purposes of this study, it will be removed. However, it should be noted that if this information has been used for scientific publications or presentations, it cannot be removed from those documents. It is important to know that you won't be individually identified in those publications or presentations. Once you have requested your information to be removed, it will no longer be included in future analysis or used for future publications and/or presentations.

PRIVACY AND CONFIDENTIALITY

Confidentiality

All research materials that would identify you will be held in strict confidence and, to the extent permitted by the applicable laws and/or regulations, will not be shared with others or made publicly available. If you agree to participate in this study, you will be assigned a unique identification number that will be used on all the documents related to this study. This unique number will be linked to your name and contact information on a "master list" of participants. This master list will be kept separately from the other research information in a locked and password secured format at the University of New Brunswick. The audio and video recordings will be stored at the University of New Brunswick on a secure SharePoint server and accessible only to approved research team members. All information collected, except for the master list, will be kept for a period of 7 years. Paper documents will be kept under lock and key in the Research Coordinators' offices for the duration of the study. These paper documents will be shredded by confidential shredder at the end of the study. A digital copy of the study records will be maintained for future analyses. Computerized databases will be password

protected. For the analysis, the principal investigators will only have access to your de-identified information and will not be able to identify you personally. The results of this study could lead to scientific or professional publications. In any of these cases, no personally identifiable information will be shared or published.

Zoom Sessions and Audio Recording

Our research team will take all necessary precautions to protect your privacy throughout the entire study. *Zoom for Healthcare* video calls will not be conducted without your consent and will be completed by trained research staff in a private location (i.e., in a room by themselves with a closed door and signage to avoid entry by another person). Each video session will only be shared with you as the participant. All research staff will be connected to secure internet connections with secure password protection.

During assessments, we may record the session so we can check to ensure that we have recorded your answers correctly. These recordings will be stored in a secure research facility (i.e., university and / or hospital network drive), accessible only to approved research team members. They will not be accessed by anyone outside of the research team. Once we have recorded the information from each session, we will delete the recordings. Because the recordings reveal identifiable information (including your face and voice), we will never share, upload, or distribute them to any outside parties in any format. For information pertaining to the security and privacy features within the *Zoom for Healthcare* platform, please see https://zoom.us/security.

Data Storage

Upon completion of the study, all data collected in paper form with the unique identification numbers will be uploaded to the Longitudinal Online Research and Imaging System (LORIS) system. This is a controlled access database located at McGill Centre for Integrative Neuroscience, situated on the campus of McGill University, Montreal, Quebec. LORIS meets international security and safety standards. There are numerous safeguards in place to keep your information confidential. In particular: your personal identifiers will be removed (e.g., name, date of birth, etc.); your data will be coded using a unique identification number; and stringent security measures will prevent unauthorized access or misuse.

CCNA is committed to advancing future research throughout Canada by developing a data repository that is accessible to other CCNA researchers. Data from this research study, with all the identifying information removed, will be made available to researchers who are approved by a data oversight committee operated by CCNA.

COMPENSATION FOR PARTICIPATION

In recognition of your participation in this study we are offering you two gift cards totaling $100. A gift card of $50 will be sent to you by mail following the immediate post- intervention follow-up assessment. A second gift card of $50 will be sent to you by mail after you have completed the six - month follow up assessment and participant interview.

PARTICIPANT'S RESPONSIBILITIES

As a participant in this research study you are required to provide all answers to the questionnaires in a truthful manner. For this project to be valid and complete, it is important that you comply with the requirements of the study (i.e., attending scheduled sessions). These requirements should be carefully considered prior to signing your consent.

PARTICIPANT'S RIGHTS

By providing your consent to participate in this study, you do not waive any of your legal rights. This also does not relieve the investigators, or the institutions involved in the study from their legal or professional responsibilities.

IN THE EVENT OF AN INJURY OR ADVERSE EVENT DURING THE STUDY

In the event of an injury or adverse event, which may or not be as a result of the study, you should contact the Research Study Staff below who will follow up with the study physicians. The research team and / or study physician will advise you as to how to access any medical / health care that you may require.

Research Manager Collaborative Care Seniors Health, Horizon Health Network:

Name: Telephone: nnn-nnn-nnnn
Email:

Project Research Assistant, University of New Brunswick:

Name: Telephone: nnn-nnn-nnnn
Email:

PARTICIPATION IN FUTURE RESEARCH STUDIES

In addition to the SYNERGIC@Home research study, we have ongoing and upcoming research studies that you may be interested in. At the end of this form, you will be given the option to consent for us to contact you with information about participating in these future research studies.

QUESTIONS REGARDING PARTICIPATION

If you have questions about the study, please feel free to contact Project Research Assistant:

by phone or e-mail: nnn-nnn-nnnn.

If you have questions about your rights as a research participant or the conduct of the study, you may contact the following individuals:

Regional Director of Ethics Services for Horizon Health Network
Telephone: nnn-nnn-nnnn Email:

If you have any questions or concerns about your privacy rights, you may contact the

Privacy Officer for Horizon Health Network
Telephone: nnn-nnn-nnnn (toll free number)

CONSENT TO PARTICIPATE IN A CLINICAL RESERCH TRIAL

TITLE OF PROTOCOL: SYNchronizing Exercises, Remedies in Galt and Cognition at Home:

Feasibility of a home-based double-blind randomized controlled trial to improve gait and cognition in individuals at risk for dementia

PRINCIPAL INVESTIGATORS:

Dr. Chris A. McGibbon, PhD
Faculty of Kinesiology and Institute of Biomedical Engineering
University of New Brunswick, Fredericton, New Brunswick,
Canada

Dr. Pamela Jarrett, MD FRCPC FACP
Department of Geriatric Medicine, Horizon Health Network,
Dalhousie Medicine New Brunswick, Saint John, New Brunswick Canada

Dr. Grant Handrigan, PhD
School of Kinesiology and Recreation, Faculty of Health Sciences and Community Services,
Université de Moncton, Moncton, New Brunswick, Canada

Dr. Ludivine Chamard - Witkowski, MD
Department of Neuroscience, Dr. Georges-L.-Dumont University Hospital Centre,
Moncton, New Brunswick, Canada

Dr. Manuel Montero-Odasso, MD, PhD, FRCPC
Schulich School of Medicine & Dentistry, London, Ontario, Canada; Departments of Medicine (Geriatrics) and of Epidemiology and Biostatistics, University of Western Ontario,
London, Ontario,Canada

RESEARCH STUDY PHYSICIANS

Dr. Wayne Sheehan, MD CCFP (COE) FCFP
Horizon Health Network, Saint John,

Dr. Patrick Feltmate, MD FRCPP
Department of Medicine, Horizon Health Network, Fredericton, New Brunswixk
Division of Medicine, Dalhousie University

Dr. Alison Rodger, MD FRCPC
Department of Geriatric Medicine, Horizon Health Network

Has this study been explained to you?	☐ Yes	☐ No
Have you had an opportunity to ask questions and discuss this study?	☐ Yes	☐ No
Are you comfortable with the information that has been provided?	☐ Yes	☐ No
Do you understand that you are free to withdraw from this study?	☐ Yes	☐ No
Do you understand that you will receive a copy of this consent?	☐ Yes	☐ No
Do you understand that your Primary Healthcare Provider will be informed that you are participating in this study?	☐ Yes	☐ No

By placing your initial on the appropriate line, you are agreeing to each of the following statements:

You agree to be VIDEO AND AUDIO-RECORDED with Zoom for Healthcare for the purpose ofstudy assessment and intervention processes:

☐ **Yes** ☐ **No** _____**Participant Initials**

You agree to provide a saliva sample.

☐**Yes** ☐**No** _____**Participant Initials**

If you provide a saliva sample, you are interested in being contacted by a research coordinator to have a portion of your saliva sample bio banked by Dr. Kathy Siminovitch in her laboratory for future research. You will be aske to sign a separate consent for this procedure.

☐**Yes** ☐**No** _____**Participant Initials**

You agree to be contacted for other studies related to this research study.

☐**Yes** ☐**No** _____**Participant Initials**

PARTICIPANT'S STATEMENT

By signing this consent, I am indicating that I have reviewed each page of this document. I hereby give my informed consent to be a participant in this study.

_____	_____	_____/_____/_____
Signature of Participant	*Name (Printed)*	*Day / Month / Year*

_____	_____	_____/_____/_____
Signature of the Person Conducting Consent Discussion	*Name (Printed)*	*Day / Month / Year*

INVESTIGATOR'S/DELEGATE'S STATEMENT

I have explained to the above participant the nature, requirements and the purpose of the study, potential benefits, and possible risks associated with participation in this study. I have answered any questions that have been raised. I believe that the participant understands the implications andthe voluntary nature of the studv.

_____		
Investigator/Delegate (Print Name)	Signature	Date

Appendix D:

CONSENT TO PARTICIPATE AS A STUDY CARE PARTNER IN A CLINCIAL RESEARCH TRIAL

Study Title

SYNchronizing Exercises, Remedies in GaIt and Cognition at Home: Feasibility of a home-based double-blind randomized controlled trial to improve gait and cognition in individuals at risk for dementia

Principal Investigators

Dr. Chris A. McGibbon, PhD
Faculty of Kinesiology and Institute of Biomedical Engineering,
University of New Brunswick, New Brunswick, Canada

Dr. Pamela Jarrett, MD FRCPC FACP
Department of Geriatric Medicine, Horizon Health Network,
Dalhousie Medicine New Brunswick, Saint John, New Brunswick Canada

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INTRODUCTION

You are invited to participate in a research project as a *study care partner* for a participant in a research study that is assessing the feasibility of administering various interventions such as exercise and cognitive training (e.g. puzzles) at home through video conferencing. We hope that in addition to learning how feasible it is to do a research study entirely at home, we can help improve memory in older adults with our interventions.

This consent form contains information that will help you to decide whether you wish to participate in this study as *a study care partner*. The decision to take part in this study is voluntary. It is important that you understand why this study is being conducted and what it will involve. Please read this form carefully and ask any questions you may have. You may choose to discuss this study with your friends and family and research team members.

BACKGROUND AND PURPOSE OF THE STUDY

There is currently an ongoing study (the SYNERGIC trial) taking place across Canada, in which various interventions are being tested with individuals who are at risk for dementia. This ongoing study has been funded by the Canadian Consortium on Neurodegeneration and Aging (CCNA) which is a pan–Canadian research initiative aimed to better understand cognitive decline in aging and dementia syndromes. The goal is to develop a clear understanding of how to best prevent the progression of memory problems leading to dementia in older adults. To date, the results are very promising.

The study you are being asked to participate as a *study care partner* in—SYNERGIC@Home— is anextension of the SYNERGIC trial that will allow you to participate in a home-based program that willuse an online virtual platform called Zoom for Healthcare. This study is part of the New BrunswickBrain Health Initiative: Preventing Alzheimer's through Lifestyle Modification (NB-PALM), funded bythe Healthy Seniors Pilot Projects, Public Health Agency of Canada and the Province of New Brunswick.

POPULATION UNDER STUDY

We are interested in studying older adults living in the community in New Brunswick who are at risk for developing dementia. Individuals between 60 and 90 years of age who have two or more risk factors for dementia, **OR** Subjective Cognitive Impairment (SCI) **OR** Mild Cognitive Impairment (MCI) are eligible to be enrolled in this study. Currently, there are no medications approved that will reduce the risk of developing dementia for persons with risk factors, SCI or MCI. Evidence suggests that some types of physical exercise and cognitive training activities (e.g. games, puzzles) may slow memory decline. The SYNERGIC@Home study will examine specifically whether physical exercise coupled with cognitive training is effective in slowing the rate of memory decline in the study group.

DESCRIPTION OF STUDY

This study, which will take place over a 10-month timeframe, is to learn about the role of certain types of exercises paired with cognitive training in delaying or preventing decline in memory. Initially, there will be assessments to evaluate the participant's current of level cognition, mobility and overall function.Following eligibility to participate, the participant will be randomly assigned (by chance) to one of fourgroups. This will be followed by 16 weeks of exercise and cognitive training sessions done in the participant's home three times a week. The time required to complete each intervention session will be approximately 90 minutes. This study will take place in the participant's home using

video conferencing called Zoom for Healthcare. All necessary equipment for participants for the study willbe provided and delivery arranged by the research team.

Over the course of the study, the participant will be involved in several assessments and interventions aimed at improving cognitive functioning and physical activity as well as assessment sessions that will measure mobility and cognitive performance. Study care partners will not be involved in the cognitive training or the exercise components of the study.

At four times, over the course of the study, you will be asked to complete a part of a questionnaire called the Clinical Dementia Rating Scale. In this questionnaire, you will be asked questions related to the participant's memory. This questionnaire will take approximately 30 minutes to complete each time. Also, you may be asked to attend a conference with the study physician (explained later); this conference may be approximately 30 minutes. Your time commitment for the entire study will be up to 2 ½ - 3 hours.

Your participation, as a study partner, will last for as long as the participant is participating in the study which could be as long as 10 months.

You will be one of approximately 64 study partners asked to complete this questionnaire across approximately two study centers in New Brunswick.

STUDY CARE PARTNER PARTICIPATION REQUIREMENTS

The study care partner:

- Is someone who either lives with the study participant or is a close relative and/or friend
- Has frequent contact with the study participant in order to provide and validate current information about the participant's memory and cognitive functioning as well as routine daily activities
- Has access to a home computer and/or a laptop / or telephone
- Have Internet access; a home computer and / or a tablet; access to and able to send and receive emails
- Able to speak, write and understand English or French.
- Able to complete the required assessments as a study partner with research staff.

The following is a list of sessions where your participation as a *study care partner* will take place:

- **Screening Session.** You will meet with one of our research staff to answer questions in the Clinical Dementia Rating Scale about the participant's memory.

- **Assessment Sessions.** Assessment sessions will take place during the study that will test thememory and activity levels of the study participant. As the *study care partner,* you will participate in the clinical assessment sessions during the time periods as follows:
    - one clinical assessment before the participant starts the interventions (called "baseline"),
    - one clinical assessment after the participant completes the interventions 4 months from baseline
    - one clinical assessment 6 months after the participant has completed the interventions.

Following the screening session, the study participant will be involved in a **Clinical Case Conference** with a study physician and members of the research team. At this session the study physician may determine that the participant will need a *study care partner* to be present. If you are required to be

present, this will be approximately 30 minutes of your time.

COVID-19 PRECAUTIONS

Considering the COVID-19 pandemic of 2020, many closures have taken place, forcing some participation in research studies to take place remotely. Part of the motivation for implementing a home-based program is because we are committed to ensuring that participants are safe. All materials delivered to the participant's home will be thoroughly sanitized using disinfectant sprays and wipes. At all times we will continue to adhere to proper sanitization practices when transporting and delivering the study materials to the participant's home.

POTENTIAL BENEFITS OF PARTICIPATION

The benefit to you in participating as a *study care partner* is an assurance that you will, to the best of your knowledge, validate the responses provided by the study participant. Beyond this, there are no direct benefits to you from participating in this study other than helping researchers advance knowledge in the area of memory and mobility in older adults.

POTENTIAL RISKS OF PARTICIPATION

Participation in this study as a *study care partner* may involve some minimal risks or discomforts as explained below.

In your role as a *study care partner*, you will be asked the same questions about the participant's memory and cognitive functioning at different times. This repetition may be frustrating, produce some fatigue or boredom. If you feel any of these emotions while completing some questions, the research staff will suggest a break.

The study physician will not perform any examinations, tests, or procedures on you. Your only involvement in the study will be to answer questions and provide information

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Participation in this research is voluntary. You have the right to refuse to participate as a *study care partner*. You may withdraw from the study at any time. Your withdrawal will have no impact on your future health care. If you choose to withdraw your information that has been collected for purposes of this study, it will be removed. However, it should be noted that if this information has been used for scientific publications or presentations, it cannot be removed from those documents. It is important to know that you won't be individually identified in those publications or presentations. Once you have requested your information to be removed, it will no longer be included in future analysis or used for future publications and/or presentations.

PRIVACY AND CONFIDENTIALITY

Confidentiality

All research materials that would identify you will be held in strict confidence and, to the extent permitted by the applicable laws and/or regulations, will not be shared with others or made publicly available. If you agree to participate in this study, you will be assigned a unique identification number that will be used on all the documents related to this study. This unique number will be linked to your name and contact information on a "master list" of participants. This master list will be kept separately from the other research information in a locked and password secured format at the University of New

Brunswick. All information collected, except for the master list, will be kept for a period of 7 years. Paper documents will be kept under lock and key in the Research Coordinators' offices for the duration of the study. These paper documents will be shredded by confidential shredder at the end of the study. A digital copy of the study records will be maintained for future analyses. Computerized databases will be password protected. For the analysis, the principal investigators will only have access to your de-identified information and will not be able to identify you personally. The results of this study could lead to scientific or professional publications. In any of these cases, no personally identifiable information will be shared or published.

Video Conferencing Calls and Audio Recording

If you use *Zoom for Healthcare*©, our research staff will take all necessary precautions to protect your privacy as a *study care partner* throughout the entire study. Video calls will not be conducted without your consent and will be completed by trained research staff in a private location (i.e., in a room by themselves with a closed door and signage to avoid entry by another person). Each video conference meeting room will only be shared with you and any other users will be barred from entering. All research staff will be connected to secure internet connections with adequate password protection.

During the assessments, we may record the session so we can check to ensure that we have recorded your answers correctly. The audio and video recordings will be stored at the University of New Brunswick on a secure SharePoint server and accessible only to approved research team members. They will not be accessed by anyone outside of the research team. Once we have verified your responses from each recording, we will delete the recordings. Because the recordings reveal identifiable information (including your face and voice), we will never share, upload, or distribute them to any outside parties in any format. For information pertaining to the security and privacy features within the *Zoom for Healthcare*© platform, please see https://zoom.us/security. All paper-based data will be stored in locked filing cabinets at UNB and / or research sites.

Data Storage

Upon completion of the study, all data collected in paper form with the unique identification numbers will be uploaded to the Longitudinal Online Research and Imaging System (LORIS) system. This is a controlled access database located at McGill Centre for Integrative Neuroscience, situated on the campus of McGill University, Montreal, Quebec. LORIS meets international security and safety standards. There are numerous safeguards are in place to keep your information confidential. In particular: your personal identifiers will be removed (i.e. name, date of birth, etc.); your data will be coded; and stringent security measures will prevent unauthorized access or misuse.

CCNA is committed to advancing future research throughout Canada by developing a data repository that is accessible to other researchers. Data from this research study, with all the identifying information removed, will be made available to researchers who are approved by a data oversight committee operated by CCNA.

COMPENSATION FOR PARTICIPATION

There is no compensation for your role as a study care partner.

PARTICIPATION IN FUTURE RESEARCH STUDIES

Besides the SYNERGIC@Home trial, we have ongoing and upcoming research studies that you may be interested in. At the end of this form, you will be given the option to consent for us to contact you with information about participating in these future research studies.

PARTICIPANT'S RESPONSIBILITIES

As a participant in this research study you are required to provide all answers to the questionnaires in a truthful manner. For this project to be valid and complete, it is important that you comply with the requirements of the study (i.e., attending scheduled sessions). These requirements should be carefully considered prior to signing your consent.

PARTICIPANT'S RIGHTS

By providing your consent to participate in this study, you do not waive any of your legal rights. This also does not relieve the investigators, or the institutions involved in the study from their legal or professional responsibilities.

QUESTIONS REGARDING PARTICIPATION

If you have questions about the study, please feel free to contact Project Research Assistant:

by phone or e-mail: nnn-nnn-nnnn

If you have questions about your rights as a study care partner or the conduct of the study, you may contact the following individuals:

Regional Director of Ethics Services for Horizon Health Network
Telephone: nnn-nnn-nnn Email:

If you have any questions or concerns about your privacy rights, you may contact the

Privacy Officer for Horizon Health Network
Telephone: nnn-nnn-nnnn (toll free number)

IN THE EVENT OF AN INJURY OR ADVERSE EVENT DURINGTHE STUDY

In the event of an injury or adverse event, which may or may not be as a result of the study, you should contact the Study Staff listed below who will follow up with the study physicians. The research team and / or study physician will advise you as to how to access any medical / health care that youmay require.

Research Manager Collaborative Care Seniors Health,
Horizon Health Network

Name:
Telephone: nnn-nnn-nnnn
Email:

Project Research Assistant,
University of New Brunswick:

Name:
Telephone: nnn-nnn-nnnn
Email:

CONSENT TO PARTICIPATE AS A STUDY CARE PARTNER IN A CLINCIAL RESEARCH TRIAL

TITLE OF PROTOCOL: SYNchronizing Exercises, Remedies in Galt and Cognition at Home: Feasibility of a home-based double-blind randomized controlled trial to improve gait and cognition in individuals at risk for dementia

PRINCIPAL INVESTIGATORS:

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Dr. Manuel Montero-Odasso, MD, PhD, FRCPC
Schulich School of Medicine & Dentistry, London, Ontario, Canada; Departments of Medicine (Geriatrics) and of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario, Canada

RESEARCH STUDY PHYSICIANS

Dr. Wayne Sheehan, MD CCFP (COE) FCFP
Horizon Health Network, Saint John, New Brunswick

Dr. Patrick Feltmate, MD FRCPP
Department of Medicine, Horizon Health Network, Fredericton, New Brunswick
Division of Medicine, Dalhousie University

Dr. Alison Rodger, MD FRCPC
Department of Geriatric Medicine, Horizon Health Network

Has this study been explained to you?	☐ Yes	☐ No
Have you had an opportunity to ask questions and discuss this study?	☐ Yes	☐ No
Are you comfortable with the information that has been provided?	☐ Yes	☐ No
Do you understand that you are free to withdraw from this study?	☐ Yes	☐ No
Do you understand that you will receive a signed copy of this consent?	☐ Yes	☐ No
Do you understand that your Primary Healthcare Provider will be informed that you are participating in this study?	☐ Yes	☐ No

By placing your initial on the appropriate line, you are agreeing to each of the following statements:

You agree to be VIDEO AND AUDIO-RECORDED with Zoom for Healthcare for the purpose of providing the information for the questionnaires.

☐Yes ☐No _____Participant Initials

You agree to be contacted for other studies related to this research study.

☐Yes ☐No _____Participant Initials

PARTICIPANT'S STATEMENT

By signing this consent, I am indicating that I have reviewed each page of this document. I hereby give my informed consent to be a participant as a Study Care Partner in this study.

_____	_____	____ / _____ / _____
Signature of Study Partner Participant	*Name (Printed)*	*Day / Month / Year*

_____	_____	____/_____/ _____
Signature of the Person Conducting Consent Discussion	*Name (Printed)*	*Day / Month / Year*

INVESTIGATOR'S/DELEGATE'S STATEMENT

I have explained to the above participant the nature, requirements and the purpose of the study, potential benefits, and possible risks associated with participation in this study. I have answered any questions that have been raised. I believe that the participant understands the implications and the voluntary nature of the study.

_____	_____	_____
Investigator/Delegate (Print Name)	Signature	Date

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____1_____
	2b	All items from the World Health Organization Trial Registration Data Set	___n/a_____
Protocol version	3	Date and version identifier	____1_____
Funding	4	Sources and types of financial, material, and other support	____16_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1,16____
	5b	Name and contact information for the trial sponsor	___n/a_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___n/a_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___n/a_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8,9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9,10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11,12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11,12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___6_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___7_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___13_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__15_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__13_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__n/a_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__n/a_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__n/a_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Appendix C & D_
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Appendix A, D & E

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Protocol Title	**SYNchronizing Exercises, Remedies in Gait and Cognition at Home: Feasibility of a home-based double-blind randomized controlled trial to improve gait and cognition in individuals at risk for dementia/ SYNchroniser l'exercice et des solutions pour la démarche et la santé cognitive chez soi**
Running Title	**SYNERGIC@Home/SYNERGIE~Chez soi**
Principal Investigators	Chris A. McGibbon, PhD Faculty of Kinesiology and Institute of Biomedical Engineering, University of New Brunswick, New Brunswick, Canada. Pamela Jarrett, MD, FRCPC, FACP Department of Geriatric Medicine, Horizon Health Network, Saint John New Brunswick, Canada; Dalhousie Medicine New Brunswick, Dalhousie University, Halifax, Nova Scotia, Canada. Grant Handrigan, PhD School of Kinesiology and Recreation, Faculty of Health Sciences and Community Services, Université de Moncton, Moncton, New Brunswick, Canada Ludivine Witkowski, MD Department of Neuroscience, Dr. Georges-L.-Dumont University Hospital Centre, Moncton, New Brunswick, Canada Manuel Montero-Odasso, MD, PhD, FRCPC Schulich School of Medicine & Dentistry, London, Ontario, Canada; Departments of Medicine (Geriatrics) and of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario, Canada
Protocol Number	SYNH001
NCT Number	NCT04997681
Version	5.0
Date	Aug 30, 2021

Protocol Changes Table

Affected Sections	Change(s)	Rationale

SYNERGIC@Home TRIAL

SYNchronizing Exercises, Remedies in Galt and Cognition @Home

Feasibility of a Home-Based Double-Blind Randomized Controlled Trial to Improve Gait and Cognition in Individuals at Risk for Dementia

Principal Investigators

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Collaborators

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SYNERGIC Project Research Manager and Coordinator: Nellie Kamkar MSc[18]

Synergic@Home Research Coordinators: Alana Gullison MSc[2], Kelly McMillan[15], Chris Pauley[9], Jacques Frigault[16]

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Confidentiality Statement. This document contains information that is privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws and regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you, which is indicated as privileged or confidential.

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1. EXECUTIVE SUMMARY

Title	SYNchronizing Exercises, Remedies in Galt and Cognition @Home (SYNERGIC@Home/Synergie~chez soi): Feasibility of a Home-Based Double-Blind Randomized Controlled Trial to Improve Gait and Cognition in Individuals at Risk for Dementia
Background & Rationale	In Canada, it is estimated that there are currently over 500,000 older adults living with Alzheimer's Disease and Related Dementias (ADRDs). Encouragingly, close to a third of ADRD cases could be prevented by addressing modifiable risk factors[1]. Physical exercise and cognitive training are emerging interventions that have the potential to enhance cognitive function and mobility in older adults with Mild Cognitive Impairment (MCI). The SYNERGIC trial (SYNchronizing Exercises, Remedies in Galt and Cognition), a large multi-site randomized control trial, showed promising preliminary data that combined aerobic exercise and progressive resistance training (AE+RT) with cognitive training (NEUROPEAK™) had a better effect on cognition than a balance and toning control (BAT) intervention and control cognitive training with web search and video (WS+V) activities. While these interventions were provided face to face in a research facility, little is known about the feasibility of providing these multi-domain interventions in older adults at home.
Study Design	This feasibility study is a factorial design Randomized Control Trial (RCT) in which participants will be randomized (in blocks of 4) into one of four arms: Arm 1: **Combined exercise (AE+RT)** + **Cognitive training** (**Neuropeak)** Arm 2: **Combined exercise (AE+RT)** + Control cognitive training (WS+V) Arm 3: Control exercise (BAT) + **Cognitive training (Neuropeak)** Arm 4: Control exercise (BAT) + Control cognitive training (WS+V) Note: The active interventions are in bold. Arm 4 has the active control interventions.

Study Duration	Estimated duration of entire trial period is approximately 24 months.
Number of Participants	N = 64 community-dwelling older adult participants.
Target Population	All Participants: • Ages 60-90. • Has a Family Physician or a Nurse Practitioner. • Internet access (have regular access to email), technology ability (able to send and receive emails), and access to a home computer and/or laptop computer device. • Self-reported levels of proficiency in English and/or French for speaking and understanding spoken and written language. • Able to comply with scheduled home-based assessments, interventions, treatment plan, and other trial procedures. • Able to ambulate at least 10 meters independently with or without a walking aid. • Being at risk of developing dementia: a) **Mild Cognitive Impairment (MCI).** Diagnosis of Mild Cognitive Impairment, in accordance with the Comprehensive Assessment of Neurodegeneration and Dementia COMPASS-ND study[2] definition (see Table 1). b) **Subjective Cognitive Impairment (SCI).** Diagnosis of Subjective Cognitive Impairment, in accordance with COMPASS-ND study[2] definition (see Table 1). c) **Cognitively Intact with Risk Factors.** Cognitively intact based on COMPASS-ND definition (in Table 1) AND have a history of ***two or more risk factors*** for dementia, defined as the following: ▪ Obesity ▪ Hypertension ▪ Diabetes

	▪ Physical Inactivity ▪ Cardiovascular disease ▪ First-Degree Family History of Dementia ▪ Dyslipidemia ▪ Poor sleep ▪ Poor diet • Preserved activities of daily living, operationalized as a score >14/23 on the Lawton-Brody Instrumental Activities of Daily Living (IADL)[3] scale and confirmed by clinician's interviews. • Must be medically able to participate in the study's exercise training program, as determined by the physician for clearance to participate in combined exercise training program.
Exclusion Criteria	• A diagnosis of dementia. • Participants living in Nursing Homes or Adult Residential Facilities (Special Care Homes) will be excluded. • Serious underlying disease, which, in the opinion of the study physician excludes engagement in interventions or may interfere with the participant's ability to participate fully in the study. • Has had surgery within the last two months or has planned surgery in the coming 12 months that, deemed by the study physician, could interfere with the participant's vision, hearing, mobility or any other ability to participate in the study. • Has a history of intracranial surgery. • Regular Benzodiazepine use by a participant that the study physician determines to be significant enough to interfere with the participants ability to participate in the assessments and interventions in the study will be excluded. • Presence of major depression, schizophrenia, severe anxiety or drug/alcohol abuse or other medical illness that would prohibit them from safely participating in the study or may cause harm to the participant.

	• Current Parkinsonism or any neurological disorder with residual motor deficits (e.g. stroke with motor deficit), active musculoskeletal disorders (e.g. severe osteoarthritis of lower limbs) or history of knee/hip replacement affecting gait performance during the baseline assessment. • Severe visual and/or auditory impairment, which, according to the vision and hearing assessment, precludes the participant from engaging in the trial. • Intention to enroll in other clinical trials during the same time period. • Active participation in an organized and planned exercise program involving aerobic exercise and/or resistance training regimen in previous 6 months.
Study Goal and Objectives	Overall Goals: • To examine feasibility and provide preliminary data on delivering combined physical exercise and cognitive training at home in older adults at risk of ADRD. • To examine participant's preference for each intervention type and to correlate this with subsequent adherence across the trial. • To assess whether the combination of physical exercise with cognitive training is more effective than the individual interventions in improving cognition, frailty, mobility, sleep, diet, and mood. Objectives: **Primary Feasibility Objectives**. Is it feasible to implement a 16-week home-based, multi-domain intervention program aimed at reducing the risk of ADRD in community-dwelling older adults and improving their global health? • **Adherence.** Adherence of study participants will be defined as attendance to a minimum of 75% of study assessment sessions.

-

Secondary Feasibility Objectives: Will participants adhere to the study protocol? How satisfied will participants be with the study at the end of the trial? What (if any) adverse events will occur during the trial?

- **Recruitment.** A successful recruitment rate is defined as the ability to recruit (and consent) a minimum of 75% of the total recruitment goal of 64 participants across all sites during the enrollment period
- **Retention**. A successful retention rate is defined as a minimum of 75% of the total number of recruited participants continuing to trial completion (at the immediate post intervention follow up session).
- **Experience and Satisfaction.** Experience and satisfaction will be defined as the results expressed by study participants in responses given to semi-structured interview questions that are designed using Kirkland's four-level model[4]. Used in numerous settings for program evaluation, this framework consists of four dimensions: reaction, learning, behavior, and results.
- **Adverse Events.** An adverse event is defined as any incident or adverse outcome that is unexpected, and related or possibly related to participation in the research study.
- **Data Loss.** Data loss due to technical failures, personnel errors, and participant non-compliance will be assessed. A minimum acceptable rate of missing data will set at <20%.

Primary Analytic Objectives. In order to determine if affinity for any one intervention is an important factor in participants' adherence to the study interventions, we designed the Intervention Preference Questionnaire (IPQ, Appendix A) that will be used to answer the question: Is interest level for a given intervention type correlated with subsequent adherence to the intervention? We will also use the IPQ to examine preference attitudes: Which intervention type (physical exercise or cognitive training) do the

	majority of participants prefer over the other? What proportion of participants have no particular preference for either intervention? Do participants adhere better if they receive the active treatments they prefer? Do their attitudes change after completing the active interventions versus the control interventions? **Secondary Analytic Objectives.** What is the estimated effect size (ES) of the interventions on cognitive improvement? What is the standard deviation of the outcome variable? • **Cognitive Improvement**. The ES for cognitive improvement will be defined using Cohen's descriptors: 0.2 = small; 0.5 = moderate; 0.8 = large. • **Mobility Improvement**. Similarly, the ES for mobility improvement will be defined using Cohen's descriptors: 0.2 = small; 0.5 = moderate; 0.8 = large.
Outcome Measures	Primary Feasibility Outcomes • **Adherence to Interventions**. Defined as the mean percent of all Intervention sessions attended of the 48 planned sessions per participant. Primary Analytic Outcome • **Preference.** The primary analytic goal of SYNERGIC@Home is to assess the relationship between participants' adherence to the interventions and their affinity for each intervention going into the trial. All participants will be given the Intervention Preference Questionnaire (IPQ, Appendix A) prior to implementation of the intervention at baseline (T0) and after the 4mo intervention (T4). Secondary Feasibility Outcomes

- **Recruitment Enrollment Rate**: Defined as the total percent of enrolled participants relative to number of people screened for eligibility.
- **Enrollment Retention Rate**: Defined as the total percent of enrolled participants who continue throughout the trial and participate in outcomes assessments.
- **Assessment Tolerability:** Defined as no voluntary dropouts occurring either during or between baseline assessment and prior to allocation to an intervention group.
- **Trial Experience**: Defined as participants' qualitative responses to semi-structured open-ended questions aimed at providing insights on their overall trial experience within the context of the Kirkland evaluation framework.
- **Adverse Events**: Frequency cross-tabulation of AE severity versus AE relation to trial.
- **Data Loss**: Defined as data lost due to technical failures, personnel errors or participant non-compliance.

Secondary Analytic Outcomes

- **Cognitive Functioning**. Cognitive outcomes will be measured using the Cognitive Functional Composite 2 (CFC-2), the telephone version of the Telephone Cognitive Screening (TCogS), the remote version of the Montreal Cognitive Assessment (MoCA), and select items from the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog Plus) as part of our additional cognitive outcomes.
    - **CFC-2**. The CFC consists of the following validated tests[5,6]. The first three tests originate from the ADAS-Cog 13, which has been used as a primary outcome measure in numerous trials with individuals at risk for ADRDs and has recently been shown to be valid for remote use[7-9]: ADAS-Cog Immediate Word Recall, ADAS-Cog Delayed Word Recall, ADAS-Cog

	Orientation, Clinical Dementia Rating scale Sum of Boxes cognitive portion (CDR-SB Cog), the Lawton-Brody Instrumental Activities of Daily Living (IADL) and the Functional Activities Questionnaire (FAQ). ○ **Additional Cognitive Outcomes**. Additional cognitive outcomes include the Oral Trail Making Test (TMT) A & B[10], the 15-item Boston Naming Test (BNT)[11], Logical Memory I & II[12], ADAS-Cog Word Recognition[7-9], the Delis-Kaplan Executive Function System (DKEFS) phonemic fluency test, and The Delis-Kaplan Executive Function System (DKEFS) semantic fluency test[13], the Digit Span Backward Test[14], and oral version of the Digit Symbol Modalities Test[15]. • **Clinical and Mobility Outcomes**. Medications, blood pressure, heart rate, exercise routines, gait speed, dual task gait parameters, Sit to Stand Test (STST) performance, fear of falling, and fall history using self-reports of falls on a fall calendar. • **Sleep Patterns**. Sleep habits will be assessed using the 18-item Pittsburgh Sleep Quality Index (PSQI-18) and the Work and Sleep Diary (WSD)[16] • **Diet Habits.** Diet habits will be assessed using the 14-item Mediterranean Diet Assessment (MDA-14) a short questionnaire for Vitamin D intake, and the Eating Pattern Self-Assessment. • **Functional Independence and Activity Level**. Additional descriptors of functional health and independence will also be tested including: the activities of daily living--using the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale, the Physical Activity Scale for the Elderly (PASE), the Life Space Questionnaire (LSQ), and the Clinical Frailty Scale (CFS). • **Mental Health and Well-Being**. Mental health and well-being will be assessed using the Short Form quality of life questionnaire (SF-36), the Generalized Anxiety Disorder 7 (GAD 7), Geriatric Depression

	Scale (GDS-30), and the COVID-19 Questionnaires. • **Health Literacy.** Health literacy will be assessed using the Short Test of Functional Health Literacy in Adults (STOFHLA). • **Technology Use and Ability**. Participant's level of technology use and ability will be assessed using the Functional Assessment of Currently Employed Technology Scale (FACETS).
Data Analysis Plan	Primary Analyses 1- Primary Feasibility Outcome: Adherence to the interventions will be analyzed using a one-sample t-test that will test the hypothesis that participants complete at least 36 of the 48 (75%) scheduled interventions sessions. This test will be used to determine of the adherence is similar to hypothesize, better than hypothesized or worse than hypothesized. 2- Primary Analytic Outcome: We will examine the relationship between interest level in and adherence to the interventions using Pearson's r. This analysis will tell us if adherence to the trial is related to participants' affinity for any one or more interventions.
Significance	In today's technological age, it is becoming more possible than ever to conduct impactful research with participants virtually. A home-based intervention program for older adults at risk for ADRDs has the advantages of allowing participants the freedom, flexibility and comfort to participate from their home—and may potentially lead to enhanced recruitment, retention and reduce social isolation.

2. ABSTRACT

BACKGROUND: Nearly half a million Canadians live with Alzheimer's Disease and Related Dementias (ADRDs), and approximately one third of those cases could have been prevented with early intervention. Early intervention is best applied in pre-dementia states such as in individuals with mild cognitive impairment (MCI)[1,17,18] and those at risk for developing dementia[19-21]. Physical exercise and cognitive training are emerging interventions that have the potential to enhance cognitive function and mobility in older adults with MCI. The SYNERGIC trial (SYNchronizing Exercises, Remedies in GaIt and Cognition), a large multi-site randomized control trial, showed promising preliminary data that individuals in an active exercise intervention combining aerobic exercise with progressive resistance training (AE+RT) *and* in a cognitive training program (NEUROPEAK™) had better cognitive outcomes than a balance and toning control (BAT) intervention paired with a control cognitive intervention consisting of website searching and watching a simple video (WS+V)[22,23]. While these interventions were provided face to face in a research facility, little is known about the feasibility of delivering these multi-domain interventions at home in older adults at risk for developing ADRDs. Thus, the primary goals of the SYNERGIC@Home feasibility study are to assess the feasibility of the home-based approach and to evaluate the relationship between participant's intervention preferences and their subsequent adherence. Secondary objectives will include the effect of the interventions on cognition, frailty, mobility, sleep, and diet.

METHODS: The SYNERGIC@Home feasibility trial is a randomized control trial (RCT) that will follow a 2 x 2 factorial design, with a 16-week home-based intervention program of combined physical exercises with cognitive training. Sixty-four participants will be randomized in blocks of four to one of the following four arms: 1) combined exercise (AE+RT) + cognitive training (NEUROPEAK™); 2) combined exercise (AE+RT) + control cognitive training (WS+V); 3) Control exercise (BAT) + cognitive training (NEUROPEAK™) ; and 4) Control exercise (BAT) + control cognitive training (WS+V). SYNERGIC@Home will be implemented entirely virtually through video and phone conferencing. Baseline, immediate post-intervention follow-up, and 6-month post-intervention follow-up assessments will include measures of cognition, frailty, mobility, sleep, diet, and psychological health. For primary feasibility objectives, we will obtain measures of recruitment and retention rates. For primary analytic objectives, we will

examine the distribution of preference ratings and determine if there is a relationship between preference for a given intervention and subsequent adherence. A series of secondary analytic outcomes examining the potential effect of the individual and combined interventions on cognitive, mobility, and general well-being will be measured at both baseline and follow-up. If we find a relatively equal split in sex our sample, we will conduct gender-based analyses as additional, exploratory research.

EXPECTED RESULTS AND DISCUSSION: The SYNERGIC@Home trial will establish the feasibility of a combined multimodal intervention program delivered at home in older adults. Similarly, it will estimate the frequency and strength of participant preference for different interventions and delineate the relationship between intervention preference and subsequent adherence. It will also build capacity for and pilot the delivery of multi-domain interventions using an entirely home-based protocol with individuals at risk for ADRDs. The SYNERGIC@Home trial will inform future larger scale studies on the feasibility and success of implementing home-based interventions for individuals at risk for ADRDs. Insights gained from this feasibility trial will be instrumental in developing various other at home, remote, and virtual intervention programs for community-dwelling older adults.

Keywords: Exercise, cognitive training, intervention preference, cognition, gait, dementia, elderly, home-based intervention program.

3. BACKGROUND

In 2015, over 46 million people lived with Alzheimer's Disease and Related Dementias (ADRDs) worldwide, with 1 new case appearing every 4.1 seconds[1]. The cost associated with these cases is over a trillion Canadian dollars[1,24,25]. There is no cure for dementia[26]. Recently, there has been an important shift in interventional studies on ADRDs to targeting early stages or pre-dementia states, such as individuals with mild cognitive impairment (MCI)[27,28]. The SYNERGIC Trial (SYNchronizing Exercises, Remedies in GaIt and Cognition) implemented a multi-domain intervention study design on individuals with MCI at various sites across Canada in Ontario, Québec, and British Columbia[22] in both English and in French. The success of the SYNERGIC trial has warranted pilot testing of a similar intervention design to be provided at home across other sites. This protocol is the new application of the SYNERGIC@Home (SYNERGIE~chez soi) feasibility trial—a home-based version of the protocol to be implemented by researchers in New Brunswick. SYNERGIC@Home (SYNERGIE~chez soi) will assess the feasibility of a protocol and intervention future home-based intervention programs. It has added assessments of preference to evaluate the relationship between preference for interventions and subsequent adherence, and it will ultimately inform on the logistics of delivering a remote, home-based intervention to individuals at risk for developing ADRDs.

3.1 RATIONALE OF THE INTERVENTIONS

The preliminary success of the original SYNERGIC program, as well as similar interventions in the literature, have illustrated that non pharmacological interventions to enhance cognition for older adults at risk of developing ADRDs that include physical exercise and cognitive training are very promising[21-23,29]. The rationale for each type of intervention to improve cognition in older adults at risk for developing ADRDs is as follows.

3.1.1 Physical Exercise

Aerobic exercise (AE) and progressive resistance training (RT) have been shown to improve cognitive outcomes, along with improved physical capacity and mobility in older adults.[30-33] Both, AE[34] and RT[35] trials have reported positive results in improving cognitive performance, with consistent findings also observed after AE interventions lasting more than 3 months.[30,36] RT has been studied less extensively than aerobic training in older adults, particularly in those at risk for developing ADRDs.

3.1.2 Cognitive Training

Cognitive training delivered using the NEUROPEAK™ protocol of the SYNERGIC trial (e.g., a computer based cognitive process training) may improve cognition, mobility, and postural control in older adults. The NEUROPEAK™ program will be used by participants via a program downloaded onto participant's home computers and/or iPad/Android tablet and will consist of a dual-task cognitive training regimen designed by our group that has demonstrated that this type of training can also improve balance in healthy older adults.[37] The rationale for implementing cognitive training in both the SYNERGIC trial and this SYNERGIC@Home trial stems from a plethora of recent research suggesting that improvements in brain plasticity occur after cognitive training.[38-40]

3.1.3 Combined Physical Exercise and Cognitive Training

In addition to the benefits of each intervention alone—there is growing evidence that combining them may lead to a synergic effect as shown in the preliminary analyses of the SYNERGIC trial.[41-43] A recent systematic review of the literature on randomized control trials with combined training found that combinations of both physical exercise and cognitive training show positive effects on cognition. Factors such as intervention intensity and frequency were found to be important in facilitating positive outcomes post intervention.[44] Mechanistically, improvements in cognitive functioning are likely the result of changes in neurological factors that improve the brain's functional and structural integrity.

Interventions that include both cognitive and physical exercises show marked benefits to the brain's structural integrity and can be instrumental in delaying neurodegeneration.[45] Combined physical exercise and cognitive training interventions have also been shown to confer improvements in gait parameters, such as walking speed in older adults.[46] A recent systematic review conceptualizing the literature on combined exercise and cognitive training interventions showed that combined interventions significantly improve gait speed, cognitive functioning, and balance in individuals with MCI[47].

Based on the literature supporting the efficacy of cognitive and exercise-based interventions with individuals at risk for ADRDs—we plan to implement similar interventions in older adults at risk for ADRDs. The critical difference between the SYNERGIC@Home study and other intervention programs discussed thus far is the home-based, virtual nature of SYNERGIC@Home. Thus, the primary goal for the SYNERGIC@Home feasibility study is to evaluate the feasibility of administering a combined exercise and cognitive training home-based program through remote interfaces for older adults at risk for developing ADRDs.

3.1.4 Rationale for Polygenic Hazard Score Testing

MCI is alarmingly prevalent in older populations with over half of individuals with MCI progressing to dementia within five years.[48] There is a growing body of recent evidence suggesting that a cluster of genetic risk factors are associated with the onset of dementia.[49] Specifically, in genome wide association studies (GWAS), a specific allelic expression in 31 single nucleotide polymorphisms (SNPs) appears to be effective in quantifying individual differences in age-specific risk for dementia; this allelic combination is termed an individual's Polygenic Hazard Score (PHS), or sometimes referred to as an individual's Polygenic Risk Score (PRS).[50] In light of the fact that participants in the SYNERGIC@Home study will predominantly consist of individuals at

risk for dementia (such as individuals with MCI), one of the research goals of the study is to assess the distribution of PRS/PHS in the study sample. This data will be instrumental in delineating research questions pertaining to efficacy of the study interventions as a function of cognitive risk. Any analyses done with PRS/PHS data will be conducted only during the analysis stage of the research project and will only be done by research personnel within the study team. The PRS/PHS is currently in the research stages and is not part of routine clinical care at this time.

3.2 SIGNIFICANCE OF THE SYNERGIC@HOME TRIAL

In addition to the convenience of participating in research from the comfort of one's home, there are critical health considerations that uniquely justify the home-based nature of the SYNERGIC@Home feasibility study. In light of the COVID-19 pandemic of 2020 and the associated risks of exposure for older populations, SYNERGIC@Home allows for safe administration of interventions for older individuals at risk for ADRDs. To ensure the safety of our participants, we are planning to administer all interventions (including exercise and cognitive training) using a home-based protocol. The primary platform that we will use is *Zoom for Healthcare©.* Members of the research team will conduct the video-conferences with participants using Zoom for Healthcare© which protects participants' confidentiality through a secured encryption method. Study participants will be assisted by research team members to set up the easy to use Zoom platform on their personal computers or laptop devices. This home-based approach will allow participants to connect with the research team remotely. This feat will not only address the feasibility goals of SYNERGIC@Home, but it will also give older individuals an opportunity to connect with others. This is particularly important at a time during which physical distancing measures may be contributing significantly to the isolation and loneliness in older populations at this time.

We plan to pioneer a flexible home-based program for at-risk individuals and demonstrate the feasibility of implementing this innovative trial with researchers in New Brunswick. SYNERGIC@Home will obtain valuable insights on the logistics of a home-

based intervention program in individuals at risk for developing dementia. The insights gained from this feasibility study can be applied to inform future larger scale projects with similar goals. SYNERGIC@Home will be among the first to pilot a home-based combined exercise and cognitive training program in a randomized control trial for older adults at risk for developing ADRDs.

4. RESEARCH QUESTIONS AND OBJECTIVES

All feasibility objectives are consistent with current recommendations on conducting feasibility trials.[51] The overarching question is: Is it feasible to implement a 16-week home-based, multi-domain intervention program to improve health and reduce the risk of ADRDs in community-dwelling older adults?

4.1 PRIMARY FEASIBILITY OBJECTIVES

It is well known that the benefits of exercise, whether physical or cognitive, can only be realized if one engages in the practice. Our primary feasibility outcome is to answer the question: Will participants adhere to the study protocol? Is it feasible to implement a 16-week home-based, multi-domain intervention program to improve health and reduce the risk of ADRDs in community-dwelling older adults?

4.1.1 Intervention Adherence

Minimum acceptable adherence of study participants will be defined as attendance to at least 75% of intervention sessions.

4.2 SECONDARY FEASIBILITY OBJECTIVES

Our secondary feasibility objectives are aimed at evaluating a variety of other feasibility outcomes to answer questions such as: How difficult is it to recruit seniors to a home-based intervention, and do they remain in the study for its duration? Will they tolerate the extensive battery of testing at baseline? How satisfied will participants be with the

interventions? What (if any) adverse events are related to the intervention(s)? What is the rate of data loss/missing data?

4.2.1 Recruitment Rate

A successful recruitment rate is defined as the ability to recruit and consent a minimum of 75% of the total recruitment goal of 64 participants during the enrollment period.

4.2.2 Retention Rate

A successful retention rate is defined as a minimum of 75% of the total number of consented participants continuing to intervention completion (at the immediate post intervention follow up session).

4.2.3 Assessment Tolerability

Successful assessment tolerability is defined as no voluntary dropouts occurring either during or between baseline assessment (both clinical and activity assessment batteries) and prior to allocation to an intervention group.

4.2.4 Trial Experience

Trial experience will be defined as a participant's overall experience and satisfaction with the presentation, organization, content, and participation in the SYNERGIC@Home feasibility study.

4.2.5 Adverse Events

Frequency of Adverse Events (AEs) will be documented throughout the trial and analyzed by severity of the AE and suspected relationship to the trial to determine if AEs are greater than chance in the active treatment arms.

4.2.6 Data Loss

Data loss due to technical failures, personnel errors, and participant non-compliance will be assessed. A minimum acceptable rate of missing data will set at <20%.

4.3. PRIMARY ANALYTIC OBJECTIVES

In order to determine if affinity for any one intervention is an important factor in participants' adherence to the study interventions, we designed the Intervention Preference Questionnaire (IPQ, Appendix A) that will be used to answer the question: Is interest level for a given intervention type correlated with subsequent adherence to the intervention?

We will also use the IPQ to examine preference attitudes: Which intervention type (physical exercise or cognitive training) do the majority of participants prefer over the other? What proportion of participants have no particular preference for either intervention? Do participants adhere better if they receive the active treatments they prefer? Do their attitudes change after completing the active interventions versus the control interventions?

4.4. SECONDARY ANALYTIC OBJECTIVES

What is the estimated effect size (ES)? What is the standard deviation of the outcome variable?

4.4.1. Cognitive Improvement

The ES for cognitive improvement will be defined using Cohen's descriptors: 0.2 = small; 0.5 = moderate; 0.8 = large.

4.4.2. Mobility Improvement.

Similarly, the ES for mobility improvement will be defined using Cohen's descriptors: 0.2 = small; 0.5 = moderate; 0.8 = large.

5. METHODS/DESIGN

5.1 STUDY DESIGN

5.1.1 Treatment Arms

The SYNERGIC@Home feasibility trial is a home-based, randomized, phase II, four-arm factorial design (2x2), double-blind control study. The SYNERGIC@Home feasibility trial will be administered virtually through *Zoom for Healthcare*© (an online video conferencing platform). A total of 64 participants at risk for ADRDs, aged 60 to 90 years of age will be enrolled and randomized, block randomization by four, into one of four arms (**Figure 1**), with 16 participants in each arm. Details pertaining to intervention and control conditions for both physical exercise and cognitive training are described in section 8.

Arm 1: **Combined exercise (AE+RT)** + **Cognitive training (Neuropeak^{TM})**.
Arm 2: **Combined exercise (AE+RT)** + Control cognitive training (WS+V).
Arm 3: Control exercise (BAT) + **Cognitive training (Neuropeak^{TM}).**
Arm 4: Control exercise (BAT) + Control cognitive training (WS+V).

Note: Experimental conditions are in bold. Arm 4 includes only the control interventions.

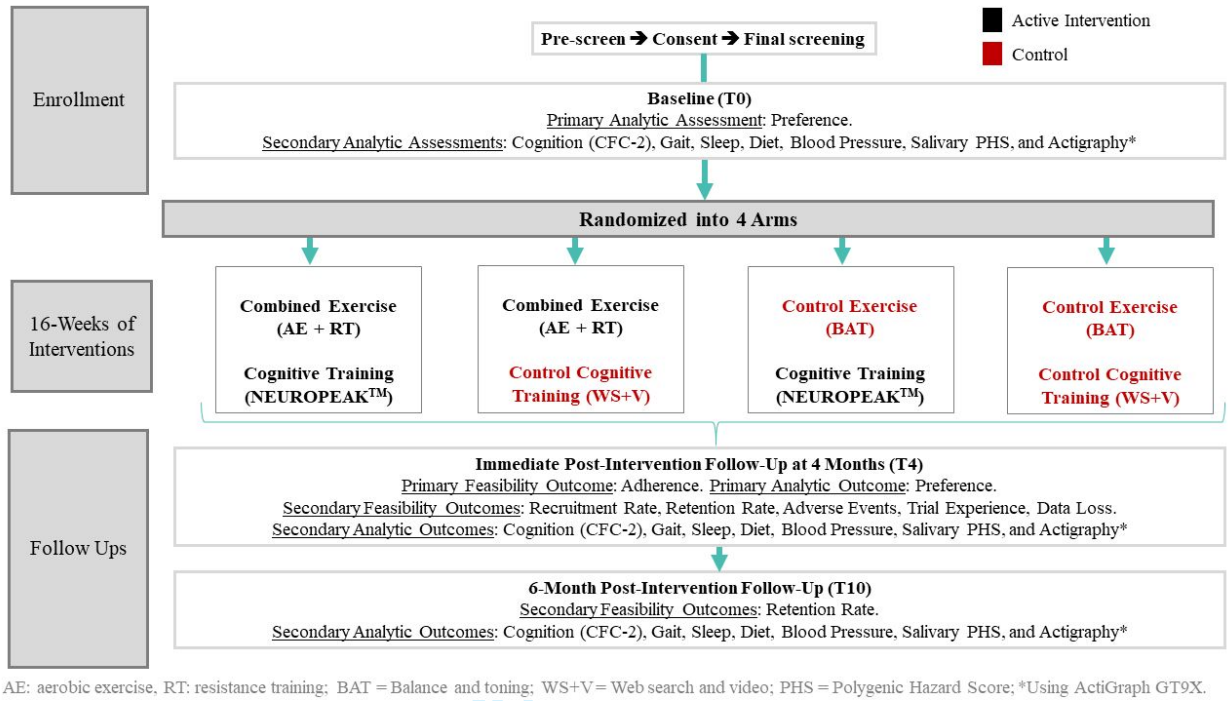


Figure 1. Design of the SYNERGIC@Home trial.

5.1.2 Study Sequence and Duration

Participants will mainly be informed through clinicians as well as recruitment pamphlets in the community or by advertisement on different medias (see 5.2.5 Strategies for Recruitment), potential participants who express an interest in learning more about the clinical trial will be contacted by the research coordinator for the study. A general overview of the study will be discussed and a Prescreening Questionnaire will be completed. This will be used to determine if the participant is eligible to be screened. This will also provide information about why potentially interested individuals are not able to be screened. This will provide useful information to inform future recruitment efforts in future studies testing these interventions.

During this prescreen, potential participants will be asked if they would prefer to participant in this study in either French or English. This study has the capacity to offer this in both official languages in New Brunswick. Those who wish to participate in

English will be directed to the research coordinator site in Horizon Health Network and those who would prefer to participate in French will be directed to the research coordinator the site in Vitalité Health Network.

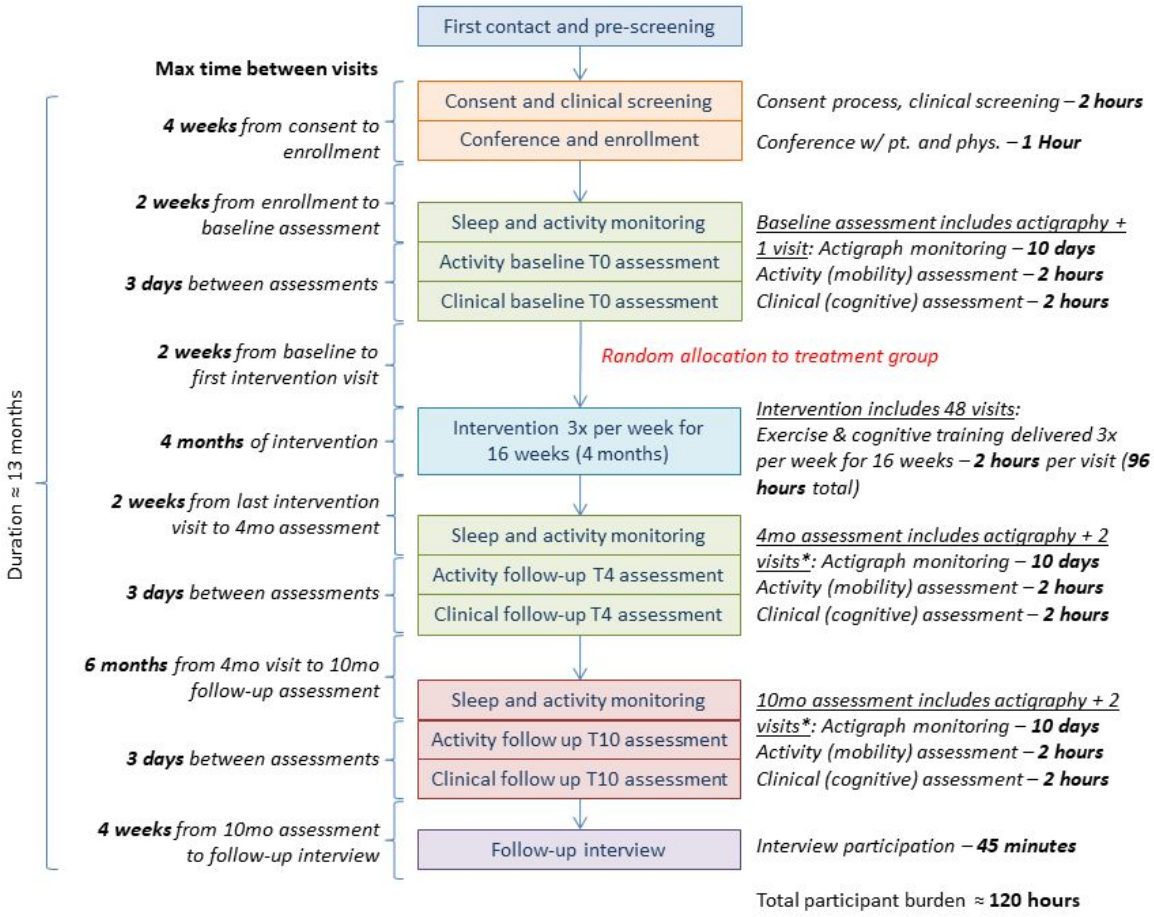
Following prescreening, informed consent will be obtained and assessments will be done during multiple visits: Screening, Baseline (T0), Immediate post intervention follow-up at 4 months (T4), and 6-month post-intervention follow-up (T10).

- Screening Assessment – This assessment will be completed over four separate time:
    - **Consent and clinical screening:** The potential participant meets virtually (via *Zoom for Healthcare*©) with the Clinical Research Coordinator/nurse and completes the consenting process. The study physician will be available to answer questions that require physician involvement during the informed consent process. Consent forms will be sent to participants via email if participant has access to a printer and scanner and via mail otherwise. Consenting participants will provide written consent and send back withregular mail their signed consent form. After the research coordinator received the consent, a copy will be sent back to the participant and the assessments will be done by the Clinical Research Coordinator. This is expected to take 2 hours.
    - **Activity (mobility) screening:** The participant meets virtually (via *Zoom for Healthcare*©) with the Kinesiology Research Assist who will conduct a battery of mobility and lifestyle assessments (see section 6.4.7). This is expected to take 2 hours.
    - **Clinical Case Conference and enrollment:** The participant will meet again virtually (via *Zoom for Healthcare*©) with the Clinical Research Coordinator/Nurse and the Study Physician who will review the results of all of the assessments and finalize the inclusion and exclusion criteria. This is expected to take 1 hour. If the participant is eligible, their baseline assessment visits are scheduled.

- Baseline Assessment (T0) – will be done within 2 weeks of successful enrollment.
- Part of the baseline assessment will consist of actigraphy monitoring for sleep and physical activity levels and two separate assessment visits:
    - **Actigraphy monitoring:** Participants will wear an ActiGraph monitor on their wrist at all times (except when bathing) for 10 consecutive days before their baseline assessment, to measure their sleep patterns and daily activity levels (see section 6.4.7). The instructions and materials needed for this monitoring will be mailed out to the participant and the research coordinator, who will meet with the participant to review the instructions.
    - **Clinical assessment:** The participants meets virtually (via *Zoom for Healthcare*©) with the Clinical Research Coordinator/Nurse who will conduct additional assessments (see Table 2). This is expected to take 2 hours.
- Randomization occurs after the Baseline assessment by allocating the participant to a treatment group from a pre-determined block-randomized sequence (see section 8.3).
- Intervention Phase (T0-T4) – Will start within 2 weeks of completion of the Baseline Assessment. The intervention will continue 3x per week for 16 weeks (see Section 8), for a total of 48 virtual sessions.
- Immediate Post-Intervention Assessment (T4) –Within 2 weeks of completion of the 16 week intervention, participants will wear the ActiGraph for 10 consecutive days. They will also undergo clinical and activity assessment in two separate visits, as described for baseline. (See Table 2) Each assessment visit is expected to take 2 hours.
- Six month Post Intervention Assessment (T10) – Within 2 weeks of the 6 month date after completion of the intervention the participants will wear the ActiGraph again for 10 consecutive. They will also have the clinical and activity

assessments in two separate virtual visits repeated. See Table 2. Each assessment visit is expected to take 2 hours.

Figure 2 shows the sequence of activities and their expected durations.



** Time between clinical and activity sessions will be kept within 3 days with an allowable range of 1-7 days.*

Figure 2. Participant timeline through the trial.

5.1.3 Setting

Participants will be recruited from across the entire province of New Brunswick, Canada. Participants must be residing and have a mailing address in New Brunswick. They will be living in their own homes in the community. Participants can be either Anglophone or Francophone. All study assessments and interventions will be done

virtually (via video conferencing through *Zoom for Healthcare*©), in the language of the participant's choice, by a research team member from the University of New Brunswick (Fredericton), Université de Moncton, Horizon Health Network, and/or Vitalité Health Network.

5.2 STUDY POPULATION

The target recruitment is N = 64 older adults aged 60 to 90 years old at risk of developing ADRDs who meet the following inclusion and exclusion criteria. Medical and clinical information will be collected by self-report by the participant. If clarification is needed regarding this clinical information, contact will be made with the participant's primary care physician/provider with the consent of the participant. Although we will make every effort to recruit equal numbers of Anglophone and Francophone participants, due to provincial distribution it may be expected that only 25-30% of recruits will be Francophone, therefore we will set a minimum recruitment of Francophone participants at 18 and maximum Anglophone recruitment at 46.

5.2.1 Inclusion Criteria

Participants must meet each of the following criteria for enrolment into the study:

- Age 60 to 90 years old.
- Has a Family Physician or a Nurse Practitioner.
- Has internet access (and have regular access to email), and the technology ability (able to send and receive emails).
- Resides in their own home/apartment in the community.
- Has access to a home computer and/or a laptop computer device.
- Self-reported levels of proficiency in English and/or French for speaking and understanding spoken and written language.
- Able to comply with scheduled home-based assessments, interventions, and other trial procedures.
- Able to ambulate at least 10 m independently with or without a walking aid.
- Being at risk of developing dementia:

a) **Mild Cognitive Impairment (MCI) Group.** Diagnosis of Mild Cognitive Impairment, in accordance with the criteria used in the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) study[2] (Table 1).

b) **Subjective Cognitive Impairment (SCI) Group.** Diagnosis of Subjective Cognitive Impairment, in accordance with the COMPASS-ND study[2] definition (Table 1).

c) **Cognitively Intact with Risk Factors Group.** Cognitively Intact based on COMPASS ND study[2] definition (Table 1)) **AND** have a history of ***two or more risk factors*** for dementia, defined as the following (Table 1):

- **Obesity**: Defined as a Body Mass Index (BMI) > 30 kg/m^2 (as derived from the National Institute of Health BMI calculator[52])
- **Hypertension**: Defined as a documented Systolic Blood Pressure > 140 mm Hg, OR a physician's diagnosis of hypertension, OR presence of physician prescribed medical treatment for hypertension, OR other approaches to treatment for hypertension (i.e., diet or exercise).
- **Diabetes**: Defined as a physician's diagnosis of diabetes, OR presence of physician prescribed medical treatment for diabetes, OR other approaches to treatment for diabetes (i.e., diet or exercise).
- **Cardiovascular disease**: Defined as a physician's diagnosis of angina, myocardial infarction, coronary revascularization or other arterial revascularization, stroke, transient ischemic attack and/or peripheral vascular disease.
- **Physical inactivity**: Defined as inactive, whereby active is defined as engaging in a minimum of 20-30 minutes of physical activity causing sweating and breathlessness, at least two times per week.

- **First-degree family history of dementia**: Defined as a physician's diagnosis of dementia in a first-degree relative, including a parent, sibling, or child.
- **Dyslipidemia**: Defined as a documented total cholesterol > 6.5 mmol/L, OR a physician's diagnosis of hypercholesterolemia, OR presence of physician prescribed medical treatment for hypercholesterolemia, OR other approaches to treatment (e.g. diet, exercise).
- **Poor sleep**: Defined as a score of 6 or higher on the PSQI-18 (higher scores indicate poorer sleep).
- **Poor diet**: Defined as a score of 7 or less on the MDA-14.

- Must be medically able to participate in the study's exercise training program, as by the study physician for clearance to participate in combined exercise training program.
- Preserved activities of daily living, operationalized as a score of > 14/23 on the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale[3] and confirmed by clinician's interviews.

Table 1. Canadian Consortium on Neurodegeneration in Aging (CCNA) Criteria for Cognitively Intact with risk factors, and Subjective and Mild Cognitive Impairment from COMPASS-ND[2]

Group	Core Diagnostic Criteria	Operationalized as
Cognitively Intact (CI) with risk factors	Absence of SCI and/or MCI based on below definitions, with two or more known risk factors for dementia.	Not having SCI or MCI, and having at least two (2) of the following risk factors: • Obesity • Hypertension • Diabetes • Cardiovascular disease • Physical inactivity • First-degree family history of dementia • Dyslipidemia • Poor sleep • Poor diet
Subjective Cognitive Impairment	Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and	Answer "yes" to both of the following questions: "Do you feel like your memory or thinking is becoming worse?" and "Does

(SCI)[54]	unrelated to an acute event.	this concern you?"
	Normal age-, sex-, and education-adjusted performance on standardized cognitive tests, which are used to classify mild cognitive impairment (MCI) or prodromal Alzheimer's Disease (AD).	Global Clinical Dementia Rating (CDR) scale = 0, Logical Memory II above Alzheimer's Disease Neuroimaging Initiative (ADNI) education-adjusted cutoffs (≥ 9 for 16+ years of education; ≥ 5 for 8-15 years of education; ≥ 3 for 0-7 years of education); Alzheimer's Disease Assessment Scale-Cognitive(ADAS-Cog) word list recall score >5; Montreal Cognitive Assessment (MoCA) total score ≥25.
Mild Cognitive Impairment (MCI)[27]	Concern regarding a change in cognition.	Report from patient and/or informant of such.
	Impairment in one or more cognitive domains.	One or more of the following: • Logical memory below ADNI cutoffs ((≥ 9 for 16+ years of education; ≥ 5 for 8-15 years of education; ≥ 3 for 0-7 years of education). • ADAS-Cog word list recall <6. • MoCA score 13-24 inclusive. • Global CDR>0.
	Preservation of independence in functional abilities.	Score >14/23 on the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale.
	Not demented.	Global CDR ≤0.5.

5.2.2 Exclusion Criteria

Participants who meet **ANY** of the following criteria will be excluded from the study:

- A diagnosis of dementia
- Participants living in Nursing Homes or Adult Residential Facilities (Special Care Homes) will be excluded.
- Serious underlying disease, which, in the opinion of the study physician excludes engagement in interventions or may interfere with the participant's ability to participate fully in the study.
- Has had surgery within the last two months or has planned surgery in the coming 12 months that, deemed by the study physician, could interfere with the

participant's vision, hearing, mobility or any other ability to participate in the study.

- Has a history of intracranial surgery.
- Regular Benzodiazepine use by a participant that the study physician determines to be significant enough to interfere with the participants ability to participate in the assessments and interventions in the study will be excluded.
- Presence of major depression, schizophrenia, severe anxiety or drug/alcohol abuse or other medical illness that would prohibit them from safely participating in the study or may cause harm to the participant.
- Current Parkinsonism or any neurological disorder with residual motor deficits (e.g. stroke with motor deficit), active musculoskeletal disorders (e.g. severe osteoarthritis of lower limbs) or history of knee/hip replacement affecting gait performance during the baseline assessment.
- Severe visual and/or auditory impairment, which, according to the vision and hearing assessment, precludes the participant from engaging in the trial.
- Intention to enroll in other clinical trials during the same time period.
- Active participation in an organized and planned exercise program involving aerobic exercise and/or resistance training regimen in previous 6 months.

5.2.3 Screen Failures

Screen failures are defined as participants who have completed the Screening Visit but do not meet the inclusion criteria for any of the three populations under study (MCI, SCI, or CI with risk factors).These participants who have failed the screening criteria are ineligible for participation and will be informed that they do not meet the study's inclusion criteria and they will be thanked for their time. They will be encouraged to try to participate in future studies for which they may be eligible and they will have an opportunity to ask questions pertaining to their screening for SYNERGIC@Home.

5.2.4 Study Care Partner

All participants will be asked about whether they wish to have a study care partner such as a spouse, close friend, or relative participate along with them in the trial. Specifically,

the care partner's role will be to participate in assessments such as the CDR (as in Table 1) as it requires a study care partner. Care partners will be specifically told that their only role is to help us complete the CDR. If the participant does not have a care partner on the day of their assessment (someone to attend the virtual visit with them), the informant portion of the assessment (the CDR) can be completed by phone.. This will be arranged and completed by the site research coordinator.

A participant will not be excluded from the study if they do not have access to or wish to have a study care partner. However, if the individual during screening is deemed to have MCI or SCI, or the study physician determines that their participation without a study care partner would be a risk—then the participant will be asked to name a study care partner for their participation in the trial.

We believe that in certain instances, such as in the case of couples, some study care partners may also be want to be a participant, however because participants are meant to be blinded as to which experimental condition they are in—we will ask that care partners remain as care partners and do not occupy the role of participant in the study.

5.2.5 Strategies for Recruitment

Community dwelling older adults from both Anglophone and Francophone communities throughout New Brunswick will be recruited using recruitment methods and tools included in Appendix B. These recruitment materials will be available in both official languages. Interested participants will be directed to contact study personnel through the NB-PALM website. A dedicated email address (synergic@unb.ca) will be established. The following recruitment tools will be used to inform potential study participants living throughout New Brunswick about the study:

- Flyer (Appendix B) for posting on various community organization websites, and healthcare provider websites, social media, and in physical offices.
- Email (Appendix B) for distribution to potential study participants referred by others.

- Paid newspaper advertisements (Appendix B) in selected local newspapers.

These tools will be applied in various ways to reach potential study participants. The offices of primary care physicians/providers and specialists will be provided with a study flyer for posting. They will be invited to refer potential participants from their practices. An information handout (See Appendix B) describing the study will be used to familiarize providers with the study. Interested participants can be directed to contact study personnel through the NB-PALM website and visit the dedicated SYNERGIC@Home study page.

Participants currently enrolled in the COMPASS ND cohort study in Saint John, NB will also be contacted to ask about their interest in participating. A follow-up email (Appendix B) will be sent to these potential participants.

Existing community resources such as the Seniors' Centres, Community Health Centres, and Community Mental Health Centres as well as recreation facilities and libraries will be provided with study information to post on social media (If available) and news/what's happening section of their websites (if available) and / or distribute to their membership via email or hard copy or digital newsletters. The Community Developers working in the Vitalité and Horizon Health Networks have many contacts and connections with formal and informal community groups and networks. Study flyers and a generic email will be provided for distribution to these organizations with whom they are connected. Study information will be provided to two particular provincial programs: Senior Goodwill Ambassador Program and Go Ahead Seniors/Aînés en Marche, both of which provide physical activity and lifestyle modification programs to community dwelling older adults. Similar organizations will also be contacted and invited to distribute information about the study.

Study flyers will be sent to the leadership of provincial English and Francophone seniors' organizations including the Association francophone des aînées et des aînés du Nouveau-Brunswick and NB Senior Citizen's Federation as well as community

partners such as the NB Alzheimer's Society for posting on their websites and social media platforms. Targeted provincial organizations like the NB Society of Retired Teachers and Société des Enseignantes et des Enseignants Retraités Francophones du Nouveau-Brunswick (SERFNB) also have websites as well as local branches to whom the study flyer and generic email will be provided for distribution.

Paid newspaper advertisements will be purchased in selected urban and community-based rural newspapers.

When a member of the research team receives an expression of interest email from a potential study participant through the NB-PALM website or other referral sources as listed above, a generic email and/or study flyer and consent package will be sent by email. Once a study participant is ready to give consent, a first contact discussion guide (Appendix B) will be followed by research personnel to ensure that a consistent approach is used to obtain participants' consent.

5.2.6 Strategies for Retention

Retention of participants will be pursued through various methods. News about the study will be posted on the NB-PALM website and participants will be encouraged to visit the page dedicated to the SYNERGIC@Home. Research personnel will be provided with key messages to use in their interactions with study participants to keep them informed.

Participants that do not comply with the intervention schedule may be withdrawn from the study at the discretion of the research team. Research Assistants will make all efforts to allow participants to have flexibility with their intervention schedules and participants will be allowed to make up missed intervention dates within the week that they occur. Since this is a feasibility study, intervention schedule deviations will be closely tracked but no rigid rule of number of missed interventions before withdrawal occurs will be employed. Each case will be individually evaluated and the benefit of the doubt given in an attempt to observe the compliance behaviour patterns of participants across the entire 16 week intervention duration.

5.3 ASSESSMENTS TOOLS

Participants in all four arms will have a series of validated assessments performed at the Screening, Baseline (T0), Immediate post intervention follow-up at 4 months (T4), and 6-month post-intervention follow-up (T10), as shown in ** Time between clinical and activity sessions will be kept within 3 days with an allowable range of 1-7 days.*

Figure 2. All elements of each assessment will be collected via video conferencing (*Zoom for Healthcare*©). All assessments are itemized in Table 2 (below).

All participants will also be given an ActiGraph (ActiGraph GT9X©) device, a measuring tape, some exercise materials (such as resistance bands or a stretching mat). Please see the complete list in Appendix B). These items will be delivered and picked up by a secure mailing and parcel service or secure courier. The ActiGraph device will be worn on the participant's wrist, hip, or ankle for 10 consecutive days, at three separate time points (baseline, immediate post intervention follow up and 6 month post intervention follow up). These devices will be used to measure nightly sleep patterns and daily activity levels.

Table 2. Assessments across Study Visits for SYNERGIC@Home Trial

Assessment	Clinical Screening	Physician Conference	Clinical T0	Activity T0	Clinical T4	Activity T4	Clinical T10	Activity T10
Consent								
Participant Informed Consent	•							
Study Partner Informed Consent	•							
General Health and Medical History								
Demographics	•							
Medical Vitals	•		•		•		•	

Assessment	Clinical Screening	Physician Conference	Clinical T0	Activity T0	Clinical T4	Activity T4	Clinical T10	Activity T10
Medical History[1]	•		•		•		•	
Inclusion and Exclusion Criteria		•						
Diagnostic Summary / Diagnostic Validation		•			•		•	
Cognitive Testing								
Telephone Cognitive Screening TCogS	•				•		•	
Full MoCA via Audio-Visual Conference	•				•		•	
Lawton-Brody IADL	•				•		•	
Cognitive Functional Composite (CFC-2)								
ADAS-Cog 3 Immediate Word Recall	•				•		•	
ADAS-Cog 3 Delayed Word Recall	•				•		•	
ADAS-Cog 3 Orientation	•				•		•	
Clinical Dementia Rating Scale (CDR) Cognitive	•				•		•	
Functional Activities Questionnaire	•				•		•	
Additional Cognitive Outcomes								
Oral Trail Making Test (Part A & B)			•		•		•	
Boston Naming Test			•		•		•	
Logical Memory I & II	•				•		•	
ADAS-Cog Word Recognition			•		•		•	
DKEFS Phonemic Fluency Test			•		•		•	
DKEFS Semantic Fluency Test			•		•		•	
Digit Span Backward Test			•		•		•	

Assessment	Clinical Screening	Physician Conference	Clinical T0	Activity T0	Clinical T4	Activity T4	Clinical T10	Activity T10
Digit Symbol Modalities Test-Oral Version			•		•		•	
Diet Assessments								
Mediterranean Diet Assessment (MDA-14)	•				•		•	
Eating Pattern Self-Assessment (EPSA)			•		•		•	
Vitamin D Intake Questionnaire			•		•		•	
Sleep Assessments								
Pittsburgh Sleep Quality Index (PSQI-18)	•				•		•	
Consensus Sleep Diary (CSD)	•				•		•	
Sleep and Activity Monitoring				•		•		•
Functional and Activity Level								
Physical Activity Scale for the Elderly (PASE)				•		•		•
Life Space Questionnaire (LSQ)				•		•		•
Clinical Frailty Scale (CFS)	•				•		•	
Mental Health and Well Being								
Short Form Quality of Life Questionnaire SF36	•				•		•	
Generalized Anxiety Disorder (GAD-7)	•				•		•	
Geriatric Depression Scale (GAD-30)	•				•		•	
COVID-19 Questionnaires	•				•		•	
Health Literacy								
Short Test of Func.Health Literacy in Adults STOFHLA			•					
Technology Ability Use								

Assessment	Clinical Screening	Physician Conference	Clinical T0	Activity T0	Clinical T4	Activity T4	Clinical T10	Activity T10
FACETS				•		•		•
Gait and mobility Assessments[2]								
Usual Gait				•		•		•
Seated Dual Task				•		•		•
Dual Task Gait Assessment				•		•		•
One Minute Sit to Stand Test (STST)				•		•		•
Get Active Questionnaire	•							
Falls Calendar			•		•		•	
Intervention Preference								
Preference Questionnaire				•		•		•
Biological Markers[3]								
Polygenic Hazard Score (PHS)	*Any point throughout trial*							
Study Exit								
Exit Questionnaire	*At time of finishing/exiting trial*							

[1]Full history collected at Clinical Screening and updated thereafter.
[2]Gait velocity assessed using Actigraphy (ActiGraph GT9X).
[3]Self-collected via an optional saliva sample.

6. OUTCOMES

6.1 PRIMARY FEASIBILITY OUTCOMES

6.1.1 Intervention Adherence

Measured as the mean percent of all Intervention sessions attended of the 48 planned sessions per participant.

6.2 SECONDARY FEASIBILITY OUTCOMES

6.2.1 Recruitment Enrollment Rate

Measured as the total percent of enrolled participants relative to number of people screened for eligibility.

6.2.2 Enrollment Retention Rate

Measured as the total percent of enrolled participants who continue throughout the trial and participate in outcomes assessments as follows (see Figure 3):

- Enrollment retention: of those enrolled participants, the % who complete immediate post intervention follow-up (T4) assessment, and;
- Follow-up retention: of those who complete the immediate post intervention follow-up (T4) assessment, the % of participants who complete the 6-month post-intervention follow-up (T10) assessment.

6.2.3 Assessment Tolerability

Measured as the number of voluntary dropouts occurring either during or between baseline assessment (both clinical and activity assessment batteries) and prior to allocation to an intervention group.

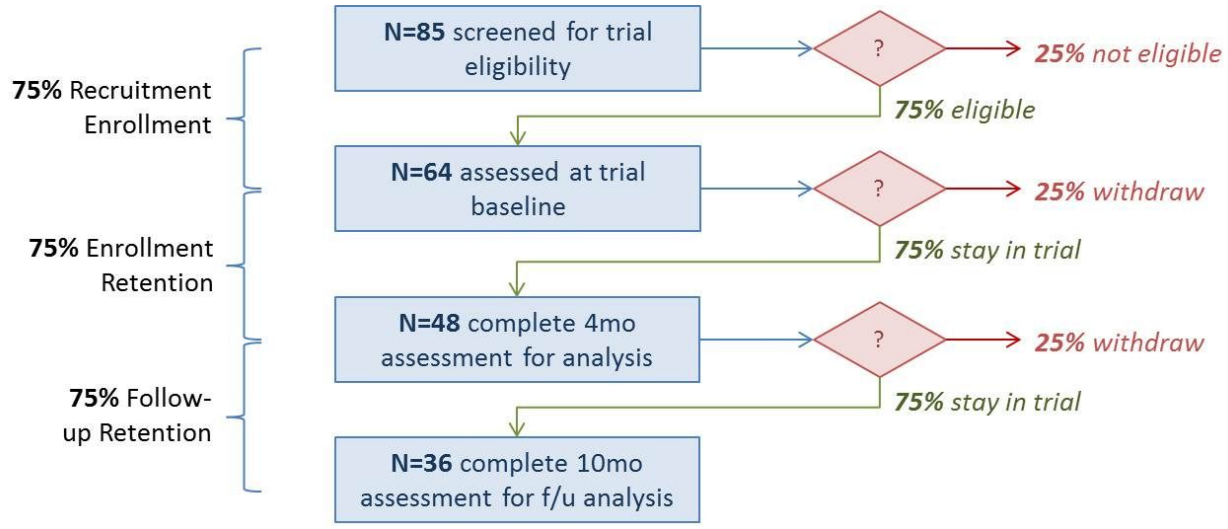


Figure 3. Attrition flowchart for SYNERGIC@Home trial.

6.2.4 Trial Experience

A mixed a methods approach will be used to explore participant experience after the trial. Trial experience is defined as participants' qualitative responses to semi-structured open-ended questions aimed at providing insights on their overall trial experience within the context of the Kirkland evaluation framework, .

6.2.5 Adverse Events

Frequency cross-tabulation of AE severity versus AE relation to trial.

6.2.6 Data Loss

Defined as data lost due to technical failures, personnel errors or participant non-compliance. Technical failures resulting in data loss include problems with electronic equipment or internet communications, for example. Personnel errors would include issuing improperly configured equipment, scheduling errors, and protocol deviations (omitting assessments, for example) that result in data loss. Participant non-compliance would encompass data loss due to participants not following instructions or omitting responses on surveys, for example.

6.3 PRIMARY ANALYTIC OUTCOMES

6.3.1 Intervention Preference

The primary analytic goal of SYNERGIC@Home is to assess the relationship between participants' adherence to the interventions and their affinity for each intervention going into the trial. All participants will be given the Intervention Preference Questionnaire (IPQ, Appendix A) prior to implementation of the intervention at baseline (T0) and after the 4mo intervention (T4).

The IPQ asks participants various questions about their affinity for the offered interventions by quantifying interest level and preferences for the interventions. When administered at T0 (prior to randomization) we will explain to participants that their responses on the questionnaire will not in any way influence the intervention group they will be randomly assigned to.

The IPQ has five questions. Question 1 asks participants to rate their interest level in each intervention type (exercise training and cognitive training independently) on a 0-10 visual analog scale. Question 2 asks participants to rate their preference between the two interventions on a 5-point scale:

-2=Strong preference for Exercise training;
-1=Slight preference for Exercise training;
0=No preference;
1=Slight preference for Cognitive training;
2=Strong preference for Cognitive training.

Questions 3 to 5 are open ended questions that will provide context to participants' responses from questions 1 and 2.

Validation: The intervention preference questionnaire has been created specifically for this feasibility trial, thus it has not been previously validated.

6.4 SECONDARY ANALYTIC OUTCOMES

6.4.1 Demographic Information and Medical History

Demographic information, chronic diseases, vascular risk factors (VRFs), medical history, medications, fall history using self-reports of falls on a fall calendar will be collected at the screening visit. In addition, medical vitals will be assessed including weight, height, blood pressure and heart rate (using a simple blood pressure cuff that will be provided to the participant).

Validation: This information will be collected by self-report and will be done via video conference. While medical history taking have not been systematically evaluated in this setting it is commonly used in remote telemedicine and is considered an acceptable practice and a reasonable alternative to face to face history taking. We are confident that results will be similar to those assessed in person. We are confident that participants will be able to adequately measure their vitals and report the findings to the study personnel.

6.4.2 Cognitive Testing

Cognitive outcomes will be measured using the Cognitive Functional Composite 2 (CFC-2), the Telephone Cognitive Screening (TCogS), the Montreal Cognitive Assessment (MoCA), and select items from the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog Plus).

TCogS and MoCA.

- **The Telephone Cognitive Screening TCogS** is a widely used tool that measures cognitive function in older individuals. The telephone version of the CogS has been standardized and will be administered via video conferencing. It consists of a 26-point assessment that measures orientation, registration, attention and calculation, recall, and language with lower scores indicating cognitive impairment[55,56].

Validation: The TCogS will be administered using the standardized and validated telephone version[56-58] via video conferencing.

- **The Full MoCA via Audio-Visual Conference** consists of a 30-point test assessing the following items: short term memory recall, visuospatial abilities, executive functioning, phonemic fluency, verbal abstraction, attention, concentration, working memory, language, and orientation[59].
  Validation: The remote version of the MoCA will be administered using the validated online full MoCA (version 8.1) via audio-visual conference[58,60].

Clinical Dementia Rating Scale (CDR). The CDR is a validated 5-point composite scale used in longitudinal Alzheimer's Disease (AD) research to characterize cognitive and global function performance applicable to AD and related dementias.[61] Information is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g. family member). The three cognitive domains include memory, orientation, and judgment/problem solving and the three functional domains include community affairs, home and hobbies and personal care. The five possible scores for each domain [0, 0.5, 1, 2, and 3] represent a range of impairment (e.g. score of 0 represents no impairment and a score of 3 represents severe impairment).

Validation: The CDR is a questionnaire which can be administered via any interface (face-to-face or video conferencing). We will administer it via video conferencing. Clinical experience dictates that this method of delivery of the CDR will be sufficient.

Lawton-Brody Instrumental Activities of Daily Living (IADL) scale. The IADL will be administered as part of the functional assessments of this trial and serve as an inclusion criteria of preservation of function (score > 14/23). It measures participant's ability to engage in instrumental activities of daily living via questionnaire assessing activities such as preparing meals and managing personal finances[3]. Responses range from 0 (normal ability) to 3 (dependent for functioning) with total scores ranging from 0 to 23.

Validation: This assessment of functional independence is collected via questionnaire, which can be administered via any interface (face-to-face or video conferencing). We will administer it via video conferencing

Cognitive Functional Composite (CFC-2). The CFC consists of the following tests[5,6]. The first three tests originate from the ADAS-Cog 13, which has been used a primary outcome measure in numerous trials with individuals at risk for developing ADRDs[7,8].

a) **ADAS-Cog Immediate Word Recall**. Participants are presented with 10 high imagery words and are given three trials to learn and recall them. The average of the 3 trials is computed for the final score.
Validation: This is a subtest of the ADAS-cog, which has been validated for remote, virtual use[9].
b) **ADAS-Cog Delayed Word Recall**. Participants are asked to recall the 10 high imagery words presented during the immediate word recall task after a delay of approximately 5 to 10 minutes.
Validation: This is a subtest of the ADAS-cog, which has been validated for remote, virtual use[9].
c) **ADAS-Cog Orientation**. Participants are asked 8 questions pertaining to their identity, the place, and the time.
Validation: This is a subtest of the ADAS-cog, which has been validated for remote, virtual use[9].
d) **Clinical Dementia Rating Sum of Boxes (CDR-SB) Cognitive portion.** The CDR is being administered in full for this trial. The sum of boxes score simply reflects the total score from all domains assessed. The CFC-2 includes the CDR-SB for all cognitive portions, which consists of a sum of scores obtained from the following CDR domains: memory, orientation, and judgement & problem solving.
Validation: The CDR is a questionnaire which can be administered via any interface (face-to-face or video conferencing). We will administer it via video conferencing. Clinical experience dictates that this method of delivery will be sufficient.

e) **Functional Activities Questionnaire.** This questionnaire will be administered as part of the functional assessments of this trial. It measures participant's ability to engage in instrumental activities of daily living via questionnaire assessing activities such as preparing meals and managing personal finances[3]. Responses range from 0 (normal ability) to 3 (dependent for functioning) with total scores ranging from 0 to 30. For the CFC-2 total score, this score will be added to obtain a total CFC-2 composite score.
Validation: This assessment of functional independence is collected via questionnaire, which can be administered via any interface (face-to-face or video conferencing). We will administer it via video conferencing.

Additional Cognitive Outcomes. We will also administer additional cognitive outcomes including the following:

- **The Oral Trail Making Test (TMT) A & B** is a two-part test that assesses attention speed, and mental flexibility and has been widely used in clinical settings for assessing deficits in attention and executive functioning.[62] The oral version of the Trail Making Test provides an assessment of sequential set-shifting without the motor and visual demands of the written Trail Making Test. [10] For Part A, participants are asked to count from 1 to 25 as quickly as possible. For Part B, participants are asked to switch between number and letter in sequential order (e.g. 1-A, 2-B, 3-C) until the number 13 is reached. Scoring is the total time to complete each part.
Validation: The oral trail making tests A & B are validated assessments that can be conducted remotely without the need for the traditional paper and pencil face-to-face modality.[10] We will administer them both using video conferencing.
- **The Boston Naming Test (BNT)** assesses visual confrontational naming and asks participants to name simple line drawings of objects.[11]
Validation: To our knowledge, the BNT has not yet been validated for remote, virtual, or phone use, thus we show participants each item on the screen during

the video conference. It is noteworthy that this mode of administration (in comparison to face-to-face-assessment) has not been methodically validated.

- **Logical Memory I & II** (Story A) from the Wechsler memory scale assesses memory and free recall[63]. This test will be completed via video conferencing in which the participant will be instructed to listen to a story and repeat it back after it has been read to the best of his/her. The participant will then be asked to recall the story approximately 30 minutes later.
  Validation: Because this test is an auditory test to begin with (i.e., it does not require visual stimuli such as paper and pencil questionnaires), it can be administered using any modality (face-to-face or via video conference). We will conduct it via video conferencing.
- **ADAS-Cog Word Recognition**. Participants are presented with a list of 12 words and are then asked to identify the words among a list of distractor words.
  Validation: This is a subtest of the ADAS-cog, which has been validated for remote, virtual use[9].
- **DKEFS Phonemic (Letter) Fluency**. The Delis-Kaplan Executive Function System (DKEFS) phonemic fluency test measures phonemic verbal fluency, whereby participants are given 60 seconds to produce as many words that begin with the letter C, followed by a second 60 second trial with the letter "F", and a third 60 second trial with the letter "L"[13].
  Validation: This test has been validated for telephone use, as results are statistically similar to those done face-to-face[64]. We will administer it via video conferencing.
- **DKEFS Semantic Fluency Test**. The Delis-Kaplan Executive Function System (DKEFS) semantic fluency test measures speed and flexibility of verbal thought, whereby participants are asked to name as many items as possible in a specified category (vegetables and animals). Unique responses during the first minute of each category are counted[13].
  Validation: This test has been validated for telephone use[14]. We will administer it via video conferencing.

- **Digit Span Backward Test**. The digit span test is an auditory attention task, in which participants are asked to recall a series of numbers forward and backward. *Validation:* This test has been validated for telephone use[14].
- **Digit Symbol Modalities Test-Oral Version**. This is a timed task that gives participants 120 seconds to orally match geometric figures with specific numbers according to a defined key (specifying which symbols are assigned to which numbers) that is provided at the top of the stimulus page[15,65].
  Validation: The oral version of this test has been validated[15] .We will administer it via video conferencing.

6.4.3 Sleep Patterns

Sleep habits will be assessed using the 18-item Pittsburgh Sleep Quality Index (PSQI-18)[66] and the Work and Sleep Diary (WSD)[16].

Validation: Both sleep assessments are done via validated questionnaires which can be administered via any interface (face-to-face or video conferencing). We will administer them via video conferencing.

6.4.4 Diet Patterns

Diet habits, food consumption, and nutrition intake will be assessed using the 14-item Mediterranean Diet Assessment (MDA-14)[67], the Eating Pattern Self-Assessment (developed by the CCNA team), and a short questionnaire for Vitamin D intake.[68]

Validation: All diet assessments are done via questionnaires which can be administered via any interface (face-to-face or video conferencing). We will administer them via video conferencing.

6.4.5 Functional Independence and Activity Level

Additional descriptors of functional health and independence will also be tested including: the activities of daily living—using the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale[3], the physical activity scale for the elderly (PASE)[69], and the Life Space Questionnaire (LSQ)[70].

Validation: All of the above assessments of functional independence and activity level are collected via questionnaires which can be administered via any interface (face-to-face or video conferencing). We will administer them via video conferencing.

We will also obtain a measure of clinical frailty using the Clinical Frailty Scale.

- **Clinical Frailty Scale (CFS).** This assessment will be performed by the Clinical Research Coordinator/nurse using the 9 point CFS instrument[71]. This will allow for a determination of the clinical frailty of the participants.
  Validation: The use of the CFS by remote video conferencing has not been evaluated but it is thought that this will be a reasonable way to gather information needed to determine the CFS score. The information needed is obtained by history and self-report from the participant.

6.4.6 Psychiatric Health and Well-Being

Psychiatric health and well-being will be assessed using the Short Form quality of life questionnaire (SF-36)[72], the Generalized Anxiety Disorder 7 (GAD-7)[73], Geriatric Depression Scale (GDS-30)[74], and the COVID-19 Questionnaires—that aim to delineate the impacts of the COVID-19 pandemic of 2020[75]. An additional New Brunswick (NB) COVID 19 questionnaire will also be administered. This tool has been adapted from a telephone survey conducted by Ability NB used to evaluate the effect of COVID 19 on participants living in the community who have physical disability.

Validation: The psychiatric health and well-being assessments (SF-36, GAD-7, and GDS-30), are well-established questionnaires, which can be administered via any interface (face-to-face or video conferencing); we will administer them via video conferencing. The COVID-19 questionnaires have been specifically developed during the pandemic of 2020. They have not yet been validated. We will administer them via video conferencing.

6.4.7 Health Literacy

Health Literacy will be assessed using the abbreviated version of the Test of Functional Health Literacy in Adults (TOFHLA)[108].The short version, STOFHLA, consists of 2 prose passages and 4 numeracy items.

Validation: A preliminary study demonstrated that the results of the S-TOFHLA administrated through a computer were equivalent to those when administered on paper.[109] We will administer the S-TOFHLA in a digital format, over video conferencing.

6.4.8 Technology Ability and Use

To assess the extent to which participants are comfortable with and familiar with basic technology, we will administer the Functional Assessment of Currently Employed Technology Scale (FACETS)[76]. The FACETS is a 10-item questionnaire with possible responses falling on a Likert-type scale, and higher scores indicating more frequent use of technology domains[77,78]. While the FACETS will not be used as part of the eligibility criteria, we feel that it will be a worthwhile endeavor to delineate the potential change in technology use over the course of the home-based remote trial.

Validation: The FACETS is typically administered via questionnaires which can be administered via any interface (face-to-face or video conferencing). We will administer it via video conferencing.

6.4.9 Gait and Mobility Assessments

Gait performance will be recorded using actigraphy, which can be used to determine spatiotemporal gait parameters and can be simply placed on the participant's hip. Specifically, gait parameters will be measured using the ActiGraph GT9X (the same device they use for sleep and activity monitoring), during which participants engage in a series of gait tasks via video conferencing with a study Kinesiology Research Assistant. If video conferencing poses any issues on participant's the ability to position the screen to allow the researcher to visualize the trial—then phone communication will commence instead. In all walks, participants will start 1 meter before the beginning of the 6-meter allocated space and continue to travel 1 meter past the end of the space. If a 6-meter

space is not available, then participants will be asked to use a 3 meter corridor within their home and for analyses, we will extrapolate based on this subset data. The procedure of allowing extra space prior to and after the walking distance is in place to ensure steady state walking and to minimize any effects of acceleration and de-acceleration during the course of the walk[79]. The reason for a 3 meter minimum distance is because this distance has been shown to sufficiently measure gait speed in older adults[80]. To avoid tripping or falls, participants will be instructed to walk on a smooth surface with no barriers.

Validation: Reliability has been previously established for this protocol in people at risk for developing ADRDs and those with MCI[81] and an instructive video can be found at the "www.gaitandbrain.com/resources" as the Guidelines for Gait Assessments in CCNA". However, the virtual administration of this procedure has not yet been validated, thus the SYNERGIC@Home study will be the first to test its feasibility and its use at home.

The dual-task conditions selected are based on previous research which demonstrated that counting backwards requires both working memory and attention[82] and naming animals is related to verbal fluency, which relies on semantic memory[83]. The evaluator will record any counting errors during walking so that it can be compared with the same mental tasks while seated. The seated assessments will be timed at 10 seconds and will be performed in the beginning of all cognitive assessments (at least one hour prior to the dual task gait condition) to prevent practice effects in dual-task gait performance. Seated gait assessments will be assessed via video conferencing, whereby participants are asked to complete the cognitive portion of the dual task gait test while seated. Gait assessments will be then follow and will also be conducted using video conferencing, whereby participants are asked to walk towards the camera while engaging in the cognitive tasks listed above. For details pertaining to the dual task protocol, please see our detailed manual of procedures.

- **Seated Dual Task.** Participants will be first asked to complete the cognitive tasks involved in the dual-task conditions, while seated. Specifically, participants will be asked to name as many animals as they are able to, count backwards by 1's, and count backwards by 7's while seated. This will be used as a comparison to determine the extent to which the dual-task reduces performance (their dual-task cost).
- **Single-Task Gait Assessment**. Gait velocity will be assessed as the time taken to walk a specified distance (minimum 3 meters) using actigraphy (ActiGraph® GT9X Systems, Inc.). This method has been used in previous studies with older adults to measure gait parameters[84]. Participants will be instructed to measure a space (minimum 5 meters) in their home and to connect with the research team via video conferencing during the gait assessments. Their gait velocity will be measured 3 times. Gait variability of spatial and temporal gait variables (stride time, stride length, double support time and step width) will be measured and the coefficient of variation calculated (CV = (standard deviation / mean) x 100). The CV is a standardized measure of variability allowing comparison of gait variables measured in different units, having different means and range of values.
- **Dual-Task Gait Assessment**. Following single-task gait, participants will perform three walks, once each under the following dual-task conditions: walking while naming animals, counting backwards from 100 by 1's, and counting backwards from 100 by 7's. Gait walks will occur within participant's homes, ideally in a large corridor or living space—but even in small spaces of at least 3 meters are suitable. Dual-tasking assessments will permit calculation of dual-task cost for all gait variables of interest.[85,86].

Additional measures of gait and mobility that we will assess include falls (via a falls calendar) and mobility (via the one-minute sit-to-stand test). Both are described in detail below.

- **Falls**. A fall is defined as 'unintentionally coming to rest on the ground, floor, or other lower level and not due to a seizure, syncope, or an acute stroke'[87]. Events

caused by overwhelming environmental hazards (e.g., being struck by a moving object) are not considered a fall. Recurrent falls are defined as 'two or more events in a 12-month period'. Falls will be recorded throughout the trial, in which participants will be provided with a falls calendars, on which they will record any falls that have occurred, and the research team will collect them monthly. Study staff will make a final decision of whether a fall event occurred based on the provided information about the fall, and may include follow-up discussion with participant and study partner if applicable. Falls will only be monitored during the active 4mo intervention period.

Validation: the falls calendar is intended for participants to use on their own, thus its administration does not differ as a function of face-to-face or remote assessments.

- **Mobility**. To further evaluate mobility, participants will be performing the one-minute sit to stand test (STST) while being assessed via video conferencing by a research team member[88].

  Validation: While the one-minute STST has been validated for use in face-to-face settings[89], there are no validations to our knowledge of its use in remote settings.

6.4.10 Biological Markers: Polygenic Hazard Score (PHS)

PHS will be collected via saliva samples that participants will self-collect at any point in time throughout the trial. That is, participants will be mailed an unopened saliva sample collection kit from DNA Genotek© (a Canadian bio sample collection company). Participants will be monitored and assisted during the sample collection process by a research team member. There are specific instructions that must be adhered during saliva collection (such as the requirement that the sample is collected in the morning prior to consuming any food or brushing one's teeth). These instructions will be shared with participants and they will be coached via video conferencing on how to collect, store, and ship their sample. Participants will be notified that providing a saliva sample is optional and they may refuse to do so and still continue their participation throughout

the trial. Once collected, participants will be instructed to mail the unidentified sample in a mailing kit with a UNB return address to the lab in which analyses will take place. Samples will be sent to the Clinical Genomics Centre in the Mount Sinai Hospital, 600 University Ave, Toronto, ON M5G 1X5, Canada and will be processed under the guidance of Dr. Kathy Siminovitch.

The saliva sample will measure the following:

- **Biomarkers of ADRDs**: Polygenic Hazard Score (PHS). PHS is derived from a panel of 31single nucleotide polymorphisms (SNPs) and has been shown to robustly predict the 10 year odds ratio of ADRDs[50].

The genetic content known as DNA, or deoxyribonucleic acid, will be analyzed in order to learn about genetic information that may increase a person's risk for developing dementia. This test is part of the overall outcome measure and is not a diagnostic test. Study participants will not receive results of this test. This test is not currently a standard of normal clinical care and is still under research to determine its utility in clinical practice.

7. STUDY INTERVENTIONS

7.1 INTERVENTION DESCRIPTION

All participants will participate in home-based intervention sessions of 90 minutes per session three times per week for 16 weeks (48 sessions), while in communication with the research team via *Zoom for Healthcare*©. This period of time for combined interventions of exercise and cognitive training has been conducted in previous studies in a clinical environment with significant and promising results[90,91], but has yet to be tested with a home-based delivery approach. Each session will last approximately 90 minutes and will consist of 20-25 minutes cognitive training (NEUROPEAK©) or the cognitive training control followed by approximately 60 minutes of combined exercise intervention (AE and RT) or BAT control exercise.

Cognitive interventions: Active (NEUROPEAK™) or Control (Website searching/video watching (WS+V)) will be set up remotely by the research team for the participant, allowing the participant to complete the cognitive training on her/his own. There will be a research assistant available online to assist with technical questions during this testing.

Exercise interventions: Active (Aerobic Exercise + Resistance Training (AE+RT)) or Control (Balance and Toning (BAT)) will be conducted under the direct supervision and coaching of a certified exercise physiologist with certification from the Canadian Society for Exercise Physiology (CSEP; or equivalent certification). These certified trainers will administer the exercise interventions in a one trainer to one participant ratio. All arms will have an equal volume and frequency of contact over the entire duration of the study. To avoid potential imbalances in exposure time, control conditions for exercise and cognitive training will have the same duration as the active interventions.

7.2 INTERVENTIONS

7.2.1 Active Exercise Intervention: Aerobic Exercise + Resistance Training (AE+RT)

The combined aerobic exercise and resistance training intervention (AE+RT) will be home-based and held three times per week between Monday and Saturday, ensuring that it is not on three consecutive days. Whenever possible, the research coordinator will ensure that the days of the week in which interventions occur are consistent within participants (i.e., a given participant may have a training schedule of Mondays, Wednesdays, and Fridays every week, or alternatively Tuesdays, Thursdays and Saturdays). Staff trained and certified in exercise training will supervise all sessions on a one-to-one trainer to participant ratio remotely. Trainers will connect virtually using video conferencing with participants and will coach them throughout the entire session for all sessions. Difficulty of aerobic and resistance exercise will be tailored to their individual functioning level, with constant monitoring by the trainers.

The exercise program described here has been developed by a trained and certified Kinesiologist. As such, it adheres to all safety guidelines and precautions necessary in developing such programs. 3 (below) presents a general overview of the active exercise intervention (AE+RT) regimen structure with the approximate time taken to complete each portion.

Table 3. General overview of active intervention exercise regimen structure.

Section	Type of Exercise	Duration (min)
Warm Up	Marching in one place with arm swings for 1 minute	1
	Dynamic Hamstring Stretching: 15 per side	1
	Shoulder Circles: 15 per direction	1
	15 Arm Reaches	0.5
	Torso Twists: 15 per direction	1
	Ankle Circles: 15 per direction per side	2
	Side Stepping for 1 minute	1
	15 Quarter Squats	1
	Total Warm Up Duration	8
Break		1
7 Strength Training Exercises	Chest	5
	Upper Back	5
	Bicep Curls	2.5
	Abdominals	2.5
	Mid/Lower Back	5
	Quadriceps	5
	Hamstrings	5
	Total Strength Training Duration	30
Break		3
Aerobic Exercise	Alternating Video for Participants	15
	Total Aerobic Exercise Duration	15
Break		3
Cool Down	Quadriceps Stretch	0.5
	Hamstring Stretch	0.5
	Calf Stretch	0.5
	2 Hip Stretches	0.5

Section	Type of Exercise	Duration (min)
	Static Torso Rotation	0.5
	Seated Side Bend	0.5
	Back and Shoulder Stretch	0.5
	Chest Stretch	0.5
	Triceps Stretch	0.5
	Neck Stretch	0.5
	Total Cool Down Duration	5
Total Time		**Approx. 65**

Warm Up. The first 5-10 minutes of the intervention exercise session will consist of a general warm-up using dynamic stretches, which include marching in place, various stretching warm up exercises, and quarter squats.

Strength training. Following the general warm-up, participants will execute the strength-training portion by performing progressive strengthening exercises (including pushes and pulls using resistance bands, and chair stands). Participants will complete 7 exercises which target major muscles, including quadriceps, hamstrings, chest, back, abdominals, and synergists such as biceps and triceps. Exercise dose characteristics will be structured to elicit the greatest muscular fitness benefits with a general starting regimen consisting of 1-2 sets of high repetition, low resistance training for the first 1 to 5 weeks of the intervention. Following this, weeks 6 to 10 will consist of 2 sets of moderate repetition, moderate resistance training. And finally, weeks 11 to 16 will consist of 1-2 sets of low repetition, high resistance training. For a visual depiction of the strength training progression across the 16 weeks, please see Table 4 (below).

Table 4. Example progression of strength training guideline across intervention.

Weeks	Sets	Repetitions	Resistance Bands
1 to 5	1	15 to 20	*Band Intensity will increase throughout the trial*
6 to 10	2	10 to 15	
11 to 16	3	8 to 12	

Table 4 presents a general guideline demonstrating the overall progression goals of the intervention. However, realistically there are significant individual differences in starting ability and mobility levels. Therefore, while the exercise physiologist will aim to follow the progression guideline of Table 4—individualized and tailored progressive training regimens may be necessary. Therefore, the certified exercise physiologist who developed the exercise program for SYNERGIC@Home has also recommended a series of progressions across the intervention that are tailored to suit individuals at varying levels of ability. These ability levels will be assessed by the site exercise physiologist at the outset of the study. Three main progressions will be offered for each muscle group to increase challenge throughout the training period for individuals of each starting mobility and exercise ability level. All participants will be instructed to rest 30-60 seconds between sets. Training prescription for all exercises was made in accordance to the ACSM guidelines for strength development in older adults (ACSM, 1998). For details pertaining to the tailored training prescription by baseline ability, please see Table 5 (below).

Table 5. Tailored resistance training prescription by mobility and exercise ability.

Low Fitness/Mobility Ability			
Muscle Group	**Starting Exercise**	**Moderate Progression**	**High Progression**
Quadriceps	Seated leg press with resistance band	Add resistance	Progress to sit-to-stand
Chest	Seated chest press (light band)/chest fly (light band)	Add Resistance	Lengthen rep time (count 3 down, 3 up)
Hamstrings	Standing hamstring curl/hip raise	Lengthen rep time (count 3 down, 3 up) + (hip raise)	Add resistance
Upper Back	Scapular squeeze/scapular wall hold	Seated resistance tube row/seated reverse fly (light band)	Add resistance
Mid/Low Back	Reverse Snow angels	Include legs simultaneously	Progress to pullover
Abdominals	Bird Dog variation (arms/legs separate)/dead bug variation	Progress to include simultaneous movements of limbs	Longer hold
Average Fitness/Mobility Ability			

Muscle Group	Starting Exercise	Moderate Progression	High Progression
Quadriceps	Squat/wall squat (knee pain)	Add resistance (either with normal bands or thigh bands to activate glutes)	Lengthen rep time (count 3 down, 3 up)/pulse
Chest	Counter Push-Up (incline approximately 45)/chest fly (mod band)	Reduce incline (shorter surface)	Lengthen rep time (count 3 down, 3 up)
Hamstrings	Resistance Tube Hamstring Curl/single-leg hip raise	Add resistance/Lengthen rep time (count 3 down, 3 up)	Change surface of planted foot (e.g. foam, bosu, etc.)
Upper Back	Standing Resistance Tube Row/Reverse Fly (mod band)	Add resistance	Lengthen rep time (count 3 out, 3 in)
Mid/Low Back	Resistance Tube Lat Pullover	Add resistance	Lengthen rep time (count 3 out, 3 in)
Abdominals	Incline Plank/bird dog progressions (simultaneous legs/arms)/dead bug progressions	Reduce incline towards horizontal)/banded bird dog/deadbug	Longer hold
High Fitness/Mobility Ability			
Muscle Group	**Starting Exercise**	**Moderate Progression**	**High Progression**
Quadriceps	Split Squat/lunges/walking lunges	Add resistance/change footing	Lengthen rep time (count 3 down, 3 up)/pulse
Chest	Floor Push-Ups (from knees or feet)/chest fly (hard band)	Lengthen rep time (count 3 down, 3 up)	Add resistance band/change hand positioning
Hamstrings	Romanian deadlift	Lengthen rep time (count 3 down, 3 up)/add resistance	Single Leg Romanian deadlift
Upper Back	Standing single arm resistance tube row/single arm reverse fly (at reasonable resistance)	Add resistance	Lengthen rep time (count 3 out, 3 in)
Mid/Low Back	Resistance Tube Lat Pulldown (high anchor, seated, kneeling, standing depending on set-up)	Add resistance	Lengthen rep time (count 3 out, 3 in), change arm position/grip
Abdominals	Forearm Plank/Hollow Hold	Hand plank/lower legs	Dynamic plank

Aerobic Exercise. The aerobic training portion will consist of 10-20 minutes of moderate intensity activity. Participants will be given one of two instructional, at home, exercise videos specifically designed for aerobic and cardiac fitness for older adults to complete via YouTube. Each video is approximately 15 minutes in length and participants will be encouraged to pause or slow down as needed; thus we expect the aerobic training to take approximately 20 minutes to complete. All participants will be monitored via video conferencing by a certified exercise physiologist while partaking in the YouTube home-based exercise. Participants will alternate between the following two videos in order to reduce boredom and maintain their interest.

Video 1: https://www.youtube.com/watch?v=aVilzXtqi8c&t=167s

Video 2: https://www.youtube.com/watch?v=afvTMIT_ZTc

French adaptations for Francophone participants are as follows:

French Video 1: https://youtu.be/nk0LcCl_UJQ

French Video 2: https://youtu.be/5MI5QWHc7II

Intensity will be set using the talk-test, whereby participants state in short sentences and Ratings of Perceived Exertion (RPE; 4-6 on Borg's 10-point scale). This intensity score will allow us to individually tailor and modify exercises based on the participant's rating.

Cool Down. Each session will end with a five-minute cool down, which will consist of the following stretches (each held for 20-30 seconds); quadriceps stretch, hamstring stretch, calf stretch, 2 hip stretches, static torso rotation, seated side bend, back and shoulder stretch, chest stretch, triceps stretch, and neck stretch.

7.2.2 Control Exercise Intervention: Balance and Toning (BAT)

Participants assigned to the BAT control exercise condition will take part in home-based balance and toning exercises, while supervised by a trainer through the video

conferencing platform as outlined for the intervention exercise group.[92-97] The format of the control exercises including the duration of activities and the amount of coaching devoted will mirror that of the intervention condition. However, in the control condition, exercises will be devoted to improving muscle tone and flexibility, without improving strength, and cardiorespiratory capacity. Resistant load and number of repetitions will not progress across exercise sessions, unless participants were unable to complete required repetitions at the beginning of the intervention. All BAT sessions will include a simple stretching mat (rather than progressive resistance bands) that will be sent to participants at the study outset. For a general overview of the BAT program, please see Table 6 (below).

Table 6. General overview of control BAT regimen structure.

Section	Type of Exercise	Duration (min)
Warm Up	Marching in one place with arm swings for 1 minute	1
	Dynamic Hamstring Stretching: 15 per side	1
	Shoulder Circles: 15 per direction	1
	15 Arm Reaches	0.5
	Torso Twists: 15 per direction	1
	Ankle Circles: 15 per direction per side	2
	Side Stepping for 1 minute	1
	15 Quarter Squats	1
	Total Warm Up Duration	8
Break		1
7 Balance and Toning Activities	Standing with Feet Together + Tandem + Single Leg Stand	10
	Core Contractions + Core & Arm Raises	8
	Shoulder Retractions	3
	Isometric Quadriceps Strength	3
	Seated Hamstring Curls	3
	Seated Arm Shake	3
	Total Balance and Toning Duration	30
Break		3
Stretching Exercise	Alternating Video for Participants	15
	Total Stretching Duration	15
Break		3

Section	Type of Exercise	Duration (min)
Cool Down	Quadriceps Stretch	0.5
	Hamstring Stretch	0.5
	Calf Stretch	0.5
	2 Hip Stretches	0.5
	Static Torso Rotation	0.5
	Seated Side Bend	0.5
	Back and Shoulder Stretch	0.5
	Chest Stretch	0.5
	Triceps Stretch	0.5
	Neck Stretch	0.5
	Total Cool Down Duration	5
Total Time		**Approx 65**

Warm Up. The session will start with the same 5-10-minute warm-up completed in the combined AE and RT group.

Balance and Toning. This will be followed by a variety of balance and toning exercises that will target the entire body. These activities are designed to match the intervention condition with respect to the time and duration—but they are not intended to physically challenge participants or progress in any way across the trial.

Stretching. Like the intervention condition, participants will alternate between two Youtube videos—but rather than an aerobic portion, the video will consist of a stretching session geared toward older adults. The following are the two videos that participants in the control condition will be presented with in alternating order.

Video 1: https://www.youtube.com/watch?v=eHXbj2Uq8mM

Video 2: https://www.youtube.com/watch?v=zVCqkiqsz4I

Cool Down. All participants in the BAT condition will end with cool down stretching that is identical to the active intervention condition.

7.2.3 Cognitive Training: NEUROPEAK™

The cognitive training intervention will take place remotely using a tablet or computer-based multimodal and multi-domain dual-task training with memory load. Participants will be instructed on how to access the program from their home computer and will be asked to complete the cognitive training program called NEUROPEAK™ on their home computer prior to each exercise training session. Specifically, participants will be assisted by research staff in connecting to the platform from their home computer/tablet. The research assistant will connect with the participant via *Zoom for Healthcare*© in order to assist with the technical questions and offer technical assistance. NEUROPEAK™ has several cognitive training modules but for this study the custom-written program consists of a dual-task training program developed at University of Western Ontario for neurorehabilitation, which has been used in previous Canadian studies[98-100]. The cognitive training includes dual-task training that requires participants to maintain and prepare for many response alternatives (working memory) and to share attention between two concurrent tasks (divided attention). Difficulty of cognitive training is tailored to their individual functioning level. The training uses a custom-written program developed for neuro-rehabilitation and has been used in previous research trials for cognitive[82,83] and mobility outcomes[39]. Cognitive training will take 30 minutes at maximum to complete, and each participant will perform the cognitive training in their own home with no assistance for the cognitive training tasks, but will have the opportunity to ask for help on setting up the program or technical questions. The participant will be asked to do this training in a quiet room within their home to reduce any potential distractions.

During each cognitive training session, participants will perform one of two different visuo-motor tasks, which include sets of visual stimuli (e.g., letters, numbers, animals, vehicles, fruits, celestial bodies) and respective hand-button correspondences (i.e., keys that are to be tapped on either the right or the left side of the screen). Participants are instructed to perform these tasks as fast as possible, while maintaining accuracy. Tasks will be performed both separately and concurrently so that task-set cost and dual-task cost can be isolated, allowing us to determine the rate at which accuracy decreases

when task demands are high. At each session, task combination for the sets of stimuli will change (from a total 18 combinations). Training will also include online feedback as well as a histogram of daily performance (a simple graph showing progression but without specific numbers) to encourage improvement.

7.2.4 Control Cognitive Training: Web Search and Video (WS+V)

The cognitive training control home-based sessions will last a maximum of 20-25 minutes to align with the same time frame as the cognitive training group. Participants will alternate between 2 different tasks (touristic searching using internet and video watching) completed using the same method as the intervention cognitive training (i.e., on a computer within a quiet room in their home). In the first session, participants will receive a short introductory lesson on how to navigate the internet. For the touristic searching using internet, participants will be required to find 3 hotels, 3 touristic places, and 3 restaurants of their own preference in a city assigned by the instructor (a new city will be selected each session). They will also need to include the respective addresses of those places on their log sheet.

For the video watching task, participants will watch a National Geographic video on YouTube selected by the instructor with a different video selected for each session. They will watch the video for 20 minutes and during the remaining 5 minutes they will answer the following questions on their log sheet: 1) What is the video about? 2) What is the most important information in your opinion? 3) Create a question based on the video and answer your own question. Regardless of whether or not participants have completed the above control cognitive training tasks, they will be stopped at 25 minutes.

7.3 RANDOMIZATION

Upon completion of the baseline assessments (T0), participants will be randomly allocated to one of the four study arms (as shown in Figure 1). Randomization will be completed by Nellie Kamkar, the study Research Coordinator located at Lawson Research Health Institute in Parkwood Hospital, London Ontario, who will distribute randomization codes (using a random number generator) to determine the treatment

arm to which each participant is allocated. Assessors and Research Assistants administering the interventions will be blinded and as such, only Nellie Kamkar and Andrew Sexton (the project manager at the University of New Brunswick) will have access to the randomization lists.

7.3.1 Method

The randomization sequence of the participants will be generated centrally using a simple excel formula that generates a random number within a sequence. A block randomization by four will be applied to ensure an appropriate balance of the participants between each arm. Permuted blocks will be employed to ensure balance over time. This trial includes 4 possible treatment arms: 1) AE+RT and NEUROPEAK™; 2) AE+RT and WS+V; 3) BAT and NEUROPEAK™; 4) BAT and WS+V. Simple randomization will not necessarily ensure that an equal number of participants will be allocated to each group (for example, we may randomly have a large proportion of participants in one group and very few or none in another). Block randomization ensures that this does not occur. Every four participants will be put into a block. For example, the first block (Block A), will consist of our first participant whose treatment arm allocation will be determined using a random number ranging from 1 to 4 (each representing the respective arms listed). Let's assume that this number happened to be 3 (BAT and NEUROPEAK™). Then, for the next participant in the block, a random number ranging from 1 to 3 will be generated (with all treatment arms *except* the BAT and NEUROPEAK™). Now, the number 1 represents AE+RT and NEUROPEAK™ (like before), the number 2 represents AE+RT and WS+V (also like before). But the number 3 represents BAT and WS+V (what used to be arm 4). This ensures that the second participant will be randomly allocated to a different arm than the first participant. The third participant in Block A will be randomly assigned to one of the two remaining arms and the fourth participant will be assigned to the last remaining arm.

7.3.2 Procedure

Each participant will have an allocated sequential randomization number. After the baseline assessment, the SYNERGIC@Home Research Coordinator at UNB (not

involved in measurement or intervention) will access the randomization list to determine the arm allocation for the participant. The Research Coordinator will maintain a separate file stored in SharePoint (accessible only by the Coordinators and PI's) that links the participant's ID with their treatment group allocation.

7.4 BLINDING

In order to minimize a source of bias, this is a double-blinded study. Research personnel performing the outcome assessments will be blinded to group allocation. Participants will be blinded to the intervention received and study hypotheses.

7.4.1 Maintaining Blinding

Only the designated Research Assistants (RAs) delivering the interventions will know the treatment group that participants belong to. As part of the training for RAs during on-boarding (in our trial SoP), they will be informed of the importance of blinding and instructed to avoid conversing with participants in a way that could reveal their group membership.

Participants will be informed at consent and reminded at enrollment of the importance of blinding and that they should refrain from discussing their treatment program with friends and family and especially with others they may know that are participating in the study.

7.4.2 Unblinding

If it is medically necessary to un-blind a participant during the trial, the RA assigned to doing the assessments or interventions will contact the study Physician and Principal Investigators to discuss the reason for the code to be broken. If it is deemed relevant to unblind the participant the study Physician will contact the Research Coordinator to break the blinding. The participant will then withdraw from the study.

7.4.3 Debriefing

At the end of the trial (immediately after participants complete their T10 assessment), participants will be unblinded such that a research assistant divulges the exact condition

that the participant was randomly allocated to. During this debriefing session, participants will have an opportunity to ask questions and to give feedback.

7.5 EARLY WITHDRAWAL

Participants will be withdrawn from the study if they no longer wish to continue their participation. Participants who voluntarily withdraw will be asked if they would be willing to continue their participation in either intervention on its own. For example, a participant who indicates that s/he would like to withdraw due to lack of satisfaction with the exercise intervention will subsequently be asked if s/he would be willing to continue with the cognitive training intervention on its own. Participants will be withdrawn if, in the opinion of one of the study physicians, it is medically necessary to do so.

Participants will be asked to complete a 20-item exit questionnaire (see Appendix D) where the purpose is to collect information about their experiences with the study circumstances and logistics. These findings will provide useful information about trial feasibility. Participants who withdraw from the study and agree to provide this feedback will be emailed a copy of the questionnaire for completion through SurveyMonkey. The completed questionnaire will either be scanned and returned by email or a hard copy will be mailed to the research coordinator using a stamped, self-addressed envelope we provide.

7.6 MIXED METHODS DESIGN: EXPERIENCE OF STUDY PARTICIPANTS

One of the secondary feasibility objectives as described at the outset aims to measure the experience of study participants who have participated in this intervention trial being conducted in home-based, on-line settings using *Zoom for Healthcare*©. Using key concepts such as satisfaction, knowledge gained, motivation/commitment, adherence, and benefits, and challenges, we will collect data about the feasibility of conducting a home-based, on-line intervention trial with an older, community-dwelling population.

7.6.1 Mixed Methods Design

An explanatory sequential mixed methods design will be used[101] where qualitative data will be collected to explore quantitative findings. This design is implemented in two phases where initially data collected using a quantitative instrument in the first phase is followed by a qualitative phase. Using mixed methods enables the quantitative results to be "sequentially" explored in more detail through this phase two qualitative approach.

A questionnaire (Appendix D) will be administered to the 64 study participants upon completion of the study intervention (T4). Semi-structured interviews will be conducted with study participants using the guide in Appendix E following the completion of their six month post-intervention follow-up assessment (T10).

7.6.2 Data Collection Instruments

Questions developed for both the quantitative and qualitative instruments were constructed using Kirkpatrick's (1975) framework—a four-level model that has been used to assess participants' benefits and experiences with different types of programs[4]. This framework consists of four dimensions as illustrated in Table 7 and has been used in numerous settings to conduct a process-focused program evaluation.

Table 7. Kirkpatrick's Framework for Evaluation of Participant Experience

Kirkpatrick's Framework for Evaluation	
Dimension	**Possible Areas for Exploration**
Reaction (to research study)	• How did participants feel about components of the study? • Were participants satisfied with the research team members implementing the intervention(s)?
Learning (new knowledge / skills; what knowledge / skills unlearned)	• What new knowledge and skills were learned? Any new knowledge about how to improve thinking and memory? • Did participants become aware of new evidence-informed practices that required them to 'unlearn' skills? For example, was there new learning with respect to physical exercise?

Kirkpatrick's Framework for Evaluation	
Dimension	**Possible Areas for Exploration**
Behaviour (change in behaviour as a result of participating in the research study)	• What does the participant identify as changes in behaviours as a result of participating in the study? • What new skills were learned? • What were motivators to change?
Results (Measurable outcomes)	• Benefits identified by participants

7.6.3 Participant Exit Questionnaire

The purpose of using a quantitative instrument (Appendix D) is to obtain a snapshot of the study circumstances and logistics from the participants' perspective. Upon completing the study intervention (at T4) each participant will be sent a one-page, short-form questionnaire via email. This questionnaire consists of 19 closed-ended questions using a 5 point Likert scale and one open-ended question. The questions consist of alternating positive and negative statements which collect participants' impressions about their experience and satisfaction with various elements of this study; i.e., such as using a computer or video-conferencing to complete the intervention and assessments. Study participants will either return the scanned questionnaire by email or mail a completed hard copy to the research coordinator using a stamped, self-addressed envelope.

7.6.3.1 Quantitative Data Analysis

The results of these questionnaires will be analyzed using a standard statistics software program such as SPSS. Descriptive statistics for the anonymized questionnaires will be compiled such as the number of responses, the percentages for each question, and the group mean and standard deviation.

7.6.4 Participant Semi-Structured Interview

A semi-structured interview guide has been developed (Appendix E) consisting of question that ask participants to comment on their study experiences. For example, the

benefits of this research approach for exercise and cognitive training programs including their reaction to the type of training they completed, their user satisfaction, the ease of participation in a virtual setting, the quality of information received; and support provided by research team members and the extent of burden and fatigued from completing the assessments will be explored.

7.6.4.1 Qualitative Data Analysis

Transcribed data from the interviews will be uploaded into NVivo, a qualitative software program used for data analysis by the team's qualitative researchers. Transcripts will be divided amongst the qualitative researchers. These team members will code the interview data, initially independently, and then meet as a group to arrive at a consensus of codes. Following coding of the data, through thematic analysis, themes and sub-themes will be generated to identify participants' perspectives of the feasibility, experience and satisfaction with this type of virtually delivered study. Study participants will be invited to review and validate the themes generated; this validation adds rigor to analysis, which ensures that the researchers "got it right".

7.6.5 Triangulation

The mixed methods design promotes methodical rigor. For this aspect of the study, triangulation of the findings takes place from two perspectives. Collecting both quantitative and qualitative data gives more insight than any one method will provide. In addition, having more than one member of the research team conduct the semi-structured interviews can significantly enhance the credibility of the findings and is particularly important for decreasing bias in gathering, analyzing data and/or reporting study findings.

7.7 COMPENSATION

In recognition for the participant's time commitment they will be given $50.00 after the immediate post-intervention follow-up (T4) assessment and $50.00 the 6-month post-intervention follow-up (T10), for a total amount of $100. Compensation will be in the form of gift cards to local grocers (Sobeys and Atlantic Superstore) and gas stations

(Irving Circle K and Ultramar) of the individual's choice, or equivalent cash value paid by cheque.

8. STATISTICAL CONSIDERATIONS

8.1 SAMPLE SIZE AND POWER ANALYSIS

A total of 64 participants will be enrolled in the SYNERGIC@Home study. Participants will be randomly allocated to each of the four arms with 16 participants per arm. Power analysis was calculated a-priori using G*Power 3.1 based on our primary analytic goal of assessing the relationship between intervention preference and subsequent adherence. Specifically, we plan on examining correlations among continuous variables with a final total sample size needed of 48 (25% loss) and with one-tailed analyses at $\alpha = .05$ for two correlation tests (equivalent to a two-tailed test at $\alpha = .1$), thus we will have 96% power to detect a moderate to large effect size (of .5 or larger) and 82% power to detect an effect size of .4 or larger. For any r greater than .6, power will be well over 99%, meaning that we will have greater than 99% power to explain a minimum of 36% of the variability in our dependent variable.

8.2 PLANNED DATA ANALYSIS

Descriptive statistics for demographic and baseline characteristics will be provided with means and standard deviations, or medians and the interquartile range where appropriate, for continuous characteristics, and frequencies and percentages for categorical variables. Analysis will be conducted as intention-to-treat (ITT) and as per-protocol analysis (PPA).

8.2.1 Primary Feasibility Outcomes

Adherence to the interventions will be analyzed using a one-sample t-test that will test the hypothesis that participants complete at least 36 of the 48 (75%) scheduled

interventions sessions. This test will be used to determine of the adherence is similar to hypothesize, better than hypothesized or worse than hypothesized.

8.2.2 Secondary Feasibility Outcomes

Enrollment recruitment target of 75% will be tested using a Chi-square goodness-of-fit test (α=.05) of actual distribution (# eligible and # screen fails) versus hypothesized distribution (75% and 25% of N). This test will be used to determine if the achieved distribution of eligible participants is similar to that hypothesized, significantly better than that hypothesized, or significantly lower than that hypothesized.

To answer the research questions pertaining to trial retention, we will examine proportions reaching our 75% enrollment retention target at the immediate post-intervention follow-up (T4) assessment and the 75% follow-up retention target at the 6-month post-intervention follow-up (T10) assessment with 95% confidence intervals (when possible). In addition, Chi-square good-of-fit test will also be used to quantify the significance of the difference between the observed and hypothesized proportions.

Assessment tolerability will use descriptive statistics (counts) to describe how many and under what circumstances (documented in CRF notes) that participants decided to drop out of the trial, not because of the interventions, but because of the extensive battery of testing they must undergo in order to start the trial.

Descriptive statistics will be used to analyze the quantitative Exit survey to determine where on the spectrum of satisfaction (completely unsatisfied to completely satisfied) participants fall in terms of the trial components (see Appendix D). Data will be analyzed using a two-way ANOVA on exercise intervention (active and control) and cognitive intervention (active and control) to determine if there is a significant interaction effect induced by the combined active treatments.

Adverse events will be analyzed using a Chi-square cross-tabulation analysis between AE severity and AE relation-to-trial. We will use this analysis to test the hypothesis that there is a relationship between AE severity and being in the trial. Furthermore, we will

stratify the sample by treatment arm and use a Chi-square goodness-of-fit test to determine if AEs are distributed differently across treatment arms against the null hypothesis of an even distribution (no relation to treatment arm).

8.2.3 Primary Analytic Outcomes

For primary analytic outcomes examining the relationship between interest level in and adherence to the interventions, we will correlate interest level (responses given on the Intervention Preference Questionnaire, See Appendix A) for each intervention with adherence rates calculated from trial logs, using Pearson's r. This analysis will tell us if adherence to the trial is related to participants' affinity for any one or more interventions.

- **Interest in the Interventions:** Question 1 on the survey rates their interest in each intervention independently, **INT_EX** and **INT_CT**, on a 0-10 scale.
- **Intervention Preference:** The second question rates their relative preference for either intervention. This will generate a single variable that gives the relative preference (-2 to 2 scale), **PR**, where low scores prefer exercise and high scores prefer cognitive training. Because we will administer preference survey at baseline and then at 4mo, we will have two measures **PR1**and **PR2**. The difference scores (**dPR=PR2-PR1**) would be negative if their preference moved toward exercise, and positive if it moved toward cognitive training.
- **Intervention Allocated:** The treatment arms can be represented by two dummy (0,1) variables **EX_ARM** and **CT_ARM**.
- **Adherence to Interventions:** Adherence to the interventions at the end of the trial, **AD_EX** and **AD_CT**, is a continuous scale variable (% exercise and cognitive training sessions attended, respectively).

8.2.3.1 Analysis Plan

What is the Relationship between Adherence and Intervention Interest? For each of the two interventions we will calculate the Pearson correlation coefficient ($\rho_{X,Y}$) with a one-tailed alpha of .05.

H0: $\rho_{X,Y} = 0$, H1: $\rho_{X,Y} > 0$, where X=**INT_EX** and Y=**AD**

H0: $\rho_{X,Y} = 0$, H1: $\rho_{X,Y} > 0$, where X=**INT_CT** and Y=**AD**

Rejection of the null hypothesis for either test will allow us to conclude that interest level in the intervention type prior to the trial explains a significant amount of variance in adherence to the trial. Failure to reject the null hypothesis would suggest that prior attitudes about the interventions does not influence how well they adhere to the interventions.

8.2.3.2 Other Analyses

Which intervention type (physical exercise or cognitive training) do the majority of participants prefer over the other? To answer this question we will use a single-sample t-test to test if the mean **PR** is directionally biased from the middle score (no preference).

What proportion of participants have no particular preference for either intervention? To answer this question we will compute the proportion of participants that selected “Equal preference” response.

Do their attitudes change after completing the active interventions versus the control interventions? To answer this question we will calculate the mean preference change **dPR** and test whether it is different from zero using a single-sample t-test.

Do participants adhere better if they receive the active treatments they prefer?

Because some participants will be randomly assigned to the active intervention that matches their preference and others will not (will get the control version of the intervention), we will transform the preference score into a logical variable **PR_MET** (1=preference met, 0=preference not met).

if (**PR1**<3 and **EX_ARM**=1) or (**PR1**>3 and **CT_ARM**=1),

then **PR_MET**= 1, else **PR_MET**=0

We will test the hypothesis that

H0: $\rho_{X,Y} = 0$, H1: $\rho_{X,Y} \neq 0$, where X=**PR_MET** and Y=**AD**

Rejection of the null hypothesis (p<.05) will allow us to conclude that adherence to the interventions is significantly influenced by receiving the active intervention they prefer.

8.2.4 Secondary Analytic Outcomes

Clinical and activity assessments will yield a rich source of information for quantifying effect sizes of trial outcomes. We will calculate Cohen's d effect sizes (mean difference/standard deviation) for cognitive, mobility and lifestyle outcomes (e.g., diet and sleep) listed in Table 2.

All statistical tests will be two-tailed, and a p-value of less than 0.05 will be considered to indicate statistical significance. All calculations will be made using the Statistical Package for the Social Sciences (SPSS version 23.0, SPSS Inc., Chicago, IL) and Stata (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

8.3 FREQUENCY OF THE DATA ANALYSES

Preliminary analysis will be performed after finishing recruitment to ascertain descriptive characteristics at baseline assessment. Interim efficacy analyses will be performed when recruitment is reaching 50% of target sample (N = 32) and final efficacy analysis will be performed at the end of the trial (N = 64, but 48 are need for final analyses), as no safety issues are anticipated in this study.

9. ADVERSE EVENTS

9.1 DEFINITIONS

9.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject that may present itself during the conduct of a research study and which may or may not have a causal relationship with the study procedures. An AE can therefore be any unfavourable or unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with a study procedure. An AE may be a new illness, worsening of a sign or symptom of a condition, or an effect from a study procedure.

9.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening, i.e., the subject was at immediate risk of death at the time of the event; it does not include any event which hypothetically might have caused death if it had occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalizations and/or surgical procedures that are scheduled to occur during the study period, for an illness or disease that existed before subject enrolment in the trial, will not be considered AEs provided the pre-existing condition did not deteriorate (e.g., surgery performed earlier than the planned date).
- Results in persistent or significant disability/incapacity

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate. In other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

9.2 CLASSIFICATION

9.2.1 Severity

Adverse events will be classified as mild, moderate or severe in severity as follows:

- **Mild**: Discomfort noticed but no disruption of normal daily activity.
- **Moderate**: Discomfort sufficient to reduce or affect normal daily activity.
- **Severe**: Incapacitating with inability to work or perform normal daily activity.

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious”, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.2.2 Attribution

The relationship of the AE to study procedure will be assessed by the investigator to be not related, unlikely, possible, probable or definite, as follows:

- **Not related**: No relationship between the AE and the study procedure, judged clearly and incontrovertibly due to extraneous causes such as concomitant medication(s) or the subject’s clinical state.
- **Unlikely**: The AE is more likely due to an alternative explanation such as concomitant medication(s), concomitant disease(s) and/or the time relationship suggests that a causal relationship is unlikely.
- **Possible**: The AE might be due to a study procedure. An alternative explanation such as concomitant medication(s), concomitant disease(s) is inconclusive. The time relationship is reasonable therefore the causal relationship cannot be excluded.

- **Probable**: The AE might be due to a study procedure. An alternative explanation such as concomitant medication(s), concomitant disease(s) is less likely. The time relationship is suggestive, i.e. it is confirmed by de-challenge.
- **Definite**: The AE cannot be reasonably explained by an alternative explanation such as concomitant medication(s), concomitant disease(s). The time relationship is very suggestive, i.e. it is confirmed by de-challenge and re-challenge.

For the purposes of safety analyses, all SAEs classified with a relationship to a study procedure of possible, probable or definite will be considered study-related events.

9.3 PROCEDURES FOR AE AND SAE REPORTING

9.3.1 Adverse Event (AE) Reporting

All AEs experienced by the subject between the signing of the Informed Consent and discontinuation of the study will be reported. All AEs must be recorded in the CRF. For both serious and non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

9.3.2 Serious Adverse Event (SAE) Reporting

All SAEs will be recorded in the CRF starting from the time of the signing of the Informed Consent up to and including the end of study. All SAEs, regardless of the relationship to study procedures, must be reported within one working day of site personnel being notified of the occurrence of the event.

SAE forms will be provided to each study site. The initial SAE report should include at a minimum: subject number, a narrative description of the event, and an assessment by the investigator of the intensity of the event and relationship of the event to study drug. The initial SAE report received from the site should be complete as soon as possible. A complete follow-up SAE report must be submitted when the information, not available at the time of the initial report, becomes available. The sponsor (or designee) may request SAE follow-up information.

Any SAE that occurs at any time after completion of the study, which the investigator considers to be related to study procedures, must be recorded in the CRF.

All SAE will be submitted to the REB.

9.3.3 Period of Observation

All AEs should be monitored to determine the outcome or until the investigator considers it medically justifiable to terminate follow-up.

All SAEs should be monitored until resolved or until the SAE is clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

10. ETHICAL AND OPERATIONAL CONSIDERATIONS

This study is conducted in compliance with International Conference on Harmonization Good Clinical Practice (ICH-GCP) and all applicable regulatory requirements. This SYNERGIC@Home study will undergo review and approval from the Research Ethics Committees/Boards of Vitalité Health Network In Moncton, New Brunswick, Horizon Health Network in Fredericton, New Brunswick, the University of New Brunswick in Fredericton New Brunswick, and Université de Moncton in Moncton, New Brunswick.

10.1 ETHICAL CONSIDERATIONS

10.1.1 Informed Consent

When potential participants have self-identified as being interested in learning more about the study to decide if they want to participate, the Clinical Research Coordinator/Nurse will contact the individual to discuss an overview of the study. If they are interested in pursuing more information the informed consent will be emailed or mailed to them for their review. Potential participants will be given a copy of the informed consent form in their language of choice.

After the potential participant agrees to be considered for recruitment the clinical research coordinator/nurse will arrange a time for a more detailed videoconference

meeting for the Screening Visit. Opportunity for discussion of the study and Informed consent will be provided and all questions will be answered. The informed consent will be completed and signed prior to beginning any study related assessments/procedures. Signing of the consent will be done via videoconference and then returned by mail using a stamped, self-addressed envelope to the clinical research coordinator/nurse who will then sign it and file the original with the participant research documents. A final signed copy of the informed consent will be provided to the participant either by email or mail depending on their choice.

10.1.2 Confidentiality and Privacy

Participants' private and identifiable information will be held in strict confidence and will not be shared outside the research team, with the exception of enforcement of applicable civil or federal laws. Research team members will only have access to private and identifiable information on a need-to-know basis or as necessary for carrying out their study tasks.

Due to the COVID-19 pandemic, many research team members will be working from a home environment. All RAs involved in assessing or delivering interventions to study participants will be provided a secure UNB laptop administered by the study Project Manager. The study laptop may only be used for study related activities and must be used for all videoconferencing activity and data storage. All research coordinators in the Health Network will be working within their institutions or from a home environment. They will be provided a secure Health authority laptop administered by Service New Brunswick. All connection will be protected behind the institution firewall. Research team members and investigators will be prohibited from discussing participant cases or sharing of private and identifiable information by email or non-secure videoconferencing.

10.1.3 Biospecimen Collection Privacy

To ensure participant privacy and confidentiality in biospecimen collection, storage, shipment, participants will be instructed to print their study ID number on their saliva

sample box (rather than their name) and to ensure that their name or any personally identifiable information is *not* indicated on their sample box. They will be given mailing materials to pack their sample in and will be given instructions on how to mail the sample back for analysis. This is in accordance with standard operating procedures for storing, shipping, and handling of bio-samples for research purposes.

10.2 STUDY SAFETY AND MONITORING COMMITTEE

There will be a Study Safety and Monitoring Committee that will consist of all NB-PALM principal investigators and site physicians, project manager and research coordinator(s), as well as a physician not associated with the study (TBD) and a community member (TBD). This committee will be responsible to receive all reports of AEs and SAEs reported for any participant as well as to monitor the overall operations of the entire research project. A log of these reports will be kept and reviewed regularly to monitor the safety of the clinical trial.

10.3 RISK MANAGEMENT AND SAFETY MONITORING PLAN

All participants will be monitored by trained research staff, and should any adverse events arise, the research team directly working with the participant will notify the Clinical Research Coordinator/Nurse, who will gather and document the appropriate information and will contact the Physician Principal Investigator and/or Study Physician. Adverse events will be documented as described above in Section 10.

Participants will be given a phone number and e-mail address to contact if there is an adverse event, or they may report AEs at the start of their training session with the RAs delivering their interventions. There will be a member from the research team available to assist with this Monday to Friday 0800-1600 (excluding statutory holidays). All participants will be encouraged to use the contact information provided to them to ask any non-urgent questions and address their concerns throughout the entirety of the study trial.

In order to ensure that participant safety is the utmost focus of the research project, we have put forth the following plan and answered the following risk management and safety monitoring questions:

10.3.1 Safety Monitoring

Participant safety will be regularly monitored during each assessment and intervention session using an ongoing paper log. This log will be filled out by the study assessor conducting the intervention session and she/he will insert detailed session notes pertaining to the events that transpired during each event. This log will be reviewed by the clinical research coordinator/nurse and if there are any concerns it will be reported to the physician principal investigator and/study physician. These will be reported to the Safety and Monitoring Committee on a monthly basis.

10.3.2 Withdrawal for Safety Reasons

During their intervention sessions which occur three times per week, participants will be monitored the Research Assistant administering the intervention. Any concerns that are medical in nature will be communicated to the Clinical Research Coordinator/nurse. Further information will be collected from the patient by the nurse and the physician principal investigator/study physician will be notified. Follow up on any medical matters will be done by the nurse and/or physician as required. If further medical care is needed the participant will be referred to their primary care physician/provider for follow up. A decision regarding early withdrawal from the study will be made by the principal investigator/study physician and all the appropriate document will be completed.

10.3.3 Study-wide Stopping Rules

In light of the fact that this intervention program has been implemented previously in the SYNERGIC trial, it is unlikely that this study would be required to stop early due to safety concerns. However, SYNERGIC@Home will be conducted remotely so it is possible that adverse events may arise that are not anticipated requiring the entire study to stop. The decision to stop the study early will rest with Study Safety and Monitoring Committee.

10.4 INCIDENTAL FINDINGS

Incidental findings include any previously undiagnosed medical finding observed throughout the trial, identified purely accidentally within the research trial. Any incidental findings observed throughout the trial will be addressed by the Clinical Research Coordinators/Nurse and Physician Principal Investigator/Study Physician. All incidental findings will be appropriately documented. Depending on the finding the participants' primary care physician/provider will be contacted so that appropriate follow up and care if necessary is received. All findings and their follow-up actions will be documented and monitored until it has been resolved or as long as the participant remains in the study.

10.5 PROTOCOL DEVIATIONS

A protocol deviation occurs when the activities of the study deviate from that which is detailed in the study protocol. All research staff will make it their priority to ensure that the protocol is abided by as closely as possible. However, in the event that a participant deviates from the protocol, a protocol deviation form (see Appendix I) will be filed and details pertaining to the deviation will be noted in a hard copy stored in locked cabinets on the UNB campus. Attempts will be made to return to study procedure as outlined in the protocol as much as possible and as swiftly as possible.

10.6 DATA MANAGEMENT AND STORAGE

10.6.1 Primary Source Data

Primary source data will be stored using SharePoint, a secure platform through the University of New Brunswick to which only designated research staff have access. Primary source data are defined as the copies of the original hard copy assessment forms completed by the research team member conducting the assessments along with any hard copy self-report questionnaires and other study document sent by a participant of collected by the site research coordinators. Hard copies of any data collection forms will be stored in locked cabinets located at the workplaces of study research staff and accessible only by study staff.

10.6.2 Secondary Source Data

Upon completion of the study, all data collected in paper form with the unique identification numbers will be uploaded to the Longitudinal Online Research and Imaging System (LORIS) system (https://ccna.loris.ca/) at the McGill Centre for Integrative Neuroscience, McGill University, Montreal, Quebec. The LORIS is an OPEN SOURCE toolset framework for storing and processing behavioural, clinical, neuroimaging and genetic data. LORIS is designed to simplify management of large datasets acquired over time in a longitudinal study, and at different locations in a multi-site study. It provides a secure web-based access to data validation and quality control modules, as well as visualization and basic statistical tools. The LORIS servers in which the data is stored are physically located on the McGill University campus, in a secure data facility. Study staff will enter data into LORIS via web-portal.

10.6.3 Video and Audio Recording

All study procedures including intervention sessions (physical activity and cognitive training) will occur via Video Conferencing using *Zoom for Healthcare*©. The screening and baseline (T0), immediate post-intervention follow-up (T4), and 6-month post-intervention follow-up (T10) assessments will be video and audio recorded. In addition, a subset of 3 intervention sessions will be selected to be video recorded per participant for quality control. Anytime during which participants will be video recorded, they will be told ahead of time that their session will be video recorded.

The audio and video recordings will only be accessed by members of the research team to verify the data that is needed for populating the assessment forms. Once scores are verified from video and audio recordings, they will be transferred to the Case Report Forms and data will be input into a data collection sheet (Appendix F) for input to LORIS as described in section 11.6.2. Data will only be linked to each study participant's unique study identification number. The audio and video recordings, will be stored at UNB on a secure Sharepoint server and discarded after the data has been transferred. Recordings will never be shared, uploaded or distributed to any individuals or organizations outside of the research team. Data obtained from the ActiGraph GT9X

devices (i.e., gait parameters, heart rate, and sleep cycle data) will also be stored at UNB on a secure Sharepoint server and discarded after it has been transferred.

Participant names will not be associated with their video recording and participants will be asked to set their *Zoom for Healthcare*© user password as their initials. Video and audio recordings will be discarded after their data has been extracted.

10.7 FUTURE USE OF STORED SPECIMENS AND DATA

Biological samples will be stored at the Clinical Genomics Centre in the Mount Sinai Hospital, 600 University Ave, Toronto, ON M5G 1X5, Canada and will be processed under the guidance of Dr. Kathy Siminovitch. Approximately half of the samples will be used for planned analyses (polygenic hazard score (PHS) testing). The rest may be available for investigators who wish to perform further analyses on the whole cohort or a subset. Participants will be asked if they are willing to be contacted at a later date to be asked whether or not they consent to have their sample biobanked for future research use. Only participants who consent being contacted at the later date, and then consent to biobanking their sample for future studies will have their sample analyzed for other purposes, the samples form patients who didn't agree for this biobanking will be destroyed. Access to these samples will be regulated by the Biological Sample Access Committee which is made up of members of CCNA (members list available on request). Requests for access will be assessed for feasibility, scientific rigour, and alignment with the consent of the participants. In order to be granted access to samples, investigators must agree that the data they generate from the samples will be included in the larger CCNA database on LORIS within 2 years of sample batch receipt. Samples will be shared within Canada only for a period of 3 years after the last sample has been collected. After that 3-year period, they will be available to international researchers, if not already depleted. The full Biological Sample Access policy document is under development and will be made available upon its finalization.

PHS testing is still in its early embryonic stages in terms of clinical development and while it holds great promise for clinical utility in the future, it is not currently a validated

diagnostic tool used in medical practice.[102] Thus, the research team will be entirely transparent with participants and inform them at the study outset that their results will not be shared with them or their healthcare professional—as it is not currently a diagnostic tool. Any and all published work from the data will only include group statistics (and not individual trends) and will always include de-identified participant identification numbers (and not participant names).

10.8 PUBLICATION AND DATA SHARING POLICY

10.8.1 Dissemination of Study Findings

Prior to submission for publication or for presentation of any data or results obtained in this study, notification of the study Investigators (Principle and Co-Principle Investigators) is required. Draft manuscripts, abstracts and presentations should be submitted to the study Investigators for review and approval well in advance of applicable submission deadlines.

10.8.2 Authorship

Authorship of publications resulting from this study should accurately reflect the academic contribution of individuals to the design and implementation of the trial, analysis of the data and preparation of the manuscript. No researcher shall include identifiable personal health information in any publication or presentation.

10.8.3 Data Ownership

The University of New Brunswick will retain the ownership of the data obtained in this study. All publications that arise from the use of data will give acknowledgement, attribution, or co-authorship as appropriate in accordance with the International Committee of Medication Journal Editors (ICMJE) standards.

11. DISCUSSION

Older adults at risk for ADRDs have incident rates of related syndromes several times higher than their cognitively healthy counterparts[103]. Additionally, these populations of individuals at risk for ADRDs have an increased risk of falling and mobility decline[104,105]. Physical exercise, and cognitive training are emerging and promising non-pharmacological interventions to enhance mobility and cognitive functioning in older adults, especially in pre-dementia states prior to onset. These interventions have been tested separately, with positive results for physical exercise and cognitive training in improving cognitive function[30,32,35,42,46]. To our knowledge, this is the first study establishing the feasibility of conducting an entirely home-based combined exercise and cognitive training intervention program for older adults at risk for ADRDs.

11.1 SIGNIFICANCE OF ESTABLISHING FEASIBILITY

The goal of establishing the feasibility of conducting a home-based combined intervention program is critical, as it has the potential to inform other researchers on the logistics of designing remote intervention programs. In addition, in light of the physical distancing procedures implemented worldwide after the 2020 COVID-19 pandemic—many older adults have been further isolated in their homes. The SYNERGIC@Home trial is one of the first studies that has adapted to these unique times, allowing older adults to take part in various intervention and assessment procedures from the safety and comfort of their homes. If successful, the methodology and procedures tested in this feasibility trial will set the standard for a new platform in which participants are no longer restricted to intervention studies conducted in a physical laboratory.

11.2 SIGNIFICANCE OF EXAMINING INTERVENTION PREFERENCE

To address our primary analytic goal of assessing participant's intervention preference, we will examine the potential relationship between preference given for an intervention and the subsequent efficacy of it. We will assess participant's preference both prior to and after the intervention and correlate these values with their adherence to the

intervention that they were randomized to receive. If we find that preferences given prior to intervention are strongly related to subsequent intervention compliance/adherence—then our data will provide unique insights on factors related to the success of lifestyle modification trials with community-dwelling older adults. We may find that strong preferences are weakly correlated with our measures of intervention fidelity. This will suggest that subsequent intervention trials will not benefit from the added complexity and cost associated with formally estimating preference effects in randomized control trials of future intervention studies. Therefore, regardless of the results of our primary analyses, we believe that the SYNERGIC@Home trial will provide unique insights the relationship between intervention preference and subsequent fidelity.

11.3 SIGNIFICANCE OF SECONDARY OUTCOMES

We believe that the two combined interventions of physical activity and cognitive training used in conjunction will lead to a cascade of improvements on our secondary outcomes, such that those in the combined intervention groups will outperform the control groups on tests of cognitive functioning. We further believe that, if successful, the combined intervention will further demonstrate a delay in their progression to dementia. The reasons why each of the interventions will pose benefits to cognitive, neurological, physical, and psychological health are delineated below.

11.4 BENEFITS OF INTERVENTIONS

11.4.1 Benefits of Exercise

Mechanistically, AE and RT exercises can provoke a cascade of biochemical, physiological, and structural changes in the brain including increases in blood flow, neurotrophic factor release, neurogenesis, immune system efficacy and metabolism. These effects of exercise could combat inflammatory processes and the atrophy of brain structures both often associated with aging and ADRDs[32,34]. Interventions using RT exercises have found substantial improvements in high-order cognition (e.g. executive functions), whereas low-order cognition (e.g. attention, processing speed) is less benefited[34]. The reason for this selective improvement in cognition is unknown, but

it is hypothesized that areas in the brain that modulate executive functions are more susceptible to both aging and physical exercises interventions. Mechanisms suggested involve modulation of insulin-like growth factor-1 and insulin sensitivity, decreasing inflammation, enhancing release of brain-derived neurotrophic factor pathways, and even decrease brain amyloid load.[35,106,107] Combined exercise interventions have also shown increased brain volume and muscle mass in older adults.[93]

11.4.2 Benefits of Cognitive Training

Cognitive training can also improve cognition through enhancing brain functioning. Individuals who practiced monitoring of two tasks at the same time (i.e. dual-task training) on computer devices have presented with improved connectivity between prefrontal and temporal cortices, areas known to be important for executive functioning and memory, when compared to control participants.[40] Furthermore, imaging in these participants showed increased activity in these cortical areas during resting state, as shown by increased blood flow. With this, implementing a dual-task cognitive training program in older adults has the potential to selectively improve high-order cognitive functioning through brain plasticity and improved activation.

11.5 STRENGTHS AND CONCLUDING REMARKS

To our knowledge, this feasibility randomized control trial is the first to test the feasibility of implementing a combined physical aerobic exercise and resistance training program with cognitive training program at home to improve cognition in a sample of community-dwelling older adults at risk for ADRDs. We also believe this is one of the first home-based intervention trials for older adults, in which all aspects of the study protocol are being administered remotely. With this study, we will build capacity in implementing a multifaceted home-based intervention to delay dementia in a sample of community-dwelling older adults. We will also establish the extent to which measuring participant preference for a given intervention is related to subsequent adherence and compliance to the intervention treatment. We believe that this will inform other researchers and scholars alike on whether or not the costs and efforts associated with tailoring

interventions in future studies to match participant preferences are a worthwhile endeavor.

Furthermore, we are collaborating with a team of expert engineers and scientists to collect and examine a wealth of data from the actigraphy devices (ActiGraph GT9X). This collaboration with an engineering team will allow us to collect and analyze a large subset of objective measures of sleep and wake cycles, cardiovascular measures including heart rate, and mobility and gait parameters on a continuous basis.

In conclusion, SYNERGIC@Home will build capacity for future research RCT design using home-based interventions in older adults at risk for ADRDs.

12. RESEARCH TIMELINE

We wish to begin this project in January 2021. This study will be completed within two years of its start date: end date estimated for October 31, 2022. It is anticipated that patient recruitment will occur over at least a 10-month period and could be extended beyond this time depending on the results obtained.

13. LIST OF ABBREVIATIONS

AD: Alzheimer's Disease

ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive

ADCS-ADL: Alzheimer Disease Cooperative Study Activities of Daily Living

ADNI: Alzheimer's Disease Neuroimaging Initiative

ADRD: Alzheimer's Disease and Related Dementia

AE: Aerobic exercise

ANCOVA: Analysis of Covariance

Aβ: amyloid-β

BAT: Balance and Toning

BDNF: Brain-Derived Neurotrophic Factor

BHSP: Brain Health Support Program

BNT: Boston Naming Test

CCNA: Canadian Consortium in Neurodegeneration and Aging

CDR: Clinical Dementia Rating

CFC 2: Cognitive Functional Composite

CI: Cognitively Intact

COMPASS-ND: The Comprehensive Assessment of Neurodegeneration and Dementia

CV: Coefficient of Variation

FACETS: Functional Assessment of Currently Employed Technology Scale

GAD 7: Generalized Anxiety Disorder 7

GDS-30: Geriatric Depression Scale

IADL: Instrumental Activities of Daily Living

ICH-GCP: International Conference on Harmonization Good Clinical Practice

ITT: Intention-To-Treat

LSQ: Life Space Questionnaire

MCI: Mild Cognitive Impairment

MDA-14: Mediterranean Diet Assessment 14-items

MoCA: Montreal Cognitive Assessment

NTB: Neuropsychological Test Battery

PASE: Physical Activity Scale for the Elderly

PSQI-18: Pittsburgh Sleep Quality Index 18-items

PPA: Per-Protocol Analysis

RT: Resistance training

SCI: Subjective Cognitive Impairment

SF-36: Short Form quality of life questionnaire

SPSS: The Statistical Package for the Social Sciences

STOFHLA: Short Test of Functional Health Literacy

STST: One Minute Sit to Stand Test

SYNERGIC: SYNchronizing Exercises, Remedies in Galt and Cognition

TCOGS: Telephone Cognitive Screening

TMT: Trail-Making Test

VBM: Voxel-Based Morphometry

VEGF: Vascular Endothelial Growth Factor

VRF = Vascular Risk Factors

WMHs: White Matter Hyper-intensities

14. DECLARATIONS

This study is conducted in compliance with International Conference on Harmonization Good Clinical Practice (ICH-GCP) and all applicable regulatory and ethical requirements. All authors and research staff have no declarations, financial or otherwise, to disclose.

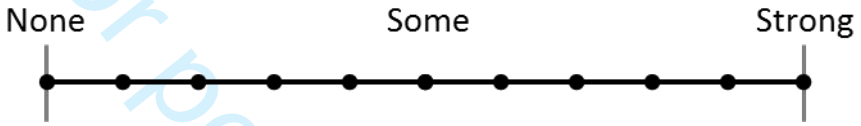
15. APPENDICES

APPENDIX A: INTERVENTION PREFERENCE QUESTIONNAIRE

Participant ID # _____
Date (dd-mm-yyyy) _____

1. Given what you know *at this point in time*, please indicate how interested you are in each of the following interventions, by placing a mark along the line between no interest and strong interest.

Rate your level of interest in **physical exercise** as a way to improve your brain health



Rate your level of interest in **brain exercise** as a way to improve your brain health

2. Please rate your preference between physical exercise and brain exercise training. Select the response below that best describes your preference at this point in time.

   ☐ Strong preference for **physical exercise**
   ☐ Slight preference for **physical exercise**
   ☐ No preference
   ☐ Slight preference for **brain exercise**
   ☐ Strong preference for **brain exercise**

3. If you have selected that you prefer one of the interventions over the other, please indicate *why* you prefer it. If you have an equal preference, then you may skip this question.

4. Are there other interventions (besides physical exercise and cognitive training) that you would prefer? If so, please describe them below:

5. Please indicate if you have any additional comments pertaining to the interventions in this study below:

APPENDIX B: MATERIALS GIVEN TO PARTICIPANTS

The following items will be given to participants.

1. An ActiGraph GT9X Activity Monitor
2. A blood pressure cuff and monitor
3. A set of colourful exercise resistance bands for individuals in the AE+RT exercise condition.
4. An exercise mat for individuals in the BAT exercise condition.
5. A standard roll of measuring tape
6. A saliva kit

APPENDIX C: RECRUITMENT PLAN AND MATERIALS

SYNERGIC@Home RECRUITMENT PLAN	
Target Organization / Group / Provider / Platform	**Methods**
NB-PALM website	• Promote SYNERGIC@Home study through email synergic@unb.ca
Horizon Health Research Registry Patient Database	• Identify potential research participants who have joined the Research Registry and have volunteered to be included in brain health related studies.
Social Media	• Materials will be specifically developed with messages appropriate for posting on Facebook and other platforms popular with community dwelling older adults
Senior Goodwill Ambassador Program **Go Ahead Seniors/Aînés en Marche**	• Trained community volunteers who promote exercise and healthy living throughout NB • Email and flyers will be provided to the volunteer leaders of these programs for distribution to participants
Provincial Anglophone and Francophone Seniors' Organizations **Seniors and Healthy Aging Secretariat**	• Email and flyers to numerous seniors' organizations for posting on website and / or distribution to members • Association francophone des aîné(e)s du Nouveau-Brunswick • NB Senior Citizen's Federation • Association des universités du 3e âge du Nouveau-Brunswick T
NB Alzheimer's Society	• Distribute flyer to facilitators/ coordinators of care giver and patient support groups • Post flyer on website • Possible e-blast using generic email
Senior Centres	• Distribute flyer for posting • Have centre distribute if membership list is available • Seniors' Information Centre – Moncton • Seniors' Resource Centre – Saint John • Stepping Stone Senior Centre - Fredericton • Johnston Avenue Senior Centre – Fredericton • Université de troisieme Age Nord Ouest • Third Age Centre, St. Thomas University

SYNERGIC@Home RECRUITMENT PLAN	
Target Organization / Group / Provider / Platform	**Methods**
Targeted Provincial Special Interest/Membership Organizations	• Use list from Seniors and Healthy Aging Secretariat to distribute flyers, email • Distribute flyer for publication in seniors' newsletters, website • NB Society of Retired Teachers • Société des Enseignantes et des Enseignants Retraités Francophones du Nouveau-Brunswick • Email to UNB, U du M. Mt A alumni associations
Geriatric Clinics	• Provide Information Sheet to Geriatricians • Distribute flyer for posting
Primary Care Physician/Providers	• Provide Information Sheet for physicians and NPs • Distribute flyer for posting in office locations
Community Health Centres and Community Mental Health Centres	• Distribute flyer for posting
Community Developers	• Community Developers to distribute generic email, flyers to networks and organizations they work with
Print media	• Newspaper advertisements in Fredericton, Moncton, Saint John • Advertise in selected rural papers
Community-based businesses	• Flyers in selected physical locations where community dwelling older adults congregate i.e., libraries, recreation centres

RECRUITMENT FLYER (Image Based)

SYNERGIC@Home

SYNchronizing Exercises, **R**emedies in **Ga**l**t** and **C**ognition **at Home**: Feasibility of a home- based double-blind randomized controlled trial to improve gait and cognition in individuals at riskfor dementia

SYNERGIC@Home is a research project assessing if it is possible to virtually deliver a home-based physical exercise and cognitive training program to older adults in New Brunswick. The hope is that this intervention will have a positive impact on memory for those at risk of developing dementia.

RESEARCH STUDY INVESTIGATORS

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Schulich School of Medicine & Dentistry, London, Ontario, Canada;
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NB-PALM
Preventing Alzheimer's by Lessening Modifiable risks

INTRODUCTION AND BACKGROUND

A study called SYNERGIC taking place in Canada, is showing promising results that exercise and cognitive training can be beneficial for older adults who are experiencing early problems with their memory. This study—**SYNERGIC@Home**— is an extension of the SYNERGIC trial. This study will engage older adults at risk of developing memory problems in a home-based program that will use an online virtual platform called Zoom.

This study is also part of the *New Brunswick Brain Health Initiative: Preventing Alzheimer's through Lifestyle Modification* (NB-PALM), funded by the HealthySeniors Pilot Projects, Public Health Agency of Canada, Province of New Brunswick.

POPULATION UNDER STUDY

We are looking for interested older adults living in New Brunswick who are at risk for developing dementia between the age of 60 and 90 years.

You may be eligible to participate if you have:

1. **No Memory Problems** but have <u>two or more of the following risk factors:</u>
   - ☐ Overweight
   - ☐ Hypertension/High blood pressure
   - ☐ Diabetes
   - ☐ Cardiovascular disease
   - ☐ Physical inactivity
   - ☐ First-degree family history of dementia (parents, children, siblings)
   - ☐ High cholesterol
   - ☐ Poor sleep
   - ☐ Poor diet
2. Been diagnosed by a physician or nurse practitioner as having **Subjective Cognitive** Impairment or **Mild Cognitive Impairment.**

DESCRIPTION OF STUDY

This study will take place over 10 months and includes an initial general health questionnaire, memory tests, and mobility assessments. Assessments will occur before the start of the physical exercise and cognitive training, immediately after the training intervention and again at 10 months follow-up. The training intervention will take place over 4 months. The physical exercise and cognitive training sessions will be done virtually over a computer or tablet with a research assistant who is a personal trainer, 3 times per week. Each session will take about 90 minutes.

▪

You are encouraged to have someone close to you who can assist you during the study, but this is not mandatory for everyone.

▪

IF YOU HAVE FURTHER QUESTIONS REGARDING PARTICIPATION OR ARE INTERESTED IN HEARING MORE ABOUT THIS PLEASE CONTACT:

Research Coordinator
Alana Gullison
Phone: 1 (506) 453-5137
email: synergic@unb.ca

Research Assistant
Molly Gallibois
Phone: 1 (506) 447-3197
email: synergic@unb.ca

RECRUITMENT FLYER

RECRUITING PARTICIPANTS FOR ONLINE EXERCISE AND MEMORY STUDY TO TAKE PLACE IN YOUR OWN HOME!

Researchers at the University of New Brunswick, Université de Moncton, Horizon Health Network, and Vitalité Health Network are inviting your to participate in *SYNERGIC@Home, a* study about the role of exercise and cognitive training in delaying the onset of dementia and Alzheimer's disease.

WHO?

We want to hear from community dwelling older adults living in Anglophone and Francophone communities throughout New Brunswick who may be otherwise healthy, but feel their memory is worsening or have received a medical diagnosis of Mild Cognitive Impairment. If you are between the ages of 60 and 90 years, and meet the following criteria please contact us at synergicinfo@nb-palm.ca

- Have access to a computer in your home that is connected to high-speed Internet,
- Capable of sending and receiving emails,
- Can read/write/speak in either English or French, and
- Able to walk 10 meters (about 32 feet) independently, with/without a walking aid.
- Have a spouse, relative, or close friend interested in being a study care partner (an exception will be made if a study partner cannot be found)

WHERE?

*Research act*ivities usually done in an exercise lab or hospital setting, will be completed in your own home. This study will help us learn how practical it is to conduct research using video-conferencing to train participants and collect data. Participants' activity and sleep patterns will be monitored using a wrist-watch like device called an activity monitor.

WHAT?

Participants will be enrolled for a total of 10 months. You will be assigned an exercise and cognitive training program delivered in 3 – 90 minute sessions per week over 16 weeks.

Sessions consist of both prescribed cognitive training and exercises. A research assistant trained in exercise science will guide participants through the exercises.

Questionnaires and assessments will be completed at various time points such as: screening for enrollment, baseline, and two follow-up sessions. Your medical history and cognitive functioning will be assessed and information collected about your lifestyle habits (e.g., how much exercise and physical activity you do, how well you sleep, your diet, and mental health)

STUDY CONTACT INFORMATION: Synergic@Home Study Research Coordinator email: synergic@unb.ca	

Initial Recruitment Email

PROCEDURE:

Following REB approval, this email along the flyer will be sent to organizations that post on their website and do an eblast to members and others including:

- Seniors organizations to include on website and newsletters
- Senior Ambassadors through Healthy Aging and Seniors Secretariat
- Community developers with HHN and VHN

Email Subject Line: Take part in a new virtual study called **SYNERGIC@Home!**

Email Content:

NB PARTICIPANTS WANTED FOR AN ONLINE EXERCISE AND MEMORY STUDY IN YOUR OWN HOME!

You are invited to take part in *SYNERGIC@Home – a research project studying how exercise a*nd cognitive training may delay the onset of dementia and Alzheimer's disease. We want to hear from community dwelling older adults living in Anglophone and Francophone communities throughout New Brunswick who may be otherwise healthy, but feel their memory is worsening or they have a medical diagnosis of Mild Cognitive Impairment. If you are between the ages of 60 and 90 years and meet the following criteria, we would like to hear from you:

- Have access to a computer in your home that is connected to the high-speed Internet,
- Capable of sending and receiving emails,
- Can read/write/speak in either English or French, and
- Able to walk 10 meters (about 32 feet) independently, with or without a walking aid.
- Have a spouse, relative, or close friend interested in being a study care partner (an exception will be made if a study partner cannot be found)

You are INELIGIBLE for our study if you have received a medical diagnosis of dementia or Alzheimer's disease by your family or specialist physician.

Promising Canadian research has shown that older adults who are at risk can benefit from participating in physical exercise and cognitive training. *We want to learn if s*tudy activities usually done in an exercise laboratory setting can be virtually completed in a participant's home. We also want to find out how practical it is to collect data from participants' about their activity levels and sleep patterns using a wrist-watch like device called an activity monitor.

For further information, please email: synergicinfo@nb-palm.ca

SYNERGIC@Home is *conducted by researchers at University of New Brunswick, Université de Moncton, Horizon and* Vitalité Health Networks *as well the University of Western Ontario. It is* part of the project *New Brunswick Brain Health Initiative: Preventing Alzheimer's through Lifestyle Modification* NB-PALM, which is funded by the Healthy Seniors Pilot Project (NB government) and the Canadian Consortium of Neurodegeneration on Aging. We are always looking for additional participants. If you think someone you know may be interested in taking part in this SYNERGIC@Home, please forward them this email.

Thank you for your interest!

Synergic@Home Study Research Coordinator

Email: synergic@unb.ca

Recruitment Newspaper Advertisement

Recruitment Newspaper Advertisement Content as follows:

SYNERGIC@Home Newspaper Advertisement

Procedure

- To advertise in selected NB newspapers assuming budget is available; i.e., Telegraph Journal (Saint John, Fredericton, Moncton issues)
- To advertise in selected rural newspapers assuming budget availability.

RECRUITING PARTICIPANTS FOR AN ONLINE EXERCISE AND MEMORY STUDY IN YOUR OWN HOME!

Feeling as if your memory is worsening?

Have you received a medical diagnosis of Mild Cognitive Impairment?

If so, you may be eligible to be a participant in

SYNERGIC@Home

A home-based virtual exercise and cognitive training research study for community living older adults residing in Anglophone and Francophone communities at risk of developing dementia and Alzheimer's Disease

For more information contact us at synergic@unb.ca

Follow-up Email

Dear****

I am a Study Research Coordinator with the SYNERGIC@Home study. I understand that you are interested in learning about our study.

I have enclosed a copy of the consent forms that provides detailed information on this project including the requirements of your participation.

I will follow up with you in a few weeks to see if you might be interested in participating.

In the meantime, if you have any questions, please email or call me as per the information below.

Thank you for your interest!

Synergic@Home Study Research Coordinator

Email: synergic@unb.ca

Study Information for Physicians / Providers

We are inviting you to discuss the following opportunity with your patients.

SYNERGIC@Home

An online exercise and cognitive training program taking place in the participant's own home

What is the Synergic@Home study?

SYNERGIC@Home, is a provincial study taking place throughout New Brunswick and will involve 64 participants from rural and urban locations who will "virtually" participate.

The study goals are twofold. The first is to learn about the role of exercise and cognitive training in preventing or delaying the onset of dementia and Alzheimer's disease; while the second goal is to find out how practical it is to conduct this research in a participant's home.

By participating in this study your patients will be making a valuable contribution about how to conduct research in a home environment that previously was conducted in hospital and university settings.

What is expected of participants?

Study participants must meet detailed inclusion and exclusion criteria which will be provide to you. A brief overview is as follows:

- Have access to a home computer that is connected to the high-speed Internet
- Capable of sending and receiving emails,
- Can read/write/speak in either English or French
- Able to walk 10 meters (about 32 feet) independently, with or without a walking aid
- Have a spouse, relative, or close friend interested in being a study care partner (an exception will be made if a study partner cannot be found)

Study participants will be randomly assigned to one of four exercise and cognitive training groups and asked to participate via Zoom. as outlined below:

The following table contains details of the study procedures /activities that you may wish to share/discuss with your patient.

Details of Research Study Assessments and Intervention		
Participant Activities	**When does this happen? How long will this take?**	**Description**
Consent & Clinical / Cognitive Screening	At consent: 2 hours	Screening is what you take part in to see if you are eligible to enter our study. The study team will review the Informed Consent Form with you to answer your questions about the study. After you sign the consent, the study team will ask questions about your: ▪ Personal and demographic information ▪ Health, family medical history, medications The study team will also test your memory and thinking skills.
Mobility & Lifestyle Screening	After giving your consent: 2 hours	You will be asked to questions about your lifestyle, physical activity, sleep patterns, and diet. You will be asked to perform tests to assess your walking speed and mobility. The study team will assist via you in taking measurements such blood pressure and waist size.
Physician & Participant Conference	After giving your consent: 1 hour	You will meet with a research physician who will review your medical history and discuss any specific concerns or questions related to your eligibility for participation in our study.
Activity Monitoring	Before the intervention begins: 10 days	You will wear an activity monitoring device similar to a wristwatch for 24 hours each day. This device records information about your activities and hours of sleep. This equipment will be sent to you via a secure courier and you will return it to the study team at the end of the 10 days.
Activity Assessment	Before the intervention begins: 2 hours	You will be asked to perform tests to assess your mobility and walking speed.
Cognitive Assessment	Before the Intervention begins: 2 hours	The study team will conduct tests to assess your memory, language, attention span, and problem-solving abilities.
Study	After you are enrolled: 96 hours	The research team will assign to a study group. You will follow exercise and cognitive training

Intervention		programs via Zoom for 2 hours per day, 3 times per week for 16 weeks. A research assistant will be present during each of the exercise sessions.
Activity Monitoring	After completing the intervention: 10 days	About four months after you began your exercise and cognitive training program, you will once again wear an activity monitoring device for a period of 10 days. This equipment will be sent to you via a secure courier and you will return it after 10 days.
Activity Assessment	After completing the intervention: 2 hours	You will be asked to perform tests to assess your mobility and walking speed.
Cognitive Assessment	After completing the intervention: 2 hours	The study team will conduct tests to assess your memory, language, attention span, and problem-solving abilities.
Activity Monitoring	10 months after beginning the study: 10 days	For the final time, you will wear an activity monitoring device. Equipment will be provided as before and you will return it after 10 days.
Activity Assessment	10 months after beginning the study: 2 hours	You will be asked to perform tests to assess your mobility and walking speed.
Cognitive Assessment	10 months after beginning the study: 2 hours	The study team will perform tests to assess your memory, language, attention span, and problem-solving abilities.
Semi-structured interview	10 months after beginning the study: 30-45 minutes	A member of the study team will arrange a time for you to be interviewed via Zoom. You will be asked questions about your experience as a study participant.

If you have questions about this study or would like to send along a referral, please contact the Synergic@Home Study Research Coordinator.

Email: synergic@unb.ca

Recruitment Discussion Guide for Obtaining Consent

PROCEDURE

- Following REB approval, this discussion guide will be used by the Research Coordinators at HHN and VHN to review the consent form with the prospective participant and obtain consent.

INTRODUCTION

Hi my name is [*insert name*]. I am a Research coordinator with [*insert name]* which is one of our study sites.

I'm calling about the research study called Synergic@Home. I understand that you contacted us to say you were interested in becoming a participant. You indicated you saw the flyer in [insert if this information is known]. The reason I am calling is to discuss the study and proceed with obtaining your consent to participate in our study if you are ready to make that decision today.

Before we start, I'd like to [confirm or obtain] some basic personal information.

Name of Potential Study Participant:

_____

Email: _____

Phone number:_____

Home address:_____

Age:_____

Next, I'd like to carefully go over different sections of our form to make sure you understand what's involved and your role as a study participant.

So if you're okay to start, let's begin.

Did you receive the consent form that we recently mailed to you or sent via email?

- You did receive it – that's terrific.

Have you had an opportunity to read through it in detail?

- You did – that's wonderful.

As you were reading through it, did you make notes by any sections or sentences that you want to discuss with me? Or that you want me in explain or clarify?

RESPONSE 1:

- The form was very informative and I am ready to sign it.

If that's the case, then before we sign it, I'd like to go over some particular sections of the form. It's my role to make sure that you fully understand and are informed about your rights as a study participant.

RESPONSE 2:

- Answer the specific questions.

Then move on to reviewing the sections of the form that were not addressed by the questions. "It's my role to make sure that you fully understand and are informed about your rights as a study participant. I noticed that there are some sections of the form that you didn't have any questions about, so before we sign it, I'd like to go over some particular sections of the form".

BEGIN TO REVIEW THE SPECIFIC SECTIONS OF THE CONSENT FORM

Let's start with you answering a FEW KEY QUESTIONS and then we'll walk through other sections of the consent. Here's the first question:

Have you discussed your participation with your any family members, friends or your family physician?

- Yes or no

Do you understand that your participation in Synergic @ Home is your decision?

- Yes or no

Are you aware that your participation in Synergic @ Home is entirely voluntary?

- Yes or no

I want to stress that you can withdraw from the study at any time

- Understood or not

Finally, will you be having a study care partner? A study care partner is a spouse or family member or friend who will be asked information about your health behaviors at various time as well as provide you with support and encouragement throughout the study.

- Yes – I have a study partner.
    - Who is going to be your study partner?
    - What is their relationship?
    - I will need contact information as this person will also need to sign a consent form.
- No study partner.

RESEARCH PURPOSE AND BACKGROUND:

Do you have any questions about why we are doing this study?

- Yes - no

We are pleased to be offering the SYNERGIC@Home feasibility trial to NB residents. We are used to doing this research in a laboratory setting at a university or health center. So, since we can no longer bring people in during the pandemic, we decided to conduct a study about exercise and cognitive training in a participant's home using video-conferencing. Your participation will help us learn about the practicalities of doing this type of research remotely.

STUDY PROCEDURES

The consent describes the study activities in various sections. When you become a participant, you will be enrolled in an exercise and cognitive training program that you take part in for three sessions each week over 16 weeks. Each of these weekly sessions will consist of both cognitive training and exercises and will last about an hour and one-half. During each of these sessions a research coordinator who is trained in exercise science will guide you through your program.

Do you have any questions about the amount of time needed to participate each week?

As a participant in our study there are numerous questionnaires you will be asked to complete along with assessments that research coordinators such as myself will be conducting with you [and your study partner].

Now as you saw in the different sections describing the study activities, there are various times during the study when we will collect information from you [and your study partner if available]. This is when we will ask you questions about your medical history as well as assess your cognitive functioning. We do this by asking you questions that test your memory and thinking skills. We also use questionnaires that ask your lifestyle habits such as how much exercise and physical activity you do, how well you sleep, your diet as well your mental health.

Any questions about the assessments and questionnaires?

In order to complete the study exercise activities you will need some equipment which we will send to your home for you to sue throughout the study. Some examples are an activity monitor, exercise mat, blood pressure cuff, and so on. If you are familiar with a Fitbit – this is what the activity monitor looks like and you wear it like a wristwatch such as shown in the picture. It records information about your activity and sleep levels and you will return this to us at various times throughout the study. We will also get you to take your blood pressure and certain other measurements.

I imagine this is a lot of information to take in, however there will always be someone guiding you on the video-conference while you are using this equipment. Some of the equipment you will be able to keep, while others like the activity monitor and blood pressure cuff you will return at the end of the study.

Do you have any questions about the equipment?

You may be wondering about our sanitation procedures. Each time after you return the equipment, it will be thoroughly cleaned and sanitized prior to mailing it back to you.

We will also be sending you a manual that will contain easy to read instructions about various aspects of the study. And remember that someone will always be available by phone, video-conference, or email if you have any questions.

It's important for you to understand that before you can become a participant, we will need to collect information during a screening visit that will help us determine if you meet the study eligibility criteria. Do you have any questions about this aspect?

It will no doubt be me that will meet with you [and your study partner] to complete this assessment. There may also be another nurse who has a background in research who will interview you. Between the two of us, we will gather information to help us decide about your suitability for our study.

RISKS AND DISCOMFORTS

Do you have any questions about the section in the form that described the risks and discomforts?

As I previously mentioned, we will be giving your cognitive training tests and exercises to do three times a week. And, depending on how much exercise you are used to doing, you may experience some discomfort while you are performing the exercises. If you do, you can stop at any time. And our research coordinator will be watching you as you exercise. S/he will ask you to stop if you are experiencing shortness of breath, chest pain, dizziness, or unsteadiness.

During the cognitive training part of each session you may experience some frustration as you complete the tasks. Also, you may feel a bit of discomfort if you are not used to wearing a wrist watch but hopefully that won't happen!

Finally, you know that we have various questions and assessments that will take some time to complete. We know this can be frustrating for some people. And we know from our experience that some questions may trigger an unpleasant memory or distressing feelings. We will watch closely for your reactions and will suggest taking a break. And as always, you can ask to take a break at any time.

We are not aware of any side effects from wearing the activity monitor.

I also want to stress that it's your right to stop your participation in the study at any time and there is no judgement or penalty if you decide to do so. Also you don't need to give a written note notifying your withdrawal. Okay?

COST/BENEFIT

There is no direct cost for you to participate. We will provide everything you need except of course your computer or laptop and the internet connection.

In relation to benefits, so far some of our participants have mentioned they are pleased to be taking part in a NB study that will help researchers learn more about how to do this type of research in a participant's own home.

Are there any questions about this section?

PRIVACY AND CONFIDENTIALITY

The section on privacy and confidentiality is quite detailed.

Do you have any questions about the procedures we described about how your personal information including your name, email, phone number, address, medical conditions and so on will be protected and kept private throughout the study?

- If yes, answer the questions…..

I know we also described numerous ways about how your personal research data will be stored. Do you have any concerns about the information that is included in this section of the form?

- If yes, answer the questions.

Now if you're ready, I'm going to ask if you would like to participate in this study?

- If no - thank you very much for your time.

- If yes – let's proceed to the section of the form where I need to obtain your consent.

Direction: Proceed to review the different sections where you need to obtain consent. I.e., get initials in each box or sentence pertaining to the various study components.

After finalizing the consent form, provide directions as to how to return the form.

- If returned by email they will need to scan the original and email it to you.

- If returned by mail, the research coordinator will need to make a copy which is then returned by email or mail to the participant.

Now before I finish our call, I'd like to get the contact information for your study partner [if one is participating]

Name of Potential Study Partner:

_____

Email: _____

Phone number:_____

Home address:_____

Thank you for taking the time to review the form and agreeing to participate. I will be in touch with you to confirm a time when we will conduct the screening assessment. In the meantime, you have my contact information [provide email and phone number]. If you have any questions don't hesitate to be in touch. Good bye for now.

APPENDIX D: EXIT QUESTIONNAIRE

SYNERGIC@Home Exit Questionnaire

Rate how much you agree or disagree with each statement	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1. *Zoom* was easy to use in completing my exercise program.	○	○	○	○	○
2. Wearing the activity monitor was not a problem for me.	○	○	○	○	○
3. I did not like using my own computer/laptop to participate.	○	○	○	○	○
4. I did not like having a research assistant supervise my exercises.	○	○	○	○	○
5. Taking part in the program 3 days per week was the right amount of time for me.	○	○	○	○	○
6. Exercising in my own home was convenient.	○	○	○	○	○
7. I encountered many problems with my internet connection.	○	○	○	○	○
8. The research assistant was helpful in assisting me to complete my exercises.	○	○	○	○	○
9. I was frustrated because the exercises were too difficult to complete in my home.	○	○	○	○	○
10, I did not enjoy completing the assessments and testing on *Zoom.*	○	○	○	○	○
11. Each week I looked forward to my cognitive training program.	○	○	○	○	○
12. Participating took too much time away from my other activities.	○	○	○	○	○

13. Wearing the activity monitor interfered with my sleep and other activities.	○	○	○	○	○
14. I was able to form a positive relationship with the research assistant.	○	○	○	○	○
15. I would have preferred exercising with a group of my peers.	○	○	○	○	○
16. I felt anxious when I was asked questions that tested my memory.	○	○	○	○	○
17. I enjoyed doing the cognitive exercises.	○	○	○	○	○
18. I would have preferred having one of my peers or someone who is my age assist with my exercises.	○	○	○	○	○

19. There were 4 intervention groups participating in the SYNERGIC@Home research study. Of the four groups listed below, which one do you think you were assigned to?

- ☐ Active exercises and active cognitive training
- ☐ Active exercises and limited cognitive training
- ☐ Limited exercises and active cognitive training
- ☐ Limited exercises and limited cognitive training

20. We are interested in hearing about what motivated you to complete the interventions. Please describe the factors or reasons that influenced your decision.

_____

_____

_____

_____

_____

APPENDIX E: SEMI-STRUCTURED INTERVIEW GUIDE

Semi-Structured Interview Guide	
Dimension	**Questions**
Reaction to Participation in Research Study	**Overarching Questions:** How satisfied were you with the study? How was the support you received during the study? **Probing Questions:** What was your experience: ▪ Doing this study over the Internet? ▪ With the equipment you used? What are your thoughts about the assessments that took place? How can this study be improved?
Learning That Occurred During the Research Study	**Overarching Questions:** What knowledge or information about exercise did you learn from your participation? What did you learn from your involvement with cognitive training?

Semi-Structured Interview Guide	
	Probing Questions: Were there any areas that you had to "unlearn"? For example, did you find out that you had been doing exercises inappropriately? Have you identified any differences in your memory or concentration?
Behaviour Changes That Occurred During the Research Study	**Overarching Questions:** Have you modified your behaviour as a result of participating in the study? If yes, what are they? Can you identify any motivators that helped you to change or modify your behaviours?
Results Identified by the Participants	**Overarching Questions** What have been the greatest results for you?
Concluding Questions / Comments Is there anything that has not been asked that needs to be brought forward? Are there any comments you would like to add?	

APPENDIX F: CASE REPORT FORMS

APPENDIX G BUDGET SUMMARY

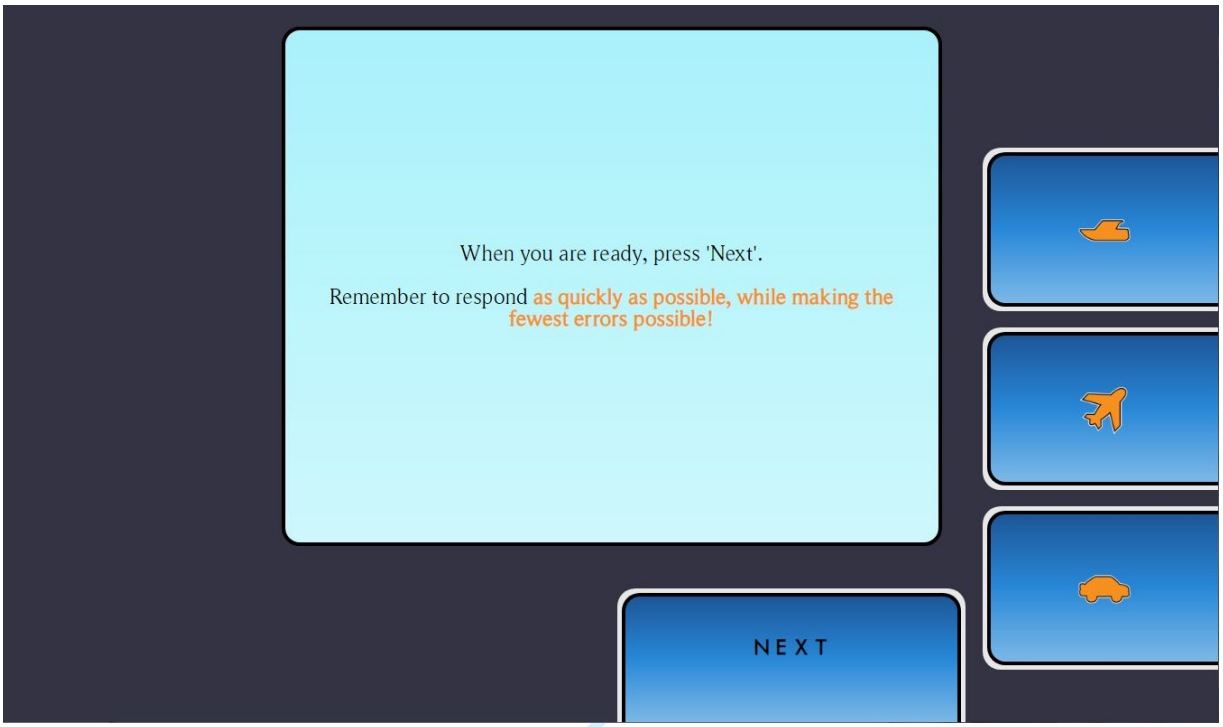
Budget Summary for Synergic@Home Study

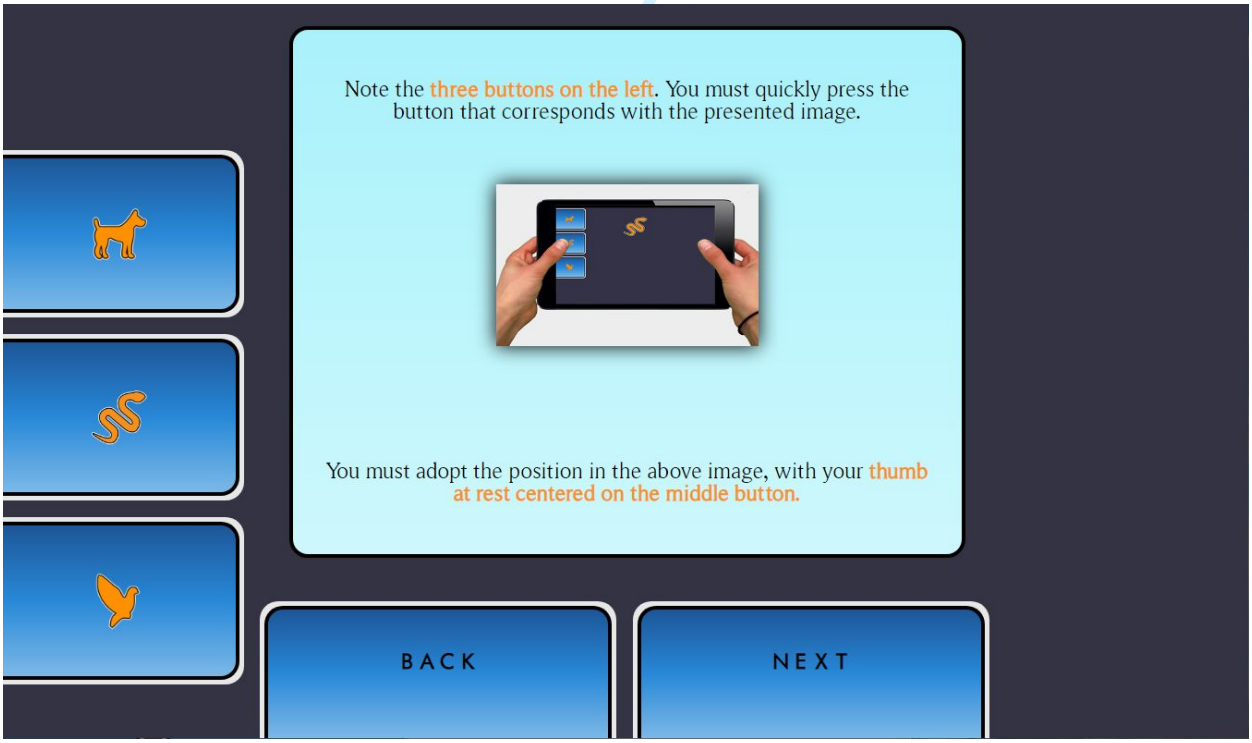
Funding Source:	Health Seniors Pilot Project (HSPP)
Project Title:	The New Brunswick Brain Health Initiative: Preventing Alzheimer's by Lessening Modifiable risk (NB-PALM)
Project Award Amount:	$2.69M
Study Title:	SYNERGIC@Home/SYNERGIE~Chez soi
Study Budget Amount:	$559,049.69

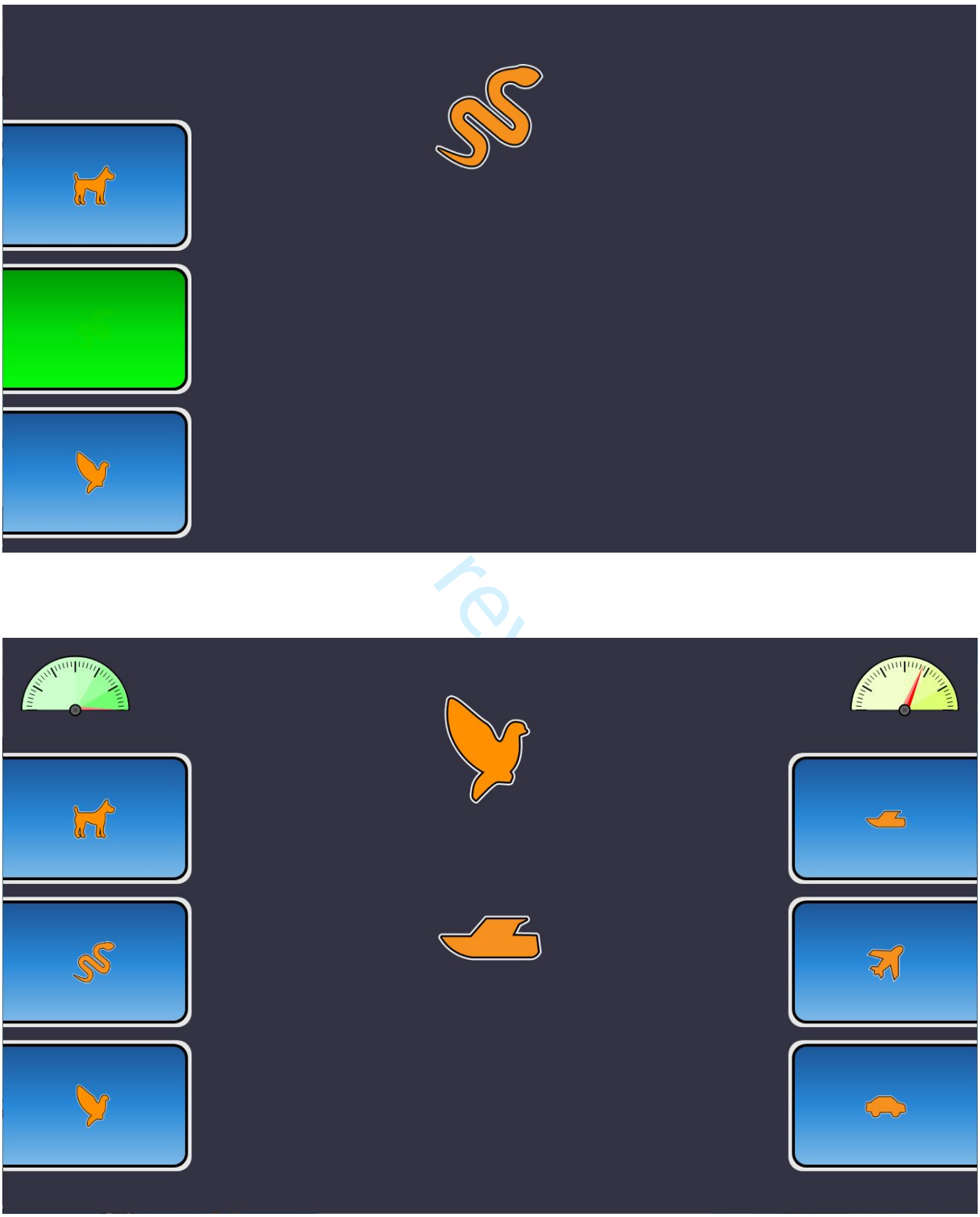
Synergic@Home Study Budget	Study Budget Nov 2020 to end Oct 2022
A) Personnel (include 20% benefits)	
HHN Clinical Research Coordinator	$ 149,760.00
VHN Clinical Research Coordinator	$ 140,400.00
UNB Study Research Coordinator	$ 112,589.28
(4) Intervention Research Assistants	$ 119,172.41
Subtotal	$ 521,921.69
B) Evaluation	
Community Consultations	
Focus Groups	
Surveys	
Venues	$ -
Software	
Subtotal	$ -
C) Travel	
Transportation	
Accomodation	
Meals and Incidentals	
Meeting Space	$ -
Subtotal	$ -
D) Materials	

Office Supplies		
Project Materials		
Printing	$	1,000.00
Postage	$	1,000.00
Other	$	-
Subtotal	$	2,000.00
E) Equipment		
Office Equipment	$	1,000.00
Computer	$	10,500.00
Furniture	$	1,000.00
Special Equipment	$	22,628.00
Other		
Subtotal	$	35,128.00
F) Rent and Utilities		
Rent	$	-
Utilities	$	-
Subtotal	$	-
G) Other (specify)		
Training	$	-
Translation/ Interpretation Fees	$	-
Membership Fees	$	-
Subtotal	$	-
Total Cost		
Total Budget	**$**	**559,049.69**

APPENDIX H: NEUROPEAK DUAL TASK SOFTWARE - SAMPLES







APPENDIX I: PROTOCOL DEVIATION FORMS

Protocol Deviations Log

Subject ID	Description of Protocol Deviation:	Deviation Category*	Deviation Code**	Date Deviation Occurred: (dd/mmm/yyyy)	Date REB Notified (if applicable):	Principal Investigator's Signature	Date Signed (dd/mmm/yyyy)

***DEVIATION CATEGORIES:**

A. Safety
B. Informed Consent
C. Eligibility
D. Protocol implementation
E. Other, specify in log

**DEVIATION CODES: Numbers listed by the sample protocol deviations

Safety (Category A)

1. Not reporting an SAE within 24 hours
2. Laboratory tests not done
3. AE/SAE is not reported to REB
4. Other, specify in log

Informed Consent (Category B)

10. Failure to obtain informed consent
11. Consent form used was not current REB-approved version
12. Consent form does not include updates or information required by REB
13. Consent form missing
14. Consent form not signed and dated by participant
15. Consent form does not contain all required signatures
16. Other, specify in log

Eligibility (Category C)

20. Participant did not meet eligibility criterion
21. Randomization of an ineligible participant
22. Participant randomized prior to completing Baseline Assessment, etc.
23. Randomization and/or treatment of participant prior to REB approval of protocol
24. Other, specify in log

Protocol implementation (Category D)

30. Failure to keep REB approval up to date
31. Participant receives wrong treatment
32. Participant seen outside visit window
33. Use of unallowable concomitant treatments
34. Prescribed dosing outside protocol guidelines
35. Missed assessment
36. Missed visit
37. Other, specify in log

***Study Title**: SYNERGIC@Home*

Protocol Deviation Form (Descriptive)

Subject ID:		**Date:**	mm / dd / yyyy
Description of Protocol Deviation:			
This form completed by:			

Version: 1.0 Nov. 30, 2020

16. REFERENCES

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Protocol for SYNchronizing Exercises, Remedies in GaIt and Cognition at Home (SYNERGIC@Home): Feasibility of a home-based double-blind randomized controlled trial to improve gait and cognition in individuals at risk for dementia

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Protocol for SYNchronizing Exercises, Remedies in GaIt and Cognition at Home (SYNERGIC@Home): Feasibility of a home-based double-blind randomized controlled trial to improve gait and cognition in individuals at risk for dementia

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ABSTRACT

Introduction: Physical exercise and cognitive training have the potential to enhance cognitive function and mobility in older adults at risk of Alzheimer's disease and related dementia (ADRD), but little is known about the feasibility of delivering multi-domain interventions in home settings of older adults at risk of ADRD. This study aims to assess the feasibility of home-based delivery of exercise and cognitive interventions, and to evaluate the relationship between participants' intervention preferences and their subsequent adherence. Secondary objectives include the effect of the interventions on ADRD risk factors including frailty, mobility, sleep, diet and psychological health.

Methods and analysis: The SYNERGIC@Home feasibility trial is a randomized control trial that follows a 2x2 factorial design, with a 16-week home-based intervention program (3 sessions per week) of physical exercises and cognitive training. Participants will be randomized in blocks of four to one of the following four arms: 1) combined exercise (aerobic and resistance) + cognitive training (NEUROPEAK™); 2) combined exercise + control cognitive training (web searching); 3) control exercise (balance and toning) + cognitive training; and 4) control exercise + control cognitive training. SYNERGIC@Home will be implemented through videoconferencing. Baseline and post-intervention assessments at 4 and 10 months follow-up will include measures of cognition, frailty, mobility, sleep, diet, and psychological health. Primary feasibility outcome is adherence to the interventions. Primary analytic outcome is the relationship between pre-allocation preference for a given intervention and subsequent adherence to the allocated intervention. A series of secondary analytic outcomes examining the potential effect of the individual and combined interventions on cognitive, mobility, and general well-being will be measured at baseline and follow-up.

Ethics and dissemination: Ethics approval was granted by the relevant Research Ethics Boards. Findings of the study will be presented to stakeholders and published in peer-reviewed journals and at provincial, national and international conferences.

Keywords: Exercise, cognitive training, remote delivery, videoconferencing, intervention preference, cognition, gait, dementia, home-based intervention program.

Strengths and limitations of this study

- This study is one of the first randomized control trials (RCTs) in Canada to establish the feasibility of fully remote recruitment, consent, assessment and delivery of bilingual, multi-domain, contactless interventions in the home for preventing dementia in at-risk older adults.
- This study will also quantify the relationship between participants' preferences for intervention type and their subsequent adherence to the interventions they were allocated to, which will provide evidence on whether alternate experimental designs that account for preference are scientifically justified.
- Consistent with a feasibility study, the sample is powered for feasibility outcomes rather than cognitive and health outcomes.
- The study intervention duration of 16-weeks is short but sufficient for evaluating feasibility and estimating effect sizes of cognitive and mobility outcomes using remote assessments.
- Elements of the study design are consistent with a full-scale double-blind RCT, including robust screening, randomization and allocation, comprehensive pre- and post-assessments with long-term follow-up assessment and semi-structured exit interview.

1 INTRODUCTION

In 2015, over 46 million people lived with Alzheimer's disease and related dementias (ADRD) worldwide, with 1 new case appearing every 4.1 seconds.[1] The cost associated with these cases is over a trillion Canadian dollars.[1-3] There is no cure for dementia[4]. Recently, there has been a shift in interventional studies on ADRD to targeting pre-dementia states, such as mild cognitive impairment (MCI).[5,6] The SYNERGIC Trial (SYNchronizing Exercises, Remedies in GaIt and Cognition) implemented a multi-domain intervention study for individuals with MCI at sites across Canada[7] in both English and in French. The positive results of multidomain trials like SYNERGIC,[8-10] and the ensuing COVID-19 pandemic, have warranted investigation of a home-based version of the protocol that can reach a wider population of older adults.

The primary goal of the SYNERGIC@Home feasibility trial is to assess the feasibility of in-home delivery of exercise and cognitive training interventions for improving cognitive and physical functioning in older adults at risk for ADRD. Remote delivery of physical exercise interventions has been of significant interest for decades[11,12] but randomised controlled trials (RCT) almost always happen in clinical or academic environments. Building capacity for conducting assessments and interventions in the home of older adults is now critical for ensuring safety and accessibility, with the added benefit of reaching a wider and more diverse population of at-risk older adults[13] while reducing costs of program delivery.[14] Despite the convenience and lower participant burden (e.g., travel to and from clinic), adherence to interventions delivered remotely suffer the same threats to continued participation as traditional delivery methods,[15] such as negative outcome expectation[16] and time constraints.[17] Challenges arising from the use of computer and internet technology may not be significant barrier for younger adults[18] but little is known about how well an older population with or at risk of cognitive decline will adhere to a virtual delivery environment.

There is a growing interest in understanding the impact of preference on clinical trial participation[19] and novel designs have been proposed that incorporate preference (practitioner and/or patient)[20,21] that could improve accrual rates and generalizability of results. Although the concept of preference trials has been around since the 1990's, these studies have focussed on trial designs and randomization schemes where preference is a treatment arm and not a measured outcome. Therefore, the analytic aim of this feasibility trial is to assess if participant's pre-allocation preference for different types of interventions is related to their subsequent adherence to the interventions allocated to them. The landmark Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)[10] supports the efficacy of multidomain interventions, but to date no studies have examined if preference plays a role in adherence to those interventions. Our study will inform whether a future preference trial design is warranted for multi-domain brain health interventions.

1.1 Rationale for the SYNERGIC@HOME Interventions

Aerobic exercise (AE) and progressive resistance training (RT) have been shown to improve cognition, physical capacity and mobility in older adults.[22-25] Both AE[26] and RT[27] trials have reported positive results in improving cognitive performance, with effects lasting more than 3 months.[22,28] Given the potential benefits of combining both types of exercise, we will deliver a

combined (AE+RT) progressive exercise program as our active exercise intervention. The control exercise will include balance and toning (BAT) exercises with equivalent time exposure but no progression. While evidence exists that BAT exercises can improve gait stability[29] and strength,[30] their effect on cognition is not demonstrated.[31]

The rationale for adding cognitive training stems from a plethora of recent research suggesting that improvements in brain plasticity occur after cognitive training,[32-34] and from the potential synergistic effect of combining it with physical exercise. Both simultaneous and sequential exercise and cognitive training have been shown efficacious for improving cognition[35] in older adults; SYNERGIC@Home adopts a sequential approach. Active cognitive training will be delivered using the NEUROPEAK™ program which consists of a dual-task cognitive training regimen designed by our group. NEUROPEAK™ has been shown to improve balance,[36] mobility,[33] and cognition[37,38] in healthy older adults. The control cognitive training will involve basic web searching and watching videos (WS+V), which is expected to have a minimal effect on cognition or mobility.

Finally, sixteen-week interventions of exercise and cognitive training has been conducted in previous studies in a clinical environment which has been shown to give significant and promising results,[39,40] however has not been tested virtually in a home setting.

1.2 Primary objectives and research questions

Our **primary feasibility objective** will measure **adherence to interventions** to answer the question: Will community-dwelling older adults adhere to a 16-week in-home, multidomain, supervised intervention program to improve their health and reduce their risk of ADRD?

To determine if affinity for any one intervention is an important factor in participants' adherence to the study interventions, we designed the Intervention Preference Questionnaire (see Appendix A) that will be used to answer the following questions:

- **Relation to adherence**: Is adherence correlated with receiving the active treatment they prefer as indicated by their pre-allocation preference ratings?
- **Preference attitudes**: Which intervention type (physical exercise or cognitive training) do most participants prefer over the other? What proportion of participants have no particular preference for either intervention?

Our **secondary feasibility objectives** will measure **recruitment rate, retention rate**, **trial experience**, **adverse events**, and **data loss** to answer the questions, respectively: How efficient is recruitment? Do participants stay in the trial for its duration? How satisfied are participants with the interventions? What adverse events are related to the intervention(s)? What is the rate of data loss when doing remote assessments?

2 METHODS AND ANALYSIS

2.1 Study design

SYNERGIC@Home is a home-based, double-blind, randomized controlled trial, with a four-arm full-factorial (2x2) design. It will be administered virtually through a secure online video conferencing platform. Block randomization by four will be used to allocate enrolled participants into one of four arms, with 16 participants in each arm (experimental conditions are in bold):

- Arm 1: **Combined exercise (AE+RT)** + **Cognitive training (NEUROPEAK™)**
- Arm 2: **Combined exercise (AE+RT)** + Control cognitive training (WS+V)
- Arm 3: Control exercise (BAT) + **Cognitive training (NEUROPEAK™)**
- Arm 4: Control exercise (BAT) + Control cognitive training (WS+V)

The experimental design is shown in Figure 1.

<Figure 1>

Assessments will occur at baseline (T0), 4mo (T4), and at 10mo follow-up (T10). The SPIRIT schedule of enrollment, interventions, and assessments is shown in Figure 2.

<Figure 2>

2.2 Participants and setting

Sixty-four older adults (age 60-90 years) at risk of developing ADRD, who live in the province of New Brunswick, Canada, and meet the inclusion and exclusion criteria will be recruited by study staff not involved in the participant's ongoing care. Participants will include francophone and anglophone and geographical recruitment areas will be both rural and urban. All intervention activity will take place in the participant's home.

2.3 Inclusion criteria

- Age 60 to 90 years
- Has a Family Physician/Nurse Practitioner
- Has internet access and basic technology ability (able to send and receive emails)
- Resides in their own home/apartment
- Has access to a home computer and/or a laptop computer device
- Self-reported levels of proficiency in English and/or French for reading, speaking and writing
- Able to comply with scheduled home-based assessments and interventions
- Able to ambulate at least 10 m independently with or without a walking aid
- At risk of developing dementia (see Table 1 and Appendix B):

    a) Mild Cognitive Impairment (MCI)
    b) Subjective Cognitive Impairment (SCI)

c) Cognitively Intact (CI) with 2 or more of the following risk factors: obesity, hypertension, diabetes, cardiovascular disease, physical inactivity, first-degree family history of dementia, dyslipidemia, poor sleep, and poor diet

- Deemed safe by the study physician to participate in exercise[31]
- Preserved activities of daily living (score of > 14/23 on the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale[41]).

<Table 1>

2.4 Exclusion criteria

- Diagnosis of dementia
- Living in Nursing Homes or Adult Residential Facilities.
- Serious underlying disease, which, in the opinion of the study physician would compromise the participant's safety
- Surgery within the last two months or in the coming 12 months
- History of intracranial surgery
- Regularly takes benzodiazepines that would interfere with participation
- Presence of major depression, schizophrenia, severe anxiety or drug/alcohol abuse or other medical illness that would prohibit safe participation
- Current Parkinsonism or any neurological disorder, active musculoskeletal disorders or history of knee/hip replacement that affects gait
- Severe visual and/or auditory impairment
- Intention to enroll in other clinical trials during the same period
- Active participation in an organized and planned exercise program involving aerobic and/or resistance training regimen in previous 6 months

2.5 Recruitment and screening

2.5.1 Recruitment procedures

Recruitment will include posters and posts on community and healthcare provider websites, public and social media, physician offices, and paid newspaper advertisements.

2.5.2 Screening and consenting procedures

Consent will be obtained (see Appendix C) before any screening activities occur. The screening visit will be done virtually using a secure online platform. Following the screening visit, a virtual meeting with the study physician will occur for diagnostic validation and determination of inclusion and exclusion criteria. Participants will then be enrolled and randomized. Participants will indicate on the consent form if acquisition and retention of their saliva sample is permitted for the Polygenic Hazard Score analysis.[42,43]

2.5.3 Study Care Partners

Each participant will be asked to identify a care partner (someone who knows them well) who can assist with some of the cognitive tests and assessments as needed. A care partner is not mandatory unless the participant has MCI or SCI. The care partner will be asked to provide informed consent as well (see Appendix D).

2.6 Randomization and allocation

Randomization will be conducted by research personnel not involved in screening, assessments or interventions using a simple excel formula that generates a random number within a sequence. A block randomization by four will be applied to ensure an appropriate balance between treatment arms. Permuted blocks will be employed to ensure balance over time.

2.7 Blinding and debriefing

To minimize bias, the study will be double-blinded. Research personnel performing the outcome assessments will be blinded to group allocation. Participants will also be blinded to which intervention they received and to study hypotheses. Only the designated research personnel delivering the interventions will know the treatment group that participants belong to and will not reveal the participants' allocation (unless it is medically necessary to do so) until the end of the trial.

2.8 Early withdrawals

Participants will be withdrawn from the study if they: 1) no longer wish to continue their participation in the study (voluntary withdrawal), or 2) in the opinion of one of the study physicians, it is medically necessary to withdraw the participant (medically necessary withdrawal).

2.8.1 Voluntary withdrawal

Participants who inform their Intervention Research Assistant (RA) that they wish to voluntarily withdraw will be asked by the Intervention Coordinator (to protect blinding) if they would be willing to continue their participation in either intervention on its own and return for their follow-up assessments. In this scenario, they will not be withdrawn from the study provided they agreed to at least the T4 assessment. Voluntary non-compliance will be captured by entering 0 values in their intervention logs for the remainder of the weekly session(s) they withdrew from.

If the participant wishes to completely withdraw from the study, s/he will be asked to complete the Exit Survey and will subsequently be withdrawn from the study.

2.8.2 Medically necessary withdrawal

Medically necessary withdrawals may be required if participants experience unanticipated adverse events or changes in medication or health status, that in the judgement of a study physician, places the participant at risk of harm.

If it is deemed medically necessary to withdraw the participant, the Clinical Research Coordinator and/or Study Physician will meet with the participant to explain the reason(s) for being withdrawn from the study, and to inquire about the elements of the study that may have led to their change in health status (if applicable). If willing, the participant will be asked to complete the Exit Survey and will subsequently be withdrawn from the study.

2.9 Interventions

The interventions in this study were adapted from the original SYNERGIC trial,[7] and represent sequentially applied cognitive training and physical exercise. All participants will receive home-based intervention sessions of 90 minutes each three times per week for 16 weeks (48 sessions). Intervention research assistants (RA) trained and certified by the Canadian Society for Exercise Physiology (CSEP) will remotely supervise all sessions via a secure online video conferencing platform. Each participant will be assigned an RA that remains with them throughout the trial. Each session will consist of 20-25 minutes of cognitive training (NEUROPEAK™) or the control cognitive training (WS+V), followed by 50-60 minutes of exercise intervention (AE+RT) or control exercise (BAT). RAs will maintain an intervention log for each participant, documenting start and end times for each activity.

2.9.1 Active Exercise Intervention: Aerobic Exercise + Resistance Training (AE+RT)

Participants receiving the AE+RT intervention will have home-based aerobic and resistance exercise (Table 2). The RA trainers will coach participants throughout the entire session and document their progress. The level of difficulty and progression for the AE+RT exercise will be tailored to their individual level with constant monitoring.

2.9.2 Control Exercise Intervention: Balance and Toning (BAT)

Participants receiving the BAT control exercise will have home-based balance and toning exercises (Table 3). The format of the BAT session including the duration of activities and the amount of coaching will mirror that of the AE+RT session except the exercises will be devoted to improving muscle tone, balance and flexibility. Resistant load and number of repetitions will *not* progress during the trial.

2.9.3 Cognitive Training Intervention: NEUROPEAK™

Participants assigned to the active cognitive intervention will first receive training on how to use NEUROPEAK™ on a tablet computer provided by the study (for uniformity). For this study a custom-written program consisting of a dual-task training program will be used[44-46] that requires participants to maintain and prepare for many response alternatives (working memory) and to share attention between two concurrent tasks (divided attention). Difficulty and progression of cognitive training is tailored to their individual functioning level and performance.

2.9.4 Control Cognitive Intervention: Web Search and Video (WS+V)

Participants assigned to the control cognitive training will received home-based sessions that alternate between two different tasks: web searching for tourist sites and video watching. For the touristic web searching, participants will be required to find hotels, touristic places, and restaurants of their own preference in a city assigned by the RA (a new city will be selected each session). For the video watching, participants will view an educational video about nature and will be asked several questions about it.

2.10 Assessment Outcomes

All feasibility objectives are consistent with current recommendations on conducting feasibility trials.[47]

2.10.1 Primary Feasibility Outcome

- **Intervention Adherence:** Defined as the percent of all intervention sessions attended of the total planned sessions per participant (48-2=46 allowing for 2 missed sessions). To account for partial sessions each intervention session will be treated as a fractional measure: number of minutes training/scheduled session minutes, where scheduled minutes are 50min for exercise interventions and 20min for cognitive interventions.

2.10.2 Secondary Feasibility Outcomes

- **Recruitment Rate**: Defined as the total percent of enrolled participants relative to number of people screened for eligibility.
- **Retention Rate:** Defined as the total percent of enrolled participants who continue throughout the trial and participate in outcomes assessments. Enrollment retention is the % of enrolled participants who complete T4 assessment, and follow-up retention is the % of those who complete the follow-up T10 assessment.
- **Trial Experience:** A mixed methods approach will be used to explore participant experience after the trial using one-on-one interviews with a sub-sample (purposive sampling, up to 5 per arm=20 to reach saturation). All participants will be invited to complete an Exit Survey about their experience.
- **Adverse Events (AEs):** Relationship between AEs severity and relation to trial.
- **Data Loss:** Defined as data lost due to technical failures resulting in data loss include problems with electronic equipment or internet communications, personnel errors such as issuing improperly configured equipment, scheduling errors, and omitting assessments, and participant non-compliance such as omitting responses on surveys or declining assessments.

2.10.3 Primary Analytic Outcomes

Intervention Preference: The primary analytic goal of SYNERGIC@Home is to assess the relationship between participants' adherence to the interventions and their affinity for each intervention going into the trial, as well as other questions about preference. All participants will be given the IPQ at T0, prior to randomization.

The IPQ asks about their affinity for the offered interventions by quantifying interest level and preferences for the interventions. We will explain to participants that their responses on the questionnaire will not in any way influence the intervention group they will be randomly assigned to.

2.10.4 Secondary Analytic Outcomes

Various cognitive and psychological tests will be administered as part of a neuropsychological test battery, as well as gait, mobility, sleep, diet and biological markers (please see Figure 2 for a fuller list).

2.11 Safety evaluation

All adverse events (AEs) and serious AEs (SAEs) that occur between consent and completion of the study will be reported. All AEs and SAEs will be monitored to determine the outcome or until the study physician and/or appropriate research personnel considers it justifiable to terminate follow-up. An SAE will be defined as an event that results in death, is life threatening, requires hospitalization or results in persistent significant disability. AEs will be classified as mild, moderate, or severe. The relationship of the AE and SAE to study procedure will be determined and classified as not related, unlikely, possible, probable, or definite. All AEs and SAEs will be reported to the Safety and Data Monitoring Committee and REBs as required.

2.12 Sample size

Power analysis was conducted using G*Power 3.1 based on our primary analytic goal of assessing the relationship between intervention preference and subsequent adherence to the interventions. Specifically (see 2.13.2 below), we plan on examining correlations among continuous variables with one-tailed analyses at $\alpha = .05$ for two pairs of variables (equivalent to a two-tailed test at $\alpha = .1$, to account for both intervention types). To achieve a power of .8 we would require 48 participants. Assuming a 25% loss, a total of sixty-four participants will be enrolled.

2.13 Statistical analysis

All calculations will be made using the Statistical Package for the Social Sciences (SPSS version 23.0, IBM Inc., Chicago, IL) and Stata (Stata Statistical Software: Release 14, StataCorp LP, College Station, TX).

Descriptive statistics for demographic and baseline characteristics will be provided with means and standard deviations, or medians and the interquartile range where appropriate, for continuous characteristics and frequencies and percentages for categorical variables.

2.13.1 Feasibility outcomes

Adherence to the interventions will be analyzed using a one-sample t-test that will test the null hypothesis that participants complete 50% of their scheduled intervention time. This test will be

used to determine if the adherence is superior to that hypothesized (feasibility target is 75%) or inferior to that hypothesized (questionable feasibility is significantly <50%).

Secondary feasibility outcomes will be analyzed using non-parametric Chi-square tests. Target enrollment retention (75%) and follow-up retention (56%) will be tested against observed frequencies using a Chi-square goodness-of-fit test. This test will be used to determine if the achieved distribution of eligible participants is similar to that hypothesized, superior to that hypothesized or inferior to that hypothesized. Adverse events will be analyzed using a Chi-square cross-tabulation analysis between AEs severity and AEs relation-to-trial. We will use this analysis to test the hypothesis that there is a relationship between AEs severity and being in the trial. Furthermore, we will stratify the sample by treatment arm and use a Chi-square goodness-of-fit test to determine if AEs are distributed differently across treatment arms against the null hypothesis of an even distribution (no relation to treatment arm).

2.13.2 Analytic outcomes

Intervention preference will be analyzed by transforming a set of variables:

- **Interest in the Interventions:** Question 1 in the IPQ rates participant's interest in each intervention independently: exercise (**INT_EX**) and cognitive training (**INT_CT**), on a 0-10 scale.
- **Intervention Preference:** The second question rates their relative preference for either intervention. This will generate a single variable that gives the relative preference (-2 to 2 scale), **PR**, where negative scores and positive scores indicate a preference for exercise or cognitive training, respectively.
- **Intervention Allocated:** The treatment arms can be represented by two dummy (0,1) variables for exercise (**EX_ARM)** and cognitive (**CT_ARM)** where 1=active treatment and 0=control treatment.
- **Adherence to Interventions:** Adherence to the interventions at the end of the trial, for exercise (**AD_EX**) and cognitive training (**AD_CT**), as well as overall **AD**, are continuous scale variables.

What is the relationship between adherence and intervention interest? We will correlate interest level for each intervention with adherence rates calculated from trial logs, using Pearson correlation coefficient ($\rho_{X,Y}$) with a one-tailed alpha of .05. The intervention is powered for testing this hypothesis (see 2.12).

H0: $\rho_{X,Y} = 0$, H1: $\rho_{X,Y} > 0$, where X=**INT_EX** and Y=**AD_EX**

H0: $\rho_{X,Y} = 0$, H1: $\rho_{X,Y} > 0$, where X=**INT_CT** and Y=**AD_CT**

Rejection of the null hypothesis for either test will allow us to conclude that interest level in the intervention type prior to the trial explains a significant amount of variance in adherence to the trial.

Do participants adhere better if they receive the active treatments they prefer? Because some participants will be randomly assigned to the active intervention that matches their preference and others will not, we will transform the **PR** score into a signed logical **PR_MET** (-1=preference not met, 0=no preference, +1=preference met) according to what intervention (**EX_ARM** and/or **CT_ARM**) they were allocated to. We will test the hypothesis that

H0: $\rho_{X,Y} = 0$, H1: $\rho_{X,Y} \neq 0$, where X=**PR_MET** and Y=**AD**

Rejection of the null hypothesis ($p<.05$) will allow us to conclude that adherence to the interventions is significantly influenced by receiving the active intervention they prefer.

How do cognitive and mobility outcomes change as a result of the interventions? Finally, intention-to-treat (ITT) analysis of cognitive and mobility outcomes with a general linear model or linear mixed model approach will be used to measure intervention effects, and we will estimate effect size based on Cohen's descriptors 0.2 = small; 0.5 = moderate; 0.8 = large for cognitive and mobility outcomes listed in Figure 2.

2.14 Data management and monitoring

All electronic data will be stored on a secure platform at the lead university site. Paper copies of assessment forms will be stored in locked cabinets located at the workplaces of remote study research staff, and then transferred to the participating hospital site. Deidentified copies of the data will also be stored on a secure server called LORIS (Longitudinal Online Research and Imaging System) at the McGill Centre for Integrative Neuroscience, McGill University, Montreal, Quebec. All data will be double entered for data quality monitoring. Assessments at T0, T4, and T10 will be video and audio recorded. In addition, a subset of three intervention sessions will be selected to be video recorded per participant for quality control. The video and audio recordings will be deleted once the data have been validated and released by LORIS.

There will be a Data Safety and Monitoring Committee chaired by an independent person not related to the study and will be comprised of the principal investigators, key research staff and researchers, an independent physician and two community representatives (anglophone and francophone). They will review all AEs, SAEs, protocol deviations, progress of the research, and audit study procedures if needed. Protocol amendments will be reported to this committee. All information related to adverse events, protocol amendments, and protocol deviations will be reported to the appropriate Research Ethics Boards.

2.15. Access to data

Access to and analyses of study data stored in LORIS may be granted to qualified persons 12 months after the principal paper answering primary research questions are published. Such requests will be made via email to the Canadian Consortium on Neurodegeneration in Aging [ccna.admin@ladydavis.ca] or via the LORIS Data Access Module. The full protocol and relevant statistical code will also be made available through LORIS.

2.16 Participant and public involvement

The SYNERGIC@Home feasibility study offers older adults and their families a unique opportunity to participate in a fully remote bilingual (French and English) RCT from their home. Participants will be invited to share their experience through questionnaires upon completion of the study as well as through individual semi-structured interviews. Participants will be able to provide direct feedback on trial improvement strategies, which could be implemented in future studies.

2.17 Ethics and dissemination

2.17.1 Research Ethics Approvals

This study is conducted in compliance with International Conference on Harmonization of Good Clinical Practice (ICH-GCP) and all applicable regulatory requirements. SYNERGIC@Home has undergone review and approval from the Research Ethics Committees/Boards of: Horizon Health Network (#2020-2954); Vitalité Health Network (#2020-35), University of New Brunswick (#2020-168), and Université de Moncton (#2021-049). Protocol modifications will be approved by all relevant boards prior to implementation of the changes.

2.17.2 Dissemination Plan and Authorship

Results of the study will be published in peer-reviewed journals, and presented to local stakeholders, and at provincial, national and international conferences. In accordance with the International Committee of Medical Journal Editors (ICMJE) standards, authorship of publications resulting from this study should accurately reflect the academic contribution of individuals to the design and implementation of the trial, analysis of the data and preparation of the manuscript. No researcher shall include identifiable personal health information in any publication or presentation.

3 DISCUSSION

Older adults at risk for ADRD have incident rates of related risk factors several times higher than their cognitively healthy counterparts.[48] Additionally, these individuals at risk for ADRD have an increased risk of falling and mobility decline.[49,50] Physical exercise and cognitive training are emerging as promising non-pharmacological interventions to enhance mobility and cognitive functioning in older adults, especially in pre-dementia states. These interventions have been tested separately, with positive results for physical exercise and cognitive training in improving cognitive function.[9,22,24,27,51] The preliminary success of the original SYNERGIC program and similar combined interventions have illustrated the promising nature of non-pharmacological exercise interventions and cognitive training to enhance cognition for older adults at risk of developing ADRD.[7,52-54]

To our knowledge, this is the first study investigating the feasibility of conducting an entirely virtual, home-based, combined exercise and cognitive training intervention program for older adults at risk for ADRD.

3.1 Significance of establishing feasibility

Establishing the feasibility of conducting a virtual, home-based, multidomain intervention has the potential to inform other researchers on the logistics of designing remote intervention programs. If successful, the methodology and procedures tested in this feasibility trial could set the standard for a new platform in which participants are no longer restricted to intervention studies conducted in a common physical space.

3.2 Significance of examining intervention preference

Establishing if preference bias plays a role in which interventions older adults at risk of ADRD will adhere to is expected to provide unique insights into multidomain trial adherence, and will inform the design of future larger RCTs if it is found warranted to control for such bias using a preference design.[20]

3.3 Significance of secondary outcomes

We expect that the combined active exercise and cognitive training arms will have the greatest improvement (or least decline) of cognitive and mobility outcomes, followed by those who receive one active treatment, and finally those receiving both control treatments having the least improvement (or greatest decline). If successful, the combined interventions will further demonstrate a delay in their progression to dementia, warranting a larger RCT.

3.4 Benefits of interventions

Mechanistically, AE and RT exercises can provoke a cascade of biochemical, physiological, and structural changes in the brain including increases in blood flow, neurotrophic factor release, neurogenesis, immune system efficacy and metabolism. These effects of exercise could combat inflammatory processes and the atrophy of brain structures often associated with aging and ADRD[32,34]. Mechanisms suggested involve modulation of insulin-like growth factor-1 and insulin sensitivity, decreasing inflammation, enhancing release of brain-derived neurotrophic factor pathways, and even a decrease in brain amyloid.[27,55,56] Combined exercise interventions have also shown increased brain volume and muscle mass in older adults.[57] Furthermore, cognitive training has also been shown to improve overall cognition.[37,38] Individuals who practiced monitoring of two tasks at the same time on computer devices have presented with improved connectivity between prefrontal and temporal cortices, areas known to be important for executive functioning and memory, when compared to control participants.[34]

3.5 Strengths and concluding remarks

To our knowledge, this fully remote RCT is the first to test the feasibility of implementing, in two official languages, a combined physical exercise program with cognitive training to improve cognition and mobility in community-dwelling older adults at risk for ADRD. We will also establish the extent to which measuring participant preference for a given intervention is related to subsequent adherence. We believe that this will inform other researchers and scholars on

whether the costs and efforts associated with tailoring interventions in future studies to match participant preferences are worthwhile.

In conclusion, SYNERGIC@Home will build capacity for future research RCT designs using home-based interventions in older adults at risk for ADRD.

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Table 1. Canadian Consortium on Neurodegeneration in Aging (CCNA) Criteria for Cognitively Intact with risk factors, and Subjective and Mild Cognitive Impairment from COMPASS-ND[58]

Group	Core Diagnostic Criteria	Operationalized as
Cognitively Intact (CI) with risk factors	Absence of SCI and/or MCI based on below definitions, with two or more known risk factors for dementia.	Not having SCI or MCI, and having at least two (2) of the following risk factors: • Obesity • Hypertension • Diabetes • Cardiovascular disease • Physical inactivity • First-degree family history of dementia • Dyslipidemia • Poor sleep • Poor diet
Subjective Cognitive Impairment (SCI)[59]	Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.	Answer "yes" to both of the following questions: "Do you feel like your memory or thinking is becoming worse?" and "Does this concern you?"
	Normal age-, sex-, and education-adjusted performance on standardized cognitive tests, which are used to classify mild cognitive impairment (MCI) or prodromal Alzheimer's Disease (AD).	Global Clinical Dementia Rating (CDR) scale = 0, Logical Memory II above Alzheimer's Disease Neuroimaging Initiative (ADNI) education-adjusted cutoffs (≥ 9 for 16+ years of education; ≥ 5 for 8-15 years of education; ≥ 3 for 0-7 years of education); Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) word list recall score > 5; Montreal Cognitive Assessment (MoCA) total score ≥ 25.
Mild Cognitive Impairment (MCI)[5]	Concern regarding a change in cognition.	Report from patient and/or informant of such.
	Impairment in one or more cognitive domains.	One or more of the following: • Logical memory below ADNI cutoffs ((≥ 9 for 16+ years of education; ≥ 5 for 8-15 years of education; ≥ 3 for 0-7 years of education). • ADAS-Cog word list recall < 6. • MoCA score 13-24 inclusive. • Global CDR > 0.
	Preservation of independence in functional abilities.	Score > 14/23 on the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale.
	Not demented.	Global CDR ≤ 0.5.

Table 2. General overview of active intervention exercise regimen structure.

Section	Type of Exercise	Duration (min)
Warm Up	Marching in one place with arm swings for 1 minute	1
	Dynamic Hamstring Stretching: 15 per side	1
	Shoulder Circles: 15 per direction	1
	15 Arm Reaches	0.5
	Torso Twists: 15 per direction	1
	Ankle Circles: 15 per direction per side	2
	Side Stepping for 1 minute	1
	15 Quarter Squats	1
	Total Warm Up Duration	8
Break		1
7 Strength Training Exercises	Chest	5
	Upper Back	5
	Bicep Curls	2.5
	Abdominals	2.5
	Mid/Lower Back	5
	Quadriceps	5
	Hamstrings	5
	Total Strength Training Duration	30
Break		3
Aerobic Exercise	Alternating Video for Participants	15
	Total Aerobic Exercise Duration	15
Break		3
Cool Down	Quadriceps Stretch	0.5
	Hamstring Stretch	0.5
	Calf Stretch	0.5
	2 Hip Stretches	0.5
	Static Torso Rotation	0.5
	Seated Side Bend	0.5
	Back and Shoulder Stretch	0.5
	Chest Stretch	0.5
	Triceps Stretch	0.5
	Neck Stretch	0.5
	Total Cool Down Duration	5
Total Time		**Approx. 65**

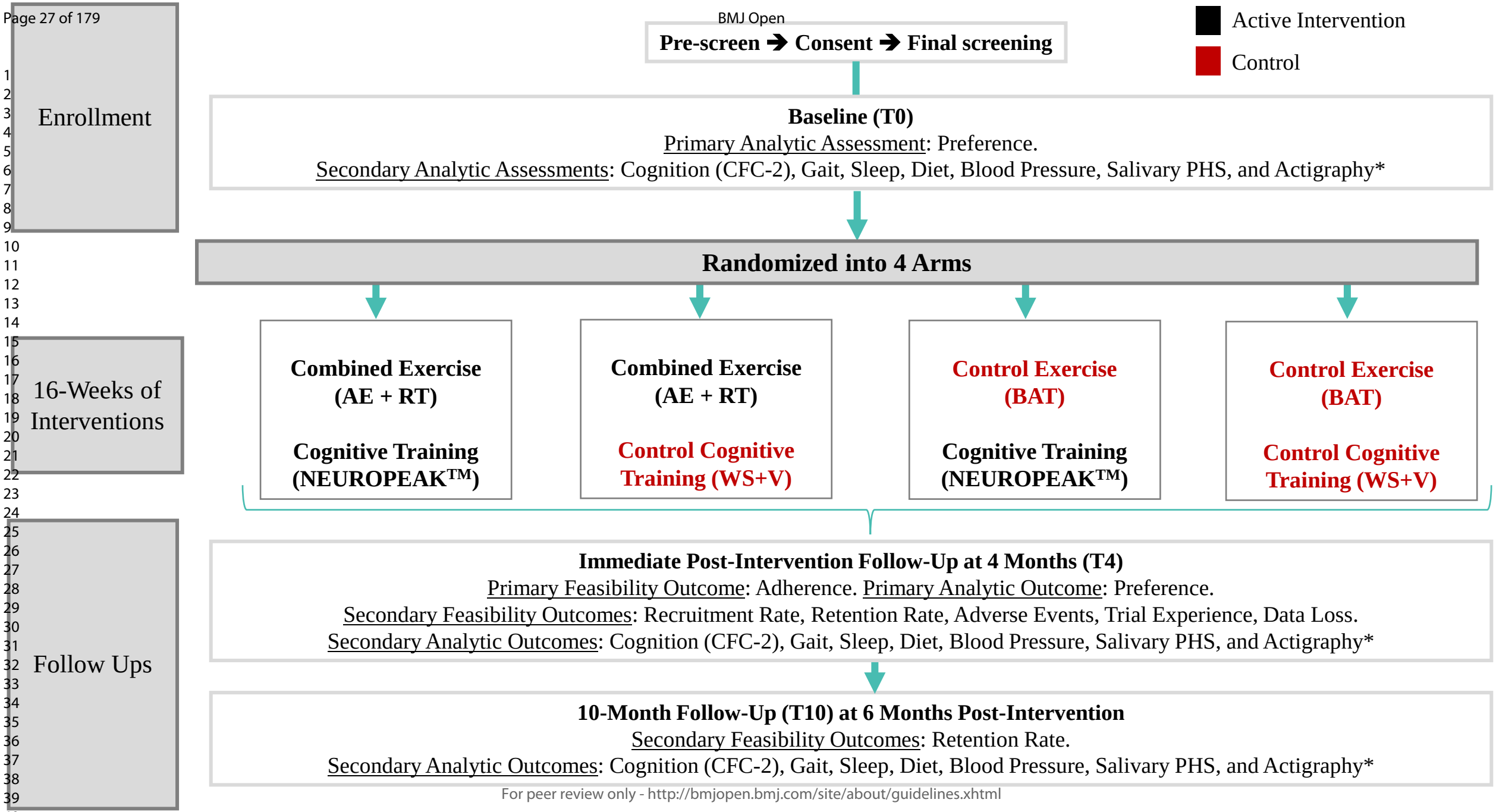
Table 3. General overview of control BAT regimen structure.

Section	Type of Exercise	Duration (min)
Warm Up	Marching in one place with arm swings for 1 minute	1
	Dynamic Hamstring Stretching: 15 per side	1
	Shoulder Circles: 15 per direction	1
	15 Arm Reaches	0.5
	Torso Twists: 15 per direction	1
	Ankle Circles: 15 per direction per side	2
	Side Stepping for 1 minute	1
	15 Quarter Squats	1
	Total Warm Up Duration	8
Break		1
7 Balance and Toning Activities	Standing with Feet Together + Tandem + Single Leg Stand	10
	Core Contractions + Core & Arm Raises	8
	Shoulder Retractions	3
	Isometric Quadriceps Strength	3
	Seated Hamstring Curls	3
	Seated Arm Shake	3
	Total Balance and Toning Duration	30
Break		3
Stretching Exercise	Alternating Video for Participants	15
	Total Stretching Duration	15
Break		3
Cool Down	Quadriceps Stretch	0.5
	Hamstring Stretch	0.5
	Calf Stretch	0.5
	2 Hip Stretches	0.5
	Static Torso Rotation	0.5
	Seated Side Bend	0.5
	Back and Shoulder Stretch	0.5
	Chest Stretch	0.5
	Triceps Stretch	0.5
	Neck Stretch	0.5
	Total Cool Down Duration	5
Total Time		**Approx. 65**

Figure Captions

Figure 1. Design of the SYNERGIC@Home feasibility trial.

Figure 2. SPIRIT schedule of enrollment, interventions and assessments. Time points are: $-t_2$ = 4 weeks prior to allocation; $-t_1$ = 2 weeks prior to allocation; t_0 = Baseline testing and allocation (T0); t_1 = first week of interventions; t_2 = last week of interventions; t_3 = 4mo follow-up assessment (T4); t_4 = 2 weeks prior to 10mo follow-up; t_5 = 10mo follow-up assessment (T10). Interventions are 3x per week for 16 weeks (t_1-t_2). [a] Pre-screening at $-t_2$ consists of exclusion screening and inclusion screening not requiring assessment, such as clinical dementia status and risk. [b] Final screening at $-t_1$ consist cognitive battery #1, diet, sleep and functional risk factors used to designate participants as not demented but having mild cognitive impairment, subjective cognitive impairment, or cognitively intact with 2 or more risk factors. [c] Cognitive battery #1 ($-t_1$, t_3, t_5) consists of: Telephone Cognitivie Screen (TCogS); Full MoCA via Audio-Visual Conference; Lawton-Brody IADL; Cognitive Functional Composite (CFC-2) consisting of ADAS-Cog 3 Immediate Word Recall, Delayed Word Recall, and Orientation, Logical Memory I & II; Clinical Dementia Rating Scale (CDR), and Cognitive Functional Activities Questionnaire. [d] Cognitive battery #2 (t_0, t_3, t_5) consists of: Oral Trail Making Test (Part A & B); Boston Naming Test; ADAS-Cog Word Recognition; DKEFS Phonemic Fluency Test and Semantic Fluency Test; WAIS III Digit Span Test; Digit Symbol Modalities Test-Oral Version. [e] Sleep and activity monitoring for 10 days prior to assessment time points ($-t_1$-t_0, t_2-t_3 and t_4-t_5) using wrist worn Actigraph (GT9X) monitor. [f] Dual task gait battery ($-t_1$, t_3, t_5) consists of: Usual Gait; Seated Dual Task; Dual Task Gait counting backwards by ones, naming animals, and counting backwards by sevens. [g] Exit survey completed at end of study or upon early withdrawal when possible. [h] Polygenic Hazard Score biomarkers assessed via saliva sample at any time point during study.



AE=Aerobic exercise, RT=Resistance training; BAT=Balance and toning; WS+V=Web search and video; PHS=Polygenic Hazard Score; *Using ActiGraph GT9X.

	STUDY PERIOD								
	Enrollment		Alloc.	Post-Allocation					End
TIMEPOINT	$-t_2$	$-t_1$	t_0	t_1	t_2	t_3	t_4	t_5	t_6
ENROLLMENT:									
[a]Pre-screen	X								
Informed consent	X								
[b]Final screening		X							
Allocation			X						
INTERVENTIONS:									
Arm 1: AE+RT + NEUROPEAK™				◆—	—◆				
Arm 2: AE+RT + WS+V (control)				◆—	—◆				
Arm 3: BAT (con.) + NEUROPEAK™				◆—	—◆				
Arm 4: BAT (con.) + WS+V (con.)				◆—	—◆				
ASSESSMENTS:									
Primary feasibility outcomes									
Intervention adherence						X		X	
Secondary feasibility outcomes									
Recruitment rate									X
Retention rate									X
Trial experience (1:1 interview)								X	
Adverse events				◆—	—	—	—	—◆	
Data loss									X
Primary analytic outcomes									
Preference Questionnaire			X			X			
Secondary analytic outcomes									
[c]Cognitive battery #1		X				X		X	
[d]Cognitive battery #2			X			X		X	
Mediterranean Diet Assessment		X				X		X	
Eating Pattern Self-Assessment			X			X		X	
Vitamin D Intake Questionnaire			X			X		X	
[e]Sleep monitoring (Actigraphy)		◆—	—◆		◆—	—◆	◆—	—◆	
Pittsburgh Sleep Quality Index		X				X		X	
Work and Sleep Diary		◆—	—◆						
[e]Activity monitoring (Actigraphy)		◆—	—◆		◆—	—◆	◆—	—◆	
Clinical Frailty Scale		X				X		X	
Generalized Anxiety Disorder		X				X		X	
Geriatric Depression Scale		X				X		X	
Falls Calendar		◆—	—	—	—	—	—	—◆	
Physical Activity Scale for the Elderly			X			X		X	
Life Space Questionnaire			X			X		X	
[f]Dual task gait battery			X			X		X	
One Minute Sit to Stand Test			X			X		X	
Short Form 36			X			X		X	
Get Active Questionnaire		X							
COVID-19 Questionnaire			X						
Technology Ability and Use			X						
STOFHLA Test		X							
[g]Exit survey or early withdrawal debrief				*At end or early withdrawal*				X	
[h]Polygenic Hazard Score		*Any time during study*							

Protocol Title	**SYNchronizing Exercises, Remedies in Galt and Cognition at Home: Feasibility of a home-based double-blind randomized controlled trial to improve gait and cognition in individuals at risk for dementia/SYNchroniser l'ExeRcice et des solutions pour la démarche et la santé coGnItivE Chez soi**
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Protocol Number	SYNH001
NCT Number	NCT04997681
Version	8.0
Date	Feb 20, 2022

Protocol Changes Table

Affected Sections	Change(s)	Rationale

SYNERGIC@Home TRIAL

SYNchronizing Exercises, Remedies in Galt and Cognition @Home

Feasibility of a Home-Based Double-Blind Randomized Controlled Trial to Improve Gait and Cognition in Individuals at Risk for Dementia

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1. EXECUTIVE SUMMARY

Title	SYNchronizing Exercises, Remedies in GaIt and Cognition @Home (SYNERGIC@Home/SYNERGIE~Chez soi): Feasibility of a Home-Based Double-Blind Randomized Controlled Trial to Improve Gait and Cognition in Individuals at Risk for Dementia
Background & Rationale	In Canada, it is estimated that there are currently over 500,000 older adults living with Alzheimer's Disease and Related Dementias (ADRDs). Encouragingly, close to a third of ADRD cases could be prevented by addressing modifiable risk factors[1]. Physical exercise and cognitive training are emerging interventions that have the potential to enhance cognitive function and mobility in older adults with Mild Cognitive Impairment (MCI). The SYNERGIC trial (SYNchronizing Exercises, Remedies in GaIt and Cognition), a large multi-site randomized control trial, showed promising preliminary data that combined aerobic exercise and progressive resistance training (AE+RT) with cognitive training (NEUROPEAK™) had a better effect on cognition than a balance and toning control (BAT) intervention and control cognitive training with web search and video (WS+V) activities. While these interventions were provided face to face in a research facility, little is known about the feasibility of providing these multi-domain interventions in older adults at home.
Study Design	This feasibility study is a factorial design Randomized Control Trial (RCT) in which participants will be randomized (in blocks of 4) into one of four arms: Arm 1: **Combined exercise (AE+RT)** + **Cognitive training** (**Neuropeak)** Arm 2: **Combined exercise (AE+RT)** + Control cognitive training (WS+V) Arm 3: Control exercise (BAT) + **Cognitive training (Neuropeak)** Arm 4: Control exercise (BAT) + Control cognitive training (WS+V) Note: The active interventions are in bold. Arm 4 has the active control interventions.

Study Duration	Estimated duration of entire trial period is approximately 24 months.
Number of Participants	N = 64 community-dwelling older adult participants.
Target Population	All Participants: • Ages 60-90. • Has a Family Physician or a Nurse Practitioner. • Internet access (have regular access to email), technology ability (able to send and receive emails), and access to a home computer and/or laptop computer device. • Self-reported levels of proficiency in English and/or French for speaking and understanding spoken and written language. • Able to comply with scheduled home-based assessments, interventions, treatment plan, and other trial procedures. • Able to ambulate at least 10 meters independently with or without a walking aid. • Being at risk of developing dementia: a) **Mild Cognitive Impairment (MCI).** Diagnosis of Mild Cognitive Impairment, in accordance with the Comprehensive Assessment of Neurodegeneration and Dementia COMPASS-ND study[2] definition (see Table 1). b) **Subjective Cognitive Impairment (SCI).** Diagnosis of Subjective Cognitive Impairment, in accordance with COMPASS-ND study[2] definition (see Table 1). c) **Cognitively Intact with Risk Factors.** Cognitively intact based on COMPASS-ND definition (in Table 1) AND have a history of ***two or more risk factors*** for dementia, defined as the following: ▪ Obesity ▪ Hypertension ▪ Diabetes

	▪ Physical Inactivity ▪ Cardiovascular disease ▪ First-Degree Family History of Dementia ▪ Dyslipidemia ▪ Poor sleep ▪ Poor diet • Preserved activities of daily living, operationalized as a score >14/23 on the Lawton-Brody Instrumental Activities of Daily Living (IADL)[3] scale and confirmed by clinician's interviews. • Must be medically able to participate in the study's exercise training program, as determined by the physician for clearance to participate in combined exercise training program.
Exclusion Criteria	• A diagnosis of dementia. • Participants living in Nursing Homes or Adult Residential Facilities (Special Care Homes) will be excluded. • Serious underlying disease, which, in the opinion of the study physician excludes engagement in interventions or may interfere with the participant's ability to participate fully in the study. • Has had surgery within the last two months or has planned surgery in the coming 12 months that, deemed by the study physician, could interfere with the participant's vision, hearing, mobility or any other ability to participate in the study. • Has a history of intracranial surgery. • Regular Benzodiazepine use by a participant that the study physician determines to be significant enough to interfere with the participants ability to participate in the assessments and interventions in the study will be excluded. • Presence of major depression, schizophrenia, severe anxiety or drug/alcohol abuse or other medical illness that would prohibit them from safely participating in the study or may cause harm to the participant.

	• Current Parkinsonism or any neurological disorder with residual motor deficits (e.g. stroke with motor deficit), active musculoskeletal disorders (e.g. severe osteoarthritis of lower limbs) or history of knee/hip replacement affecting gait performance during the baseline assessment. • Severe visual and/or auditory impairment, which, according to the vision and hearing assessment, precludes the participant from engaging in the trial. • Intention to enroll in other clinical trials during the same time period. • Active participation in an organized and planned exercise program involving aerobic exercise and/or resistance training regimen in previous 6 months.
Study Goal and Objectives	Overall Goals: • To examine feasibility and provide preliminary data on delivering combined physical exercise and cognitive training at home in older adults at risk of ADRD. • To examine participant's preference for each intervention type and to correlate this with subsequent adherence across the trial. • To assess whether the combination of physical exercise with cognitive training is more effective than the individual interventions in improving cognition, frailty, mobility, sleep, diet, and mood. Objectives: **Primary Feasibility Objectives**. Is it feasible to implement a 16-week home-based, multi-domain intervention program aimed at reducing the risk of ADRD in community-dwelling older adults and improving their global health? • **Adherence.** Adherence of study participants will be defined as attendance to a minimum of 75% of study assessment sessions.

	• **Secondary Feasibility Objectives:** Will participants adhere to the study protocol? How satisfied will participants be with the study at the end of the trial? What (if any) adverse events will occur during the trial? • **Recruitment.** A successful recruitment rate is defined as the ability to recruit (and consent) a minimum of 75% of the total recruitment goal of 64 participants across all sites during the enrollment period • **Retention**. A successful retention rate is defined as a minimum of 75% of the total number of recruited participants continuing to trial completion (at the immediate post intervention follow up session). • **Experience and Satisfaction.** Experience and satisfaction will be defined as the results expressed by study participants in responses given to semi-structured interview questions that are designed using Kirkland's four-level model[4]. Used in numerous settings for program evaluation, this framework consists of four dimensions: reaction, learning, behavior, and results. • **Adverse Events.** An adverse event is defined as any incident or adverse outcome that is unexpected, and related or possibly related to participation in the research study. • **Data Loss.** Data loss due to technical failures, personnel errors, and participant non-compliance will be assessed. A minimum acceptable rate of missing data will set at <20%. **Primary Analytic Objectives.** In order to determine if affinity for any one intervention is an important factor in participants' adherence to the study interventions, we designed the Intervention Preference Questionnaire (IPQ, Appendix A) that will be used to answer the question: Is interest level for a given intervention type correlated with subsequent adherence to the intervention? We will also use the IPQ to examine preference attitudes: Which intervention type (physical exercise or cognitive training) do the

	majority of participants prefer over the other? What proportion of participants have no particular preference for either intervention? Do participants adhere better if they receive the active treatments they prefer? Do their attitudes change after completing the active interventions versus the control interventions? **Secondary Analytic Objectives.** What is the estimated effect size (ES) of the interventions on cognitive improvement? What is the standard deviation of the outcome variable? • **Cognitive Improvement**. The ES for cognitive improvement will be defined using Cohen's descriptors: 0.2 = small; 0.5 = moderate; 0.8 = large. • **Mobility Improvement**. Similarly, the ES for mobility improvement will be defined using Cohen's descriptors: 0.2 = small; 0.5 = moderate; 0.8 = large.
Outcome Measures	Primary Feasibility Outcomes • **Adherence to Interventions**. Defined as the mean percent of all Intervention sessions attended of the 48 planned sessions per participant. Primary Analytic Outcome • **Preference.** The primary analytic goal of SYNERGIC@Home is to assess the relationship between participants' adherence to the interventions and their affinity for each intervention going into the trial. All participants will be given the Intervention Preference Questionnaire (IPQ, Appendix A) prior to implementation of the intervention at baseline (T0) and after the 4mo intervention (T4). Secondary Feasibility Outcomes

- **Recruitment Enrollment Rate**: Defined as the total percent of enrolled participants relative to number of people screened for eligibility.
- **Enrollment Retention Rate**: Defined as the total percent of enrolled participants who continue throughout the trial and participate in outcomes assessments.
- **Assessment Tolerability:** Defined as no voluntary dropouts occurring either during or between baseline assessment and prior to allocation to an intervention group.
- **Trial Experience**: Defined as participants' qualitative responses to semi-structured open-ended questions aimed at providing insights on their overall trial experience within the context of the Kirkland evaluation framework.
- **Adverse Events**: Frequency cross-tabulation of AE severity versus AE relation to trial.
- **Data Loss**: Defined as data lost due to technical failures, personnel errors or participant non-compliance.

Secondary Analytic Outcomes

- **Cognitive Functioning**. Cognitive outcomes will be measured using the Cognitive Functional Composite 2 (CFC-2), the telephone version of the Telephone Cognitive Screening (TCogS), the remote version of the Montreal Cognitive Assessment (MoCA), and select items from the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog Plus) as part of our additional cognitive outcomes.
    - **CFC-2**. The CFC consists of the following validated tests[5,6]. The first three tests originate from the ADAS-Cog 13, which has been used as a primary outcome measure in numerous trials with individuals at risk for ADRDs and has recently been shown to be valid for remote use[7-9]: ADAS-Cog Immediate Word Recall, ADAS-Cog Delayed Word Recall, ADAS-Cog

Orientation, Clinical Dementia Rating scale Sum of Boxes cognitive portion (CDR-SB Cog), the Lawton-Brody Instrumental Activities of Daily Living (IADL) and the Functional Activities Questionnaire (FAQ).

- **Additional Cognitive Outcomes**. Additional cognitive outcomes include the Oral Trail Making Test (TMT) A & B[10], the 15-item Boston Naming Test (BNT)[11], Logical Memory I & II[12], ADAS-Cog Word Recognition[7-9], the Delis-Kaplan Executive Function System (DKEFS) phonemic fluency test, and The Delis-Kaplan Executive Function System (DKEFS) semantic fluency test[13], the Digit Span Backward Test[14], and oral version of the Digit Symbol Modalities Test[15].

- **Clinical and Mobility Outcomes**. Medications, blood pressure, heart rate, exercise routines, gait speed, dual task gait parameters, Sit to Stand Test (STST) performance, fear of falling, and fall history using self-reports of falls on a fall calendar.
- **Sleep Patterns**. Sleep habits will be assessed using the 18-item Pittsburgh Sleep Quality Index (PSQI-18) and the Work and Sleep Diary (WSD)[16]
- **Diet Habits.** Diet habits will be assessed using the 14-item Mediterranean Diet Assessment (MDA-14) a short questionnaire for Vitamin D intake, and the Eating Pattern Self-Assessment.
- **Functional Independence and Activity Level**. Additional descriptors of functional health and independence will also be tested including: the activities of daily living--using the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale, the Physical Activity Scale for the Elderly (PASE), the Life Space Questionnaire (LSQ), and the Clinical Frailty Scale (CFS).
- **Mental Health and Well-Being**. Mental health and well-being will be assessed using the Short Form quality of life questionnaire (SF-36),

	the Generalized Anxiety Disorder 7 (GAD 7), Geriatric Depression Scale (GDS-30), and the COVID-19 Questionnaires. • **Health Literacy.** Health literacy will be assessed using the Short Test of Functional Health Literacy in Adults (STOFHLA). • **Technology Use and Ability**. Participant's level of technology use and ability will be assessed using the Functional Assessment of Currently Employed Technology Scale (FACETS).
Data Analysis Plan	Primary Analyses 1- Primary Feasibility Outcome: Adherence to the interventions will be analyzed using a one-sample t-test that will test the hypothesis that participants complete at least 36 of the 48 (75%) scheduled interventions sessions. This test will be used to determine of the adherence is similar to hypothesize, better than hypothesized or worse than hypothesized. 2- Primary Analytic Outcome: We will examine the relationship between interest level in and adherence to the interventions using Pearson's r. This analysis will tell us if adherence to the trial is related to participants' affinity for any one or more interventions.
Significance	In today's technological age, it is becoming more possible than ever to conduct impactful research with participants virtually. A home-based intervention program for older adults at risk for ADRDs has the advantages of allowing participants the freedom, flexibility and comfort to participate from their home—and may potentially lead to enhanced recruitment, retention and reduce social isolation.

2. ABSTRACT

BACKGROUND: Nearly half a million Canadians live with Alzheimer's Disease and Related Dementias (ADRDs), and approximately one third of those cases could have been prevented with early intervention. Early intervention is best applied in pre-dementia states such as in individuals with mild cognitive impairment (MCI)[1,17,18] and those at risk for developing dementia[19-21]. Physical exercise and cognitive training are emerging interventions that have the potential to enhance cognitive function and mobility in older adults with MCI. The SYNERGIC trial (SYNchronizing Exercises, Remedies in GaIt and Cognition), a large multi-site randomized control trial, showed promising preliminary data that individuals in an active exercise intervention combining aerobic exercise with progressive resistance training (AE+RT) *and* in a cognitive training program (NEUROPEAK^{TM}) had better cognitive outcomes than a balance and toning control (BAT) intervention paired with a control cognitive intervention consisting of website searching and watching a simple video (WS+V)[22,23]. While these interventions were provided face to face in a research facility, little is known about the feasibility of delivering these multi-domain interventions at home in older adults at risk for developing ADRDs. Thus, the primary goals of the SYNERGIC@Home feasibility study are to assess the feasibility of the home-based approach and to evaluate the relationship between participant's intervention preferences and their subsequent adherence. Secondary objectives will include the effect of the interventions on cognition, frailty, mobility, sleep, and diet.

METHODS: The SYNERGIC@Home feasibility trial is a randomized control trial (RCT) that will follow a 2 x 2 factorial design, with a 16-week home-based intervention program of combined physical exercises with cognitive training. Sixty-four participants will be randomized in blocks of four to one of the following four arms: 1) combined exercise (AE+RT) + cognitive training (NEUROPEAK^{TM}); 2) combined exercise (AE+RT) + control cognitive training (WS+V); 3) Control exercise (BAT) + cognitive training (NEUROPEAK^{TM}) ; and 4) Control exercise (BAT) + control cognitive training (WS+V). SYNERGIC@Home will be implemented entirely virtually through video and phone conferencing. Baseline, immediate post-intervention follow-up, and 6-month post-intervention follow-up assessments will include measures of cognition, frailty, mobility, sleep, diet, and psychological health. For primary feasibility objectives, we will obtain measures of recruitment and retention rates. For primary analytic objectives, we will

examine the distribution of preference ratings and determine if there is a relationship between preference for a given intervention and subsequent adherence. A series of secondary analytic outcomes examining the potential effect of the individual and combined interventions on cognitive, mobility, and general well-being will be measured at both baseline and follow-up. If we find a relatively equal split in sex our sample, we will conduct gender-based analyses as additional, exploratory research.

EXPECTED RESULTS AND DISCUSSION: The SYNERGIC@Home trial will establish the feasibility of a combined multimodal intervention program delivered at home in older adults. Similarly, it will estimate the frequency and strength of participant preference for different interventions and delineate the relationship between intervention preference and subsequent adherence. It will also build capacity for and pilot the delivery of multi-domain interventions using an entirely home-based protocol with individuals at risk for ADRDs. The SYNERGIC@Home trial will inform future larger scale studies on the feasibility and success of implementing home-based interventions for individuals at risk for ADRDs. Insights gained from this feasibility trial will be instrumental in developing various other at home, remote, and virtual intervention programs for community-dwelling older adults.

Keywords: Exercise, cognitive training, intervention preference, cognition, gait, dementia, elderly, home-based intervention program.

3. BACKGROUND

In 2015, over 46 million people lived with Alzheimer's Disease and Related Dementias (ADRDs) worldwide, with 1 new case appearing every 4.1 seconds[1]. The cost associated with these cases is over a trillion Canadian dollars[1,24,25]. There is no cure for dementia[26]. Recently, there has been an important shift in interventional studies on ADRDs to targeting early stages or pre-dementia states, such as individuals with mild cognitive impairment (MCI)[27,28]. The SYNERGIC Trial (SYNchronizing Exercises, Remedies in GaIt and Cognition) implemented a multi-domain intervention study design on individuals with MCI at various sites across Canada in Ontario, Québec, and British Columbia[22] in both English and in French. The success of the SYNERGIC trial has warranted pilot testing of a similar intervention design to be provided at home across other sites. This protocol is the new application of the SYNERGIC@Home (SYNERGIE~chez soi) feasibility trial—a home-based version of the protocol to be implemented by researchers in New Brunswick. SYNERGIC@Home (SYNERGIE~chez soi) will assess the feasibility of a protocol and intervention future home-based intervention programs. It has added assessments of preference to evaluate the relationship between preference for interventions and subsequent adherence, and it will ultimately inform on the logistics of delivering a remote, home-based intervention to individuals at risk for developing ADRDs.

3.1 RATIONALE OF THE INTERVENTIONS

The preliminary success of the original SYNERGIC program, as well as similar interventions in the literature, have illustrated that non pharmacological interventions to enhance cognition for older adults at risk of developing ADRDs that include physical exercise and cognitive training are very promising[21-23,29]. The rationale for each type of intervention to improve cognition in older adults at risk for developing ADRDs is as follows.

3.1.1 Physical Exercise

Aerobic exercise (AE) and progressive resistance training (RT) have been shown to improve cognitive outcomes, along with improved physical capacity and mobility in older

adults.[30-33] Both, AE[34] and RT[35] trials have reported positive results in improving cognitive performance, with consistent findings also observed after AE interventions lasting more than 3 months.[30,36] RT has been studied less extensively than aerobic training in older adults, particularly in those at risk for developing ADRDs.

3.1.2 Cognitive Training

Cognitive training delivered using the NEUROPEAK™ protocol of the SYNERGIC trial (e.g., a computer based cognitive process training) may improve cognition, mobility, and postural control in older adults. The NEUROPEAK™ program will be used by participants via a program downloaded onto participant's home computers and/or iPad/Android tablet and will consist of a dual-task cognitive training regimen designed by our group that has demonstrated that this type of training can also improve balance in healthy older adults.[37] The rationale for implementing cognitive training in both the SYNERGIC trial and this SYNERGIC@Home trial stems from a plethora of recent research suggesting that improvements in brain plasticity occur after cognitive training.[38-40]

3.1.3 Combined Physical Exercise and Cognitive Training

In addition to the benefits of each intervention alone—there is growing evidence that combining them may lead to a synergic effect as shown in the preliminary analyses of the SYNERGIC trial.[41-43] A recent systematic review of the literature on randomized control trials found that sequential and simultaneous combinations of physical exercise and cognitive training show positive effects on cognition compared to exercise alone or cognitive training alone. Factors such as intervention intensity and frequency were found to be important in facilitating positive outcomes post intervention.[44] Mechanistically, improvements in cognitive functioning are likely the result of changes in neurological factors that improve the brain's functional and structural integrity.

Interventions that include both cognitive and physical exercises show marked benefits to the brain's structural integrity and can be instrumental in delaying

neurodegeneration.[45] Combined physical exercise and cognitive training interventions have also been shown to confer improvements in gait parameters, such as walking speed in older adults.[46] A recent systematic review conceptualizing the literature on combined exercise and cognitive training interventions showed that combined interventions significantly improve gait speed, cognitive functioning, and balance in individuals with MCI[47].

Based on the literature supporting the efficacy of cognitive and exercise-based interventions with individuals at risk for ADRDs—we plan to implement similar interventions in older adults at risk for ADRDs. The critical difference between the SYNERGIC@Home study and other intervention programs discussed thus far is the home-based, virtual nature of SYNERGIC@Home. Thus, the primary goal for the SYNERGIC@Home feasibility study is to evaluate the feasibility of administering a combined exercise and cognitive training home-based program through remote interfaces for older adults at risk for developing ADRDs.

3.1.4 Rationale for Polygenic Hazard Score Testing

MCI is alarmingly prevalent in older populations with over half of individuals with MCI progressing to dementia within five years.[48] There is a growing body of recent evidence suggesting that a cluster of genetic risk factors are associated with the onset of dementia.[49] Specifically, in genome wide association studies (GWAS), a specific allelic expression in 31 single nucleotide polymorphisms (SNPs) appears to be effective in quantifying individual differences in age-specific risk for dementia; this allelic combination is termed an individual's Polygenic Hazard Score (PHS), or sometimes referred to as an individual's Polygenic Risk Score (PRS).[50] In light of the fact that participants in the SYNERGIC@Home study will predominantly consist of individuals at risk for dementia (such as individuals with MCI), one of the research goals of the study is to assess the distribution of PRS/PHS in the study sample. This data will be instrumental in delineating research questions pertaining to efficacy of the study interventions as a function of cognitive risk. Any analyses done with PRS/PHS data will be conducted only during the analysis stage of the research project and will only be

done by research personnel within the study team. The PRS/PHS is currently in the research stages and is not part of routine clinical care at this time.

3.2 SIGNIFICANCE OF THE SYNERGIC@HOME TRIAL

In addition to the convenience of participating in research from the comfort of one's home, there are critical health considerations that uniquely justify the home-based nature of the SYNERGIC@Home feasibility study. In light of the COVID-19 pandemic of 2020 and the associated risks of exposure for older populations, SYNERGIC@Home allows for safe administration of interventions for older individuals at risk for ADRDs. To ensure the safety of our participants, we are planning to administer all interventions (including exercise and cognitive training) using a home-based protocol. The primary platform that we will use is *Zoom for Healthcare©.* Members of the research team will conduct the video-conferences with participants using Zoom for Healthcare© which protects participants' confidentiality through a secured encryption method. Study participants will be assisted by research team members to set up the easy to use Zoom platform on their personal computers or laptop devices. This home-based approach will allow participants to connect with the research team remotely. This feat will not only address the feasibility goals of SYNERGIC@Home, but it will also give older individuals an opportunity to connect with others. This is particularly important at a time during which physical distancing measures may be contributing significantly to the isolation and loneliness in older populations at this time.

We plan to pioneer a flexible home-based program for at-risk individuals and demonstrate the feasibility of implementing this innovative trial with researchers in New Brunswick. SYNERGIC@Home will obtain valuable insights on the logistics of a home-based intervention program in individuals at risk for developing dementia. The insights gained from this feasibility study can be applied to inform future larger scale projects with similar goals. SYNERGIC@Home will be among the first to pilot a home-based combined exercise and cognitive training program in a randomized control trial for older adults at risk for developing ADRDs.

4. RESEARCH QUESTIONS AND OBJECTIVES

All feasibility objectives are consistent with current recommendations on conducting feasibility trials.[51] The overarching question is: Is it feasible to implement a 16-week home-based, multi-domain intervention program to improve health and reduce the risk of ADRDs in community-dwelling older adults?

4.1 PRIMARY FEASIBILITY OBJECTIVES

It is well known that the benefits of exercise, whether physical or cognitive, can only be realized if one engages in the practice. Our primary feasibility outcome is to answer the question: Will participants adhere to the study protocol? Is it feasible to implement a 16-week home-based, multi-domain intervention program to improve health and reduce the risk of ADRDs in community-dwelling older adults?

4.1.1 Intervention Adherence

Minimum acceptable adherence of study participants will be defined as attendance to at least 75% of intervention sessions.

4.2 SECONDARY FEASIBILITY OBJECTIVES

Our secondary feasibility objectives are aimed at evaluating a variety of other feasibility outcomes to answer questions such as: How difficult is it to recruit seniors to a home-based intervention, and do they remain in the study for its duration? Will they tolerate the extensive battery of testing at baseline? How satisfied will participants be with the interventions? What (if any) adverse events are related to the intervention(s)? What is the rate of data loss/missing data?

4.2.1 Recruitment Rate

A successful recruitment rate is defined as the ability to recruit and consent a minimum of 75% of the total recruitment goal of 64 participants during the enrollment period.

4.2.2 Retention Rate

A successful retention rate is defined as a minimum of 75% of the total number of consented participants continuing to intervention completion (at the immediate post intervention follow up session).

4.2.3 Assessment Tolerability

Successful assessment tolerability is defined as no voluntary dropouts occurring either during or between baseline assessment (both clinical and activity assessment batteries) and prior to allocation to an intervention group.

4.2.4 Trial Experience

Trial experience will be defined as a participant's overall experience and satisfaction with the presentation, organization, content, and participation in the SYNERGIC@Home feasibility study.

4.2.5 Adverse Events

Frequency of Adverse Events (AEs) will be documented throughout the trial and analyzed by severity of the AE and suspected relationship to the trial to determine if AEs are greater than chance in the active treatment arms.

4.2.6 Data Loss

Data loss due to technical failures, personnel errors, and participant non-compliance will be assessed. A minimum acceptable rate of missing data will set at <20%.

4.3. PRIMARY ANALYTIC OBJECTIVES

In order to determine if affinity for any one intervention is an important factor in participants' adherence to the study interventions, we designed the Intervention Preference Questionnaire (IPQ, Appendix A) that will be used to answer the question: Is interest level for a given intervention type correlated with subsequent adherence to the intervention?

We will also use the IPQ to examine preference attitudes: Which intervention type (physical exercise or cognitive training) do the majority of participants prefer over the other? What proportion of participants have no particular preference for either

intervention? Do participants adhere better if they receive the active treatments they prefer? Do their attitudes change after completing the active interventions versus the control interventions?

4.4. SECONDARY ANALYTIC OBJECTIVES

What is the estimated effect size (ES)? What is the standard deviation of the outcome variable?

4.4.1. Cognitive Improvement

The ES for cognitive improvement will be defined using Cohen's descriptors: 0.2 = small; 0.5 = moderate; 0.8 = large.

4.4.2. Mobility Improvement.

Similarly, the ES for mobility improvement will be defined using Cohen's descriptors: 0.2 = small; 0.5 = moderate; 0.8 = large.

5. METHODS/DESIGN

5.1 STUDY DESIGN

5.1.1 Treatment Arms

The SYNERGIC@Home feasibility trial is a home-based, randomized, phase II, four-arm factorial design (2x2), double-blind control study. The SYNERGIC@Home feasibility trial will be administered virtually through *Zoom for Healthcare*© (an online video conferencing platform). A total of 64 participants at risk for ADRDs, aged 60 to 90 years of age will be enrolled and randomized, block randomization by four, into one of four arms (**Figure 1**), with 16 participants in each arm. Details pertaining to intervention and control conditions for both physical exercise and cognitive training are described in section 8.

Arm 1: **Combined exercise (AE+RT)** + **Cognitive training (Neuropeak^{TM})**.
Arm 2: **Combined exercise (AE+RT)** + Control cognitive training (WS+V).

Arm 3: Control exercise (BAT) + **Cognitive training (Neuropeak™).**

Arm 4: Control exercise (BAT) + Control cognitive training (WS+V).

Note: Experimental conditions are in bold. Arm 4 includes only the control interventions.

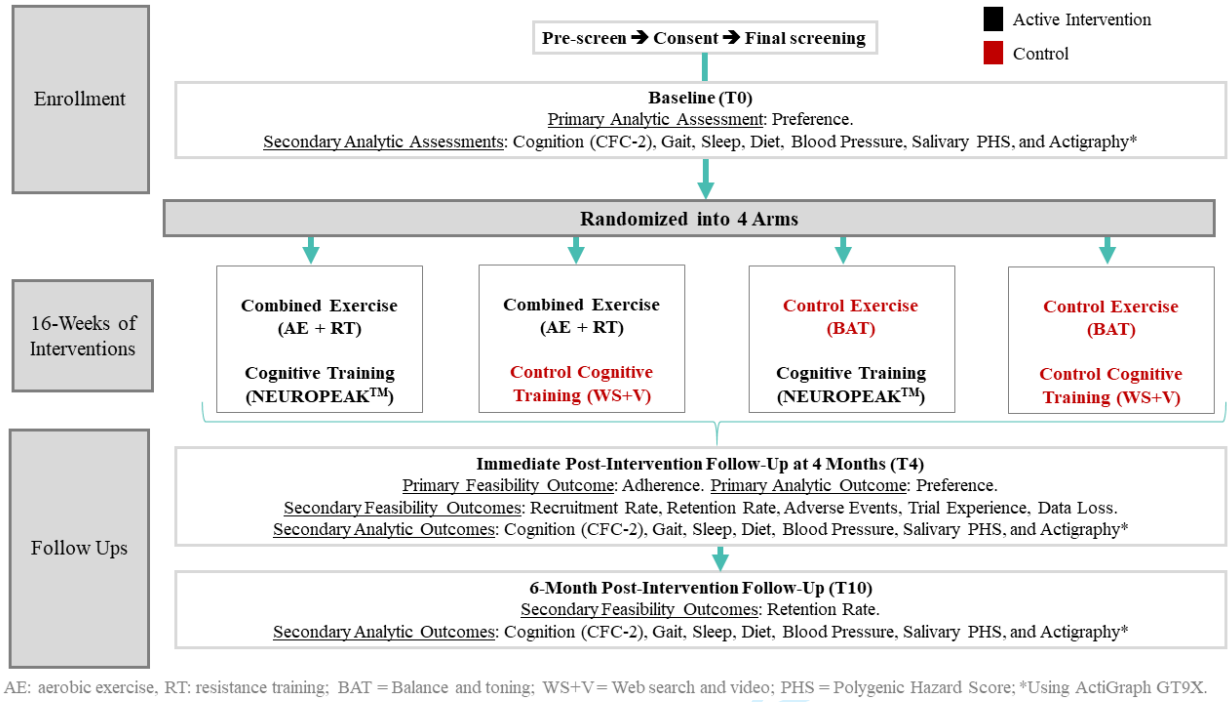


Figure 1. Design of the SYNERGIC@Home trial.

5.1.2 Study Sequence and Duration

Participants will mainly be informed through clinicians as well as recruitment pamphlets in the community or by advertisement on different medias (see 5.2.5 Strategies for Recruitment), potential participants who express an interest in learning more about the clinical trial will be contacted by the research coordinator for the study. A general overview of the study will be discussed and a Prescreening Questionnaire will be completed. This will be used to determine if the participant is eligible to be screened. This will also provide information about why potentially interested individuals are not

able to be screened. This will provide useful information to inform future recruitment efforts in future studies testing these interventions.

During this prescreen, potential participants will be asked if they would prefer to participant in this study in either French or English. This study has the capacity to offer this in both official languages in New Brunswick. Those who wish to participate in English will be directed to the research coordinator site in Horizon Health Network and those who would prefer to participate in French will be directed to the research coordinator the site in Vitalité Health Network.

Following prescreening, informed consent will be obtained and assessments will be done during multiple visits: Screening, Baseline (T0), Immediate post intervention follow-up at 4 months (T4), and 6-month post-intervention follow-up (T10).

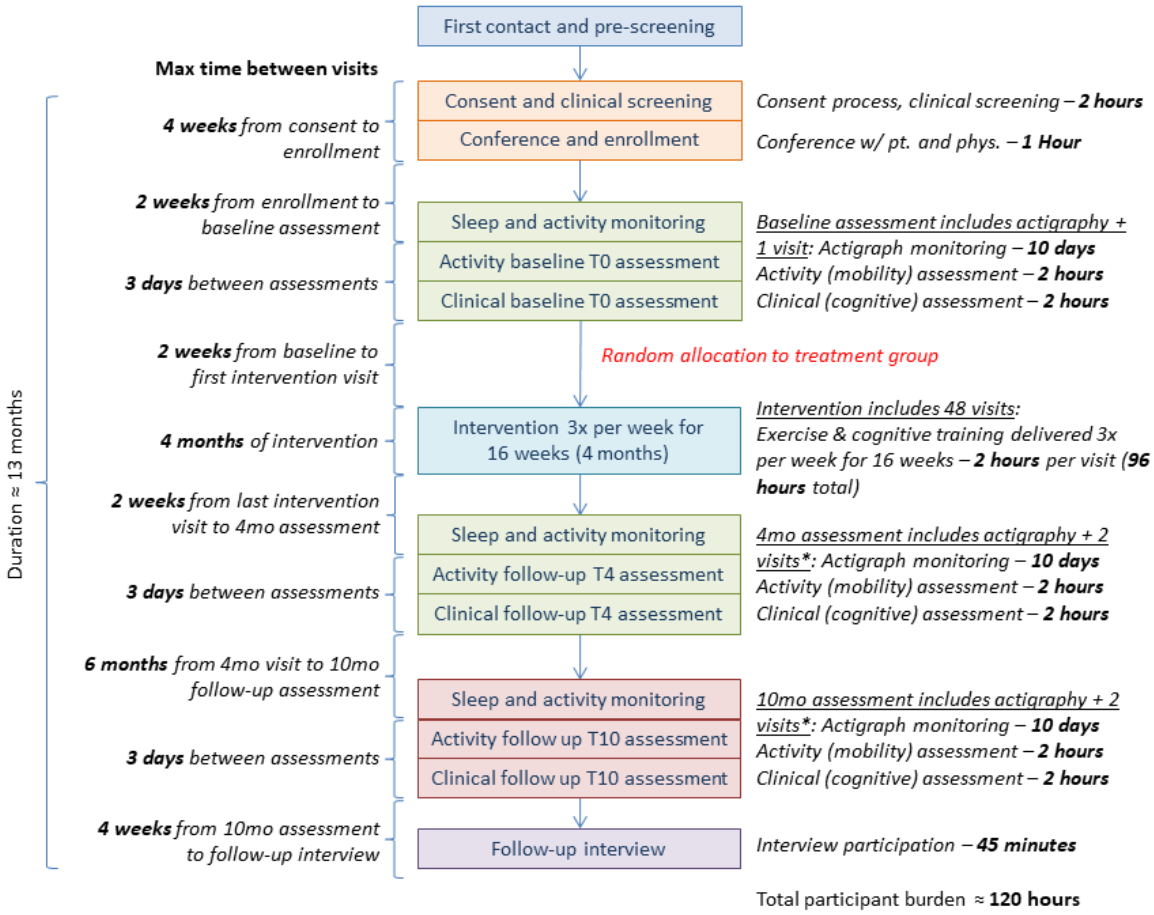
- Screening Assessment – This assessment will be completed over four separate time:
    - **Consent and clinical screening:** The potential participant meets virtually (via *Zoom for Healthcare*©) with the Clinical Research Coordinator/nurse and completes the consenting process. The study physician will be available to answer questions that require physician involvement during the informed consent process. Consent forms will be sent to participants via email if participant has access to a printer and scanner and via mail otherwise. Consenting participants will provide written consent and send back withregular mail their signed consent form. After the research coordinator received the consent, a copy will be sent back to the participant and the assessments will be done by the Clinical Research Coordinator. This is expected to take 2 hours.
    - **Activity (mobility) screening:** The participant meets virtually (via *Zoom for Healthcare*©) with the Kinesiology Research Assist who will conduct a battery of mobility and lifestyle assessments (see section 6.4.7). This is expected to take 2 hours.
    - **Clinical Case Conference and enrollment:** The participant will meet again virtually (via *Zoom for Healthcare*©) with the Clinical Research

Coordinator/Nurse and the Study Physician who will review the results of all of the assessments and finalize the inclusion and exclusion criteria. This is expected to take 1 hour. If the participant is eligible, their baseline assessment visits are scheduled.

- Baseline Assessment (T0) – will be done within 2 weeks of successful enrollment.
- Part of the baseline assessment will consist of actigraphy monitoring for sleep and physical activity levels and two separate assessment visits:
    - **Actigraphy monitoring:** Participants will wear an ActiGraph monitor on their wrist at all times (except when bathing) for 10 consecutive days before their baseline assessment, to measure their sleep patterns and daily activity levels (see section 6.4.7). The instructions and materials needed for this monitoring will be mailed out to the participant and the research coordinator, who will meet with the participant to review the instructions.
    - **Clinical assessment:** The participants meets virtually (via *Zoom for Healthcare*©) with the Clinical Research Coordinator/Nurse who will conduct additional assessments (see Table 2). This is expected to take 2 hours.
- Randomization occurs after the Baseline assessment by allocating the participant to a treatment group from a pre-determined block-randomized sequence (see section 8.3).
- Intervention Phase (T0-T4) – Will start within 2 weeks of completion of the Baseline Assessment. The intervention will continue 3x per week for 16 weeks (see Section 8), for a total of 48 virtual sessions.
- Immediate Post-Intervention Assessment (T4) –Within 2 weeks of completion of the 16 week intervention, participants will wear the ActiGraph for 10 consecutive days. They will also undergo clinical and activity assessment in two separate visits, as described for baseline. (See Table 2) Each assessment visit is expected to take 2 hours.
- Six month Post Intervention Assessment (T10) – Within 2 weeks of the 6 month date after completion of the intervention the participants will wear the ActiGraph

again for 10 consecutive. They will also have the clinical and activity assessments in two separate virtual visits repeated. See Table 2. Each assessment visit is expected to take 2 hours.

Figure 2 shows the sequence of activities and their expected durations.



** Time between clinical and activity sessions will be kept within 3 days with an allowable range of 1-7 days.*

Figure 2. Participant timeline through the trial.

5.1.3 Setting

Participants will be recruited from across the entire province of New Brunswick, Canada. Participants must be residing and have a mailing address in New Brunswick. They will be living in their own homes in the community. Participants can be either Anglophone or Francophone. All study assessments and interventions will be done virtually (via video conferencing through *Zoom for Healthcare*©), in the language of the

participant's choice, by a research team member from the University of New Brunswick (Fredericton), Université de Moncton, Horizon Health Network, and/or Vitalité Health Network.

5.2 STUDY POPULATION

The target recruitment is N = 64 older adults aged 60 to 90 years old at risk of developing ADRDs who meet the following inclusion and exclusion criteria. Medical and clinical information will be collected by self-report by the participant. If clarification is needed regarding this clinical information, contact will be made with the participant's primary care physician/provider with the consent of the participant. Although we will make every effort to recruit equal numbers of Anglophone and Francophone participants, due to provincial distribution it may be expected that only 25-30% of recruits will be Francophone, therefore we will set a minimum recruitment of Francophone participants at 18 and maximum Anglophone recruitment at 46.

5.2.1 Inclusion Criteria

Participants must meet each of the following criteria for enrolment into the study:

- Age 60 to 90 years old.
- Has a Family Physician or a Nurse Practitioner.
- Has internet access (and have regular access to email), and the technology ability (able to send and receive emails).
- Resides in their own home/apartment in the community.
- Has access to a home computer and/or a laptop computer device.
- Self-reported levels of proficiency in English and/or French for speaking and understanding spoken and written language.
- Able to comply with scheduled home-based assessments, interventions, and other trial procedures.
- Able to ambulate at least 10 m independently with or without a walking aid.
- Being at risk of developing dementia:
    a) **Mild Cognitive Impairment (MCI) Group.** Diagnosis of Mild Cognitive Impairment, in accordance with the criteria used in the Comprehensive

Assessment of Neurodegeneration and Dementia (COMPASS-ND) study[2] (Table 1).

b) **Subjective Cognitive Impairment (SCI) Group.** Diagnosis of Subjective Cognitive Impairment, in accordance with the COMPASS-ND study[2] definition (Table 1).

c) **Cognitively Intact with Risk Factors Group.** Cognitively Intact based on COMPASS ND study[2] definition (Table 1)) **AND** have a history of ***two or more risk factors*** for dementia, defined as the following (Table 1):

- **Obesity**: Defined as a Body Mass Index (BMI) > 30 kg/m^2 (as derived from the National Institute of Health BMI calculator[52])
- **Hypertension**: Defined as a documented Systolic Blood Pressure > 140 mm Hg, OR a physician's diagnosis of hypertension, OR presence of physician prescribed medical treatment for hypertension, OR other approaches to treatment for hypertension (i.e., diet or exercise).
- **Diabetes**: Defined as a physician's diagnosis of diabetes, OR presence of physician prescribed medical treatment for diabetes, OR other approaches to treatment for diabetes (i.e., diet or exercise).
- **Cardiovascular disease**: Defined as a physician's diagnosis of angina, myocardial infarction, coronary revascularization or other arterial revascularization, stroke, transient ischemic attack and/or peripheral vascular disease.
- **Physical inactivity**: Defined as inactive, whereby active is defined as engaging in a minimum of 20-30 minutes of physical activity causing sweating and breathlessness, at least two times per week.
- **First-degree family history of dementia**: Defined as a physician's diagnosis of dementia in a first-degree relative, including a parent, sibling, or child.
- **Dyslipidemia**: Defined as a documented total cholesterol > 6.5 mmol/L, OR a physician's diagnosis of hypercholesterolemia, OR presence of physician prescribed medical treatment for

hypercholesterolemia, OR other approaches to treatment (e.g. diet, exercise).

- ☐ **Poor sleep**: Defined as a score of 6 or higher on the PSQI-18 (higher scores indicate poorer sleep).
- ☐ **Poor diet**: Defined as a score of 7 or less on the MDA-14.

- Must be medically able to participate in the study's exercise training program, as by the study physician for clearance to participate in combined exercise training program.
- Preserved activities of daily living, operationalized as a score of > 14/23 on the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale[3] and confirmed by clinician's interviews.

Table 1. Canadian Consortium on Neurodegeneration in Aging (CCNA) Criteria for Cognitively Intact with risk factors, and Subjective and Mild Cognitive Impairment from COMPASS-ND[2]

Group	Core Diagnostic Criteria	Operationalized as
Cognitively Intact (CI) with risk factors	Absence of SCI and/or MCI based on below definitions, with two or more known risk factors for dementia.	Not having SCI or MCI, and having at least two (2) of the following risk factors: • Obesity • Hypertension • Diabetes • Cardiovascular disease • Physical inactivity • First-degree family history of dementia • Dyslipidemia • Poor sleep • Poor diet
Subjective Cognitive Impairment (SCI)[54]	Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.	Answer "yes" to both of the following questions: "Do you feel like your memory or thinking is becoming worse?" and "Does this concern you?"
	Normal age-, sex-, and education-adjusted performance on standardized cognitive tests, which are used to classify mild cognitive impairment (MCI) or prodromal Alzheimer's Disease (AD).	Global Clinical Dementia Rating (CDR) scale = 0, Logical Memory II above Alzheimer's Disease Neuroimaging Initiative (ADNI) education-adjusted cutoffs (≥ 9 for 16+ years of education; ≥ 5 for 8-15 years of education; ≥ 3 for 0-7 years of education); Alzheimer's Disease Assessment Scale-Cognitive(ADAS-Cog) word list recall score >5; Montreal Cognitive Assessment (MoCA) total score ≥25.

Mild Cognitive Impairment (MCI)[27]	Concern regarding a change in cognition.	Report from patient and/or informant of such.
	Impairment in one or more cognitive domains.	One or more of the following: • Logical memory below ADNI cutoffs ((≥ 9 for 16+ years of education; ≥ 5 for 8-15 years of education; ≥ 3 for 0-7 years of education). • ADAS-Cog word list recall <6. • MoCA score 13-24 inclusive. • Global CDR>0.
	Preservation of independence in functional abilities.	Score >14/23 on the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale.
	Not demented.	Global CDR ≤0.5.

5.2.2 Exclusion Criteria

Participants who meet **ANY** of the following criteria will be excluded from the study:

- A diagnosis of dementia
- Participants living in Nursing Homes or Adult Residential Facilities (Special Care Homes) will be excluded.
- Serious underlying disease, which, in the opinion of the study physician excludes engagement in interventions or may interfere with the participant's ability to participate fully in the study.
- Has had surgery within the last two months or has planned surgery in the coming 12 months that, deemed by the study physician, could interfere with the participant's vision, hearing, mobility or any other ability to participate in the study.
- Has a history of intracranial surgery.
- Regular Benzodiazepine use by a participant that the study physician determines to be significant enough to interfere with the participants ability to participate in the assessments and interventions in the study will be excluded.
- Presence of major depression, schizophrenia, severe anxiety or drug/alcohol abuse or other medical illness that would prohibit them from safely participating in the study or may cause harm to the participant.
- Current Parkinsonism or any neurological disorder with residual motor deficits (e.g. stroke with motor deficit), active musculoskeletal disorders (e.g. severe

osteoarthritis of lower limbs) or history of knee/hip replacement affecting gait performance during the baseline assessment.

- Severe visual and/or auditory impairment, which, according to the vision and hearing assessment, precludes the participant from engaging in the trial.
- Intention to enroll in other clinical trials during the same time period.
- Active participation in an organized and planned exercise program involving aerobic exercise and/or resistance training regimen in previous 6 months.

5.2.3 Screen Failures

Screen failures are defined as participants who have completed the Screening Visit but do not meet the inclusion criteria for any of the three populations under study (MCI, SCI, or CI with risk factors).These participants who have failed the screening criteria are ineligible for participation and will be informed that they do not meet the study's inclusion criteria and they will be thanked for their time. They will be encouraged to try to participate in future studies for which they may be eligible and they will have an opportunity to ask questions pertaining to their screening for SYNERGIC@Home.

5.2.4 Study Care Partner

All participants will be asked about whether they wish to have a study care partner such as a spouse, close friend, or relative participate along with them in the trial. Specifically, the care partner's role will be to participate in assessments such as the CDR (as in Table 1) as it requires a study care partner. Care partners will be specifically told that their only role is to help us complete the CDR. If the participant does not have a care partner on the day of their assessment (someone to attend the virtual visit with them), the informant portion of the assessment (the CDR) can be completed by phone.. This will be arranged and completed by the site research coordinator.

A participant will not be excluded from the study if they do not have access to or wish to have a study care partner. However, if the individual during screening is deemed to have MCI or SCI, or the study physician determines that their participation without a study care partner would be a risk—then the participant will be asked to name a study care partner for their participation in the trial.

We believe that in certain instances, such as in the case of couples, some study care partners may also be want to be a participant, however because participants are meant to be blinded as to which experimental condition they are in—we will ask that care partners remain as care partners and do not occupy the role of participant in the study.

5.2.5 Strategies for Recruitment

Community dwelling older adults from both Anglophone and Francophone communities throughout New Brunswick will be recruited using recruitment methods and tools included in Appendix B. These recruitment materials will be available in both official languages. Interested participants will be directed to contact study personnel through the NB-PALM website. A dedicated email address (synergic@unb.ca) will be established. The following recruitment tools will be used to inform potential study participants living throughout New Brunswick about the study:

- Flyer (Appendix B) for posting on various community organization websites, and healthcare provider websites, social media, and in physical offices.
- Email (Appendix B) for distribution to potential study participants referred by others.
- Paid newspaper advertisements (Appendix B) in selected local newspapers.

These tools will be applied in various ways to reach potential study participants. The offices of primary care physicians/providers and specialists will be provided with a study flyer for posting. They will be invited to refer potential participants from their practices. An information handout (See Appendix B) describing the study will be used to familiarize providers with the study. Interested participants can be directed to contact study personnel through the NB-PALM website and visit the dedicated SYNERGIC@Home study page.

Participants currently enrolled in the COMPASS ND cohort study in Saint John, NB will also be contacted to ask about their interest in participating. A follow-up email (Appendix B) will be sent to these potential participants.

Existing community resources such as the Seniors' Centres, Community Health Centres, and Community Mental Health Centres as well as recreation facilities and

libraries will be provided with study information to post on social media (If available) and news/what's happening section of their websites (if available) and / or distribute to their membership via email or hard copy or digital newsletters. The Community Developers working in the Vitalité and Horizon Health Networks have many contacts and connections with formal and informal community groups and networks. Study flyers and a generic email will be provided for distribution to these organizations with whom they are connected. Study information will be provided to two particular provincial programs: Senior Goodwill Ambassador Program and Go Ahead Seniors/Aînés en Marche, both of which provide physical activity and lifestyle modification programs to community dwelling older adults. Similar organizations will also be contacted and invited to distribute information about the study.

Study flyers will be sent to the leadership of provincial English and Francophone seniors' organizations including the Association francophone des aînées et des aînés du Nouveau-Brunswick and NB Senior Citizen's Federation as well as community partners such as the NB Alzheimer's Society for posting on their websites and social media platforms. Targeted provincial organizations like the NB Society of Retired Teachers and Société des Enseignantes et des Enseignants Retraités Francophones du Nouveau-Brunswick (SERFNB) also have websites as well as local branches to whom the study flyer and generic email will be provided for distribution.

Paid newspaper advertisements will be purchased in selected urban and community-based rural newspapers.

When a member of the research team receives an expression of interest email from a potential study participant through the NB-PALM website or other referral sources as listed above, a generic email and/or study flyer and consent package will be sent by email. Once a study participant is ready to give consent, a first contact discussion guide (Appendix B) will be followed by research personnel to ensure that a consistent approach is used to obtain participants' consent.

5.2.6 Strategies for Retention

Retention of participants will be pursued through various methods. News about the study will be posted on the NB-PALM website and participants will be encouraged to

visit the page dedicated to the SYNERGIC@Home. Research personnel will be provided with key messages to use in their interactions with study participants to keep them informed.

Participants that do not comply with the intervention schedule may be withdrawn from the study at the discretion of the research team. Research Assistants will make all efforts to allow participants to have flexibility with their intervention schedules and participants will be allowed to make up missed intervention dates within the week that they occur. Since this is a feasibility study, intervention schedule deviations will be closely tracked but no rigid rule of number of missed interventions before withdrawal occurs will be employed. Each case will be individually evaluated and the benefit of the doubt given in an attempt to observe the compliance behaviour patterns of participants across the entire 16 week intervention duration.

5.3 ASSESSMENTS TOOLS

Participants in all four arms will have a series of validated assessments performed at the Screening, Baseline (T0), Immediate post intervention follow-up at 4 months (T4), and 6-month post-intervention follow-up (T10), as shown in ** Time between clinical and activity sessions will be kept within 3 days with an allowable range of 1-7 days.*

Figure 2. All elements of each assessment will be collected via video conferencing (*Zoom for Healthcare*©). All assessments are itemized in Table 2 (below).

All participants will also be given an ActiGraph (ActiGraph GT9X©) device, a measuring tape, some exercise materials (such as resistance bands or a stretching mat). Please see the complete list in Appendix B). These items will be delivered and picked up by a secure mailing and parcel service or secure courier. The ActiGraph device will be worn on the participant's wrist, hip, or ankle for 10 consecutive days, at three separate time points (baseline, immediate post intervention follow up and 6 month post intervention follow up). These devices will be used to measure nightly sleep patterns and daily activity levels.

Table 2. Assessments across Study Visits for SYNERGIC@Home Trial

Assessment	Clinical Screening	Physician Conference	Clinical T0	Activity T0	Clinical T4	Activity T4	Clinical T10	Activity T10
Consent								
Participant Informed Consent	•							
Study Partner Informed Consent	•							
General Health and Medical History								
Demographics	•							
Medical Vitals	•		•		•		•	
Medical History[1]	•		•		•		•	
Inclusion and Exclusion Criteria		•						
Diagnostic Summary / Diagnostic Validation		•			•		•	
Cognitive Testing								
Telephone Cognitive Screening TCogS	•				•		•	
Full MoCA via Audio-Visual Conference	•				•		•	
Cognitive Functional Composite (CFC-2)								
ADAS-Cog 3 Immediate Word Recall	•				•		•	
ADAS-Cog 3 Delayed Word Recall	•				•		•	
ADAS-Cog 3 Orientation	•				•		•	
Clinical Dementia Rating Scale (CDR) Cognitive	•				•		•	
Functional Activities Questionnaire	•				•		•	
Additional Cognitive Outcomes								
Oral Trail Making Test (Part A & B)			•		•		•	
Boston Naming Test			•		•		•	
Logical Memory I & II	•				•		•	
ADAS-Cog Word Recognition			•		•		•	

Assessment	Clinical Screening	Physician Conference	Clinical T0	Activity T0	Clinical T4	Activity T4	Clinical T10	Activity T10
DKEFS Phonemic Fluency Test			•		•		•	
DKEFS Semantic Fluency Test			•		•		•	
Digit Span Backward Test			•		•		•	
Digit Symbol Modalities Test-Oral Version			•		•		•	
Diet Assessments								
Mediterranean Diet Assessment (MDA-14)	•				•		•	
Eating Pattern Self-Assessment (EPSA)			•		•		•	
Vitamin D Intake Questionnaire			•		•		•	
Sleep Assessments								
Pittsburgh Sleep Quality Index (PSQI-18)	•				•		•	
Consensus Sleep Diary (CSD)	•				•		•	
Sleep and Activity Monitoring				•		•		•
Functional and Activity Level								
Physical Activity Scale for the Elderly (PASE)				•		•		•
Life Space Questionnaire (LSQ)				•		•		•
Clinical Frailty Scale (CFS)	•				•		•	
Lawton-Brody IADL	•				•		•	
Mental Health and Well Being								
Short Form Quality of Life Questionnaire SF36	•				•		•	
Generalized Anxiety Disorder (GAD-7)	•				•		•	
Geriatric Depression Scale (GAD-30)	•				•		•	
COVID-19 Questionnaires	•				•		•	
Health Literacy								

Assessment	Clinical Screening	Physician Conference	Clinical T0	Activity T0	Clinical T4	Activity T4	Clinical T10	Activity T10
Short Test of Func.Health Literacy in Adults STOFHLA			•					
Technology Ability Use								
FACETS				•		•		•
Gait and mobility Assessments[2]								
Usual Gait				•		•		•
Seated Dual Task				•		•		•
Dual Task Gait Assessment				•		•		•
One Minute Sit to Stand Test (STST)				•		•		•
Get Active Questionnaire	•							
Falls Calendar			•		•		•	
Intervention Preference								
Preference Questionnaire				•		•		•
Biological Markers[3]								
Polygenic Hazard Score (PHS)	*Any point throughout trial*							
Study Exit								
Exit Questionnaire	*At time of finishing/exiting trial*							

[1]Full history collected at Clinical Screening and updated thereafter.
[2]Gait velocity assessed using Actigraphy (ActiGraph GT9X).
[3]Self-collected via an optional saliva sample.

6. OUTCOMES

6.1 PRIMARY FEASIBILITY OUTCOMES

6.1.1 Intervention Adherence

Measured as the mean percent of all Intervention sessions attended of the 48 planned sessions per participant.

6.2 SECONDARY FEASIBILITY OUTCOMES

6.2.1 Recruitment Enrollment Rate

Measured as the total percent of enrolled participants relative to number of people screened for eligibility.

6.2.2 Enrollment Retention Rate

Measured as the total percent of enrolled participants who continue throughout the trial and participate in outcomes assessments as follows (see Figure 3):

- Enrollment retention: of those enrolled participants, the % who complete immediate post intervention follow-up (T4) assessment, and;
- Follow-up retention: of those who complete the immediate post intervention follow-up (T4) assessment, the % of participants who complete the 6-month post-intervention follow-up (T10) assessment.

6.2.3 Assessment Tolerability

Measured as the number of voluntary dropouts occurring either during or between baseline assessment (both clinical and activity assessment batteries) and prior to allocation to an intervention group.

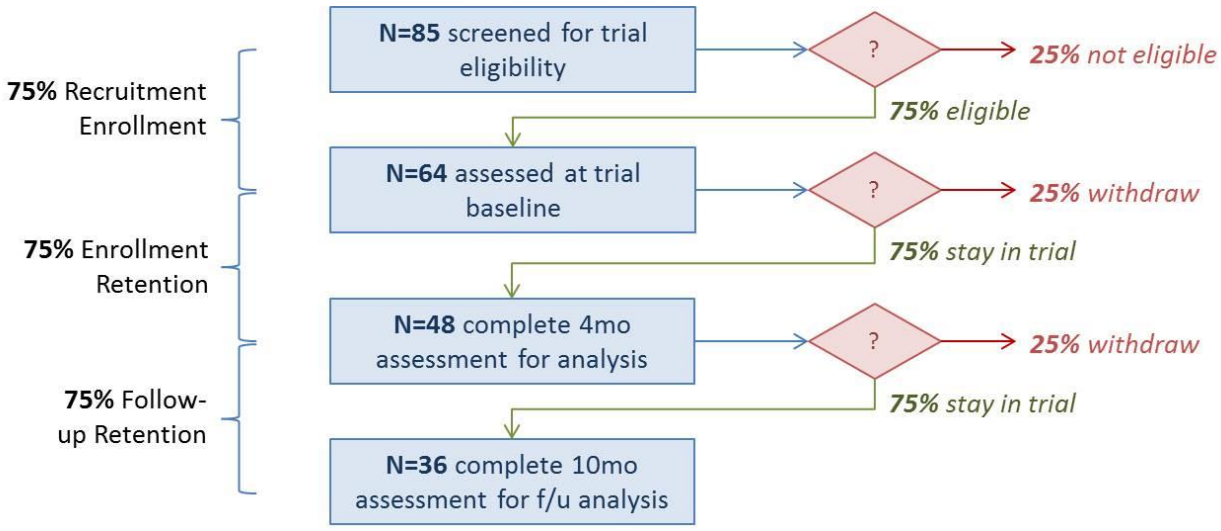


Figure 3. Attrition flowchart for SYNERGIC@Home trial.

6.2.4 Trial Experience

A mixed a methods approach will be used to explore participant experience after the trial. Trial experience is defined as participants' qualitative responses to semi-structured open-ended questions aimed at providing insights on their overall trial experience within the context of the Kirkland evaluation framework.

6.2.5 Adverse Events

Frequency cross-tabulation of AE severity versus AE relation to trial.

6.2.6 Data Loss

Defined as data lost due to technical failures, personnel errors or participant non-compliance. Technical failures resulting in data loss include problems with electronic equipment or internet communications, for example. Personnel errors would include issuing improperly configured equipment, scheduling errors, and protocol deviations (omitting assessments, for example) that result in data loss. Participant non-compliance would encompass data loss due to participants not following instructions or omitting responses on surveys, for example.

6.3 PRIMARY ANALYTIC OUTCOMES

6.3.1 Intervention Preference

The primary analytic goal of SYNERGIC@Home is to assess the relationship between participants' adherence to the interventions and their affinity for each intervention going into the trial. All participants will be given the Intervention Preference Questionnaire (IPQ, Appendix A) prior to implementation of the intervention at baseline (T0) and after the 4mo intervention (T4).

The IPQ asks participants various questions about their affinity for the offered interventions by quantifying interest level and preferences for the interventions. When administered at T0 (prior to randomization) we will explain to participants that their responses on the questionnaire will not in any way influence the intervention group they will be randomly assigned to.

The IPQ has five questions. Question 1 asks participants to rate their interest level in each intervention type (exercise training and cognitive training independently) on a 0-10 visual analog scale. Question 2 asks participants to rate their preference between the two interventions on a 5-point scale:

-2=Strong preference for Exercise training;
-1=Slight preference for Exercise training;
0=No preference;
1=Slight preference for Cognitive training;
2=Strong preference for Cognitive training.

Questions 3 to 5 are open ended questions that will provide context to participants' responses from questions 1 and 2.

Validation: The intervention preference questionnaire has been created specifically for this feasibility trial, thus it has not been previously validated.

6.4 SECONDARY ANALYTIC OUTCOMES

6.4.1 Demographic Information and Medical History

Demographic information, chronic diseases, vascular risk factors (VRFs), medical history, medications, fall history using self-reports of falls on a fall calendar will be collected at the screening visit. In addition, medical vitals will be assessed including weight, height, blood pressure and heart rate (using a simple blood pressure cuff that will be provided to the participant).

Validation: This information will be collected by self-report and will be done via video conference. While medical history taking have not been systematically evaluated in this setting it is commonly used in remote telemedicine and is considered an acceptable practice and a reasonable alternative to face to face history taking. We are confident that results will be similar to those assessed in person. We are confident that participants will be able to adequately measure their vitals and report the findings to the study personnel.

6.4.2 Cognitive Testing

Cognitive outcomes will be measured using the Cognitive Functional Composite 2 (CFC-2), the Telephone Cognitive Screening (TCogS), the Montreal Cognitive Assessment (MoCA), and select items from the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog Plus).

TCogS and MoCA.

- **The Telephone Cognitive Screening TCogS** is a widely used tool that measures cognitive function in older individuals. The telephone version of the CogS has been standardized and will be administered via video conferencing. It consists of a 26-point assessment that measures orientation, registration, attention and calculation, recall, and language with lower scores indicating cognitive impairment[55,56].
  Validation: The TCogS will be administered using the standardized and validated telephone version[56-58] via video conferencing.

- **The Full MoCA via Audio-Visual Conference** consists of a 30-point test assessing the following items: short term memory recall, visuospatial abilities, executive functioning, phonemic fluency, verbal abstraction, attention, concentration, working memory, language, and orientation[59].
  Validation: The remote version of the MoCA will be administered using the validated online full MoCA (version 8.1) via audio-visual conference[58,60].

Clinical Dementia Rating Scale (CDR). The CDR is a validated 5-point composite scale used in longitudinal Alzheimer's Disease (AD) research to characterize cognitive and global function performance applicable to AD and related dementias.[61] Information is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g. family member). The three cognitive domains include memory, orientation, and judgment/problem solving and the three functional domains include community affairs, home and hobbies and personal care. The five possible scores for each domain [0, 0.5, 1, 2, and 3] represent a range of impairment (e.g. score of 0 represents no impairment and a score of 3 represents severe impairment).

Validation: The CDR is a questionnaire which can be administered via any interface (face-to-face or video conferencing). We will administer it via video conferencing. Clinical experience dictates that this method of delivery of the CDR will be sufficient.

Cognitive Functional Composite (CFC-2). The CFC consists of the following tests[5,6]. The first three tests originate from the ADAS-Cog 13, which has been used a primary outcome measure in numerous trials with individuals at risk for developing ADRDs[7,8].

a) **ADAS-Cog Immediate Word Recall**. Participants are presented with 10 high imagery words and are given three trials to learn and recall them. The average of the 3 trials is computed for the final score.
   Validation: This is a subtest of the ADAS-cog, which has been validated for remote, virtual use[9].
b) **ADAS-Cog Delayed Word Recall**. Participants are asked to recall the 10 high imagery words presented during the immediate word recall task after a delay of approximately 5 to 10 minutes.

Validation: This is a subtest of the ADAS-cog, which has been validated for remote, virtual use[9].

c) **ADAS-Cog Orientation**. Participants are asked 8 questions pertaining to their identity, the place, and the time.
Validation: This is a subtest of the ADAS-cog, which has been validated for remote, virtual use[9].

d) **Clinical Dementia Rating Sum of Boxes (CDR-SB) Cognitive portion.** The CDR is being administered in full for this trial. The sum of boxes score simply reflects the total score from all domains assessed. The CFC-2 includes the CDR-SB for all cognitive portions, which consists of a sum of scores obtained from the following CDR domains: memory, orientation, and judgement & problem solving.
Validation: The CDR is a questionnaire which can be administered via any interface (face-to-face or video conferencing). We will administer it via video conferencing. Clinical experience dictates that this method of delivery will be sufficient.

e) **Functional Activities Questionnaire.** This questionnaire will be administered as part of the functional assessments of this trial. It measures participant's ability to engage in instrumental activities of daily living via questionnaire assessing activities such as preparing meals and managing personal finances[3]. Responses range from 0 (normal ability) to 3 (dependent for functioning) with total scores ranging from 0 to 30. For the CFC-2 total score, this score will be added to obtain a total CFC-2 composite score.
Validation: This assessment of functional independence is collected via questionnaire, which can be administered via any interface (face-to-face or video conferencing). We will administer it via video conferencing.

Additional Cognitive Outcomes. We will also administer additional cognitive outcomes including the following:

- **The Oral Trail Making Test (TMT) A & B** is a two-part test that assesses attention speed, and mental flexibility and has been widely used in clinical settings for assessing deficits in attention and executive functioning.[62] The oral version of the Trail Making Test provides an assessment of sequential set-

shifting without the motor and visual demands of the written Trail Making Test. [10] For Part A, participants are asked to count from 1 to 25 as quickly as possible. For Part B, participants are asked to switch between number and letter in sequential order (e.g. 1-A, 2-B, 3-C) until the number 13 is reached. Scoring is the total time to complete each part.

Validation: The oral trail making tests A & B are validated assessments that can be conducted remotely without the need for the traditional paper and pencil face-to-face modality.[10] We will administer them both using video conferencing.

- **The Boston Naming Test (BNT)** assesses visual confrontational naming and asks participants to name simple line drawings of objects.[11]

  Validation: To our knowledge, the BNT has not yet been validated for remote, virtual, or phone use, thus we show participants each item on the screen during the video conference. It is noteworthy that this mode of administration (in comparison to face-to-face-assessment) has not been methodically validated.

- **Logical Memory I & II** (Story A) from the Wechsler memory scale assesses memory and free recall[63]. This test will be completed via video conferencing in which the participant will be instructed to listen to a story and repeat it back after it has been read to the best of his/her ability. The participant will then be asked to recall the story approximately 30 minutes later.

  Validation: Because this test is an auditory test to begin with (i.e., it does not require visual stimuli such as paper and pencil questionnaires), it can be administered using any modality (face-to-face or via video conference). We will conduct it via video conferencing.

- **ADAS-Cog Word Recognition**. Participants are presented with a list of 12 words and are then asked to identify the words among a list of distractor words.

  Validation: This is a subtest of the ADAS-cog, which has been validated for remote, virtual use[9].

- **DKEFS Phonemic (Letter) Fluency**. The Delis-Kaplan Executive Function System (DKEFS) phonemic fluency test measures phonemic verbal fluency, whereby participants are given 60 seconds to produce as many words that begin with the letter C, followed by a second 60 second trial with the letter “F”, and a third 60 second trial with the letter “L”[13].

Validation: This test has been validated for telephone use, as results are statistically similar to those done face-to-face[64]. We will administer it via video conferencing.

- **DKEFS Semantic Fluency Test**. The Delis-Kaplan Executive Function System (DKEFS) semantic fluency test measures speed and flexibility of verbal thought, whereby participants are asked to name as many items as possible in a specified category (vegetables and animals). Unique responses during the first minute of each category are counted[13].
  Validation: This test has been validated for telephone use[14]. We will administer it via video conferencing.
- **Digit Span Backward Test**. The digit span test is an auditory attention task, in which participants are asked to recall a series of numbers forward and backward.
  Validation: This test has been validated for telephone use[14].
- **Digit Symbol Modalities Test-Oral Version**. This is a timed task that gives participants 120 seconds to orally match geometric figures with specific numbers according to a defined key (specifying which symbols are assigned to which numbers) that is provided at the top of the stimulus page[15,65].
  Validation: The oral version of this test has been validated[15] .We will administer it via video conferencing.

6.4.3 Sleep Patterns

Sleep habits will be assessed using the 18-item Pittsburgh Sleep Quality Index (PSQI-18)[66] and the unpublished Work and Sleep Diary (WSD).

Validation: Both sleep assessments are done via validated questionnaires which can be administered via any interface (face-to-face or video conferencing). We will administer them via video conferencing.

6.4.4 Diet Patterns

Diet habits, food consumption, and nutrition intake will be assessed using the 14-item Mediterranean Diet Assessment (MDA-14)[67], the Eating Pattern Self-Assessment (developed by the CCNA team), and a short questionnaire for Vitamin D intake.[68]

Validation: All diet assessments are done via questionnaires which can be administered via any interface (face-to-face or video conferencing). We will administer them via video conferencing.

6.4.5 Functional Independence and Activity Level

Additional descriptors of functional health and independence will also be tested including: the activities of daily living—using the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale[3], the physical activity scale for the elderly (PASE)[69], and the Life Space Questionnaire (LSQ)[70].

Validation: All of the above assessments of functional independence and activity level are collected via questionnaires which can be administered via any interface (face-to-face or video conferencing). We will administer them via video conferencing.

Clinical Frailty Scale (CFS). We will also obtain a measure of clinical frailty using the Clinical Frailty Scale. This will allow for a determination of the clinical frailty of the participants. This assessment will be performed by the Clinical Research Coordinator/nurse using the 9-point CFS instrument. Excluding the last two categories which are not applicable to our sample (bedridden), it is effectively the validated 7-point CFS[71].

Validation: The use of the CFS by remote video conferencing has not been evaluated but it is thought that this will be a reasonable way to gather information needed to determine the CFS score. The information needed is obtained by history and self-report from the participant.

Lawton-Brody Instrumental Activities of Daily Living (IADL) scale. The IADL will be administered as part of the functional assessments of this trial and serve as an inclusion criterion of preservation of function (score > 14/23). It measures participant's ability to engage in instrumental activities of daily living via questionnaire assessing activities such as preparing meals and managing personal finances[3]. Total scores range from 0 to 23, with 23 being totally independent.

Validation: This assessment of functional independence is collected via questionnaire, which can be administered via any interface (face-to-face or video conferencing). We will administer it via video conferencing.

6.4.6 Psychiatric Health and Well-Being

Psychiatric health and well-being will be assessed using the Short Form quality of life questionnaire (SF-36)[72], the Generalized Anxiety Disorder 7 (GAD-7)[73], Geriatric Depression Scale (GDS-30)[74], and the COVID-19 Questionnaires—that aim to delineate the impacts of the COVID-19 pandemic of 2020[75]. An additional New Brunswick (NB) COVID 19 questionnaire will also be administered. This tool has been adapted from a telephone survey conducted by Ability NB used to evaluate the effect of COVID 19 on participants living in the community who have physical disability.

Validation: The psychiatric health and well-being assessments (SF-36, GAD-7, and GDS-30), are well-established questionnaires, which can be administered via any interface (face-to-face or video conferencing); we will administer them via video conferencing. The COVID-19 questionnaires have been specifically developed during the pandemic of 2020. They have not yet been validated. We will administer them via video conferencing.

6.4.7 Health Literacy

Health Literacy will be assessed using the abbreviated version of the Test of Functional Health Literacy in Adults (TOFHLA)[108].The short version, STOFHLA, consists of 2 prose passages and 4 numeracy items.

Validation: A preliminary study demonstrated that the results of the S-TOFHLA administrated through a computer were equivalent to those when administered on paper.[109] We will administer the S-TOFHLA in a digital format, over video conferencing.

6.4.8 Technology Ability and Use

To assess the extent to which participants are comfortable with and familiar with basic technology, we will administer the Functional Assessment of Currently Employed

Technology Scale (FACETS)[76]. The FACETS is a 10-item questionnaire with possible responses falling on a Likert-type scale, and higher scores indicating more frequent use of technology domains[76,78]. While the FACETS will not be used as part of the eligibility criteria, we feel that it will be a worthwhile endeavor to delineate the potential change in technology use over the course of the home-based remote trial.

Validation: The FACETS is typically administered via questionnaires which can be administered via any interface (face-to-face or video conferencing). We will administer it via video conferencing.

6.4.9 Gait and Mobility Assessments

The Get Active Questionnaire (GAQ)[53] will be used at screening to ensure to it is safe for participants to exercise, and will be reviewed by the intervention RA (after allocation) when tailoring the participant's intervention to their level of function.

Gait performance will be recorded using actigraphy, which can be used to determine spatiotemporal gait parameters and can be simply placed on the participant's hip. Specifically, gait parameters will be measured using the ActiGraph GT9X (the same device they use for sleep and activity monitoring), during which participants engage in a series of gait tasks via video conferencing with a study Kinesiology Research Assistant. If video conferencing poses any issues on participant's the ability to position the screen to allow the researcher to visualize the trial—then phone communication will commence instead. In all walks, participants will start 1 meter before the beginning of the 6-meter allocated space and continue to travel 1 meter past the end of the space. If a 6-meter space is not available, then participants will be asked to use a 3 meter corridor within their home and for analyses, we will extrapolate based on this subset data. The procedure of allowing extra space prior to and after the walking distance is in place to ensure steady state walking and to minimize any effects of acceleration and de-acceleration during the course of the walk[79]. The reason for a 3 meter minimum distance is because this distance has been shown to sufficiently measure gait speed in older adults[80]. To avoid tripping or falls, participants will be instructed to walk on a smooth surface with no barriers.

Validation: Reliability has been previously established for this protocol in people at risk for developing ADRDs and those with MCI[81] and an instructive video can be found at the "www.gaitandbrain.com/resources" as the Guidelines for Gait Assessments in CCNA". However, the virtual administration of this procedure has not yet been validated, thus the SYNERGIC@Home study will be the first to test its feasibility and its use at home.

The dual-task conditions selected are based on previous research which demonstrated that counting backwards requires both working memory and attention[82] and naming animals is related to verbal fluency, which relies on semantic memory[83]. The evaluator will record any counting errors during walking so that it can be compared with the same mental tasks while seated. The seated assessments will be timed at 10 seconds and will be performed in the beginning of all cognitive assessments (at least one hour prior to the dual task gait condition) to prevent practice effects in dual-task gait performance. Seated gait assessments will be assessed via video conferencing, whereby participants are asked to complete the cognitive portion of the dual task gait test while seated. Gait assessments will be then follow and will also be conducted using video conferencing, whereby participants are asked to walk towards the camera while engaging in the cognitive tasks listed above. For details pertaining to the dual task protocol, please see our detailed manual of procedures.

- **Seated Dual Task.** Participants will be first asked to complete the cognitive tasks involved in the dual-task conditions, while seated. Specifically, participants will be asked to name as many animals as they are able to, count backwards by 1's, and count backwards by 7's while seated. This will be used as a comparison to determine the extent to which the dual-task reduces performance (their dual-task cost).
- **Single-Task Gait Assessment**. Gait velocity will be assessed as the time taken to walk a specified distance (minimum 3 meters) using actigraphy (ActiGraph® GT9X Systems, Inc.). This method has been used in previous studies with older adults to measure gait parameters[84]. Participants will be instructed to measure a space (minimum 5 meters) in their home and to connect with the research team via video conferencing during the gait assessments. Their gait velocity will be

measured 3 times. Gait variability of spatial and temporal gait variables (stride time, stride length, double support time and step width) will be measured and the coefficient of variation calculated (CV = (standard deviation / mean) x 100). The CV is a standardized measure of variability allowing comparison of gait variables measured in different units, having different means and range of values.

- **Dual-Task Gait Assessment**. Following single-task gait, participants will perform three walks, once each under the following dual-task conditions: walking while naming animals, counting backwards from 100 by 1's, and counting backwards from 100 by 7's. Gait walks will occur within participant's homes, ideally in a large corridor or living space—but even in small spaces of at least 3 meters are suitable. Dual-tasking assessments will permit calculation of dual-task cost for all gait variables of interest.[85,86].

Additional measures of gait and mobility that we will assess include falls (via a falls calendar) and mobility (via the one-minute sit-to-stand test). Both are described in detail below.

- **Falls**. A fall is defined as 'unintentionally coming to rest on the ground, floor, or other lower level and not due to a seizure, syncope, or an acute stroke'[87]. Events caused by overwhelming environmental hazards (e.g., being struck by a moving object) are not considered a fall. Recurrent falls are defined as 'two or more events in a 12-month period'. Falls will be recorded throughout the trial, in which participants will be provided with a falls calendars, on which they will record any falls that have occurred, and the research team will collect them monthly. Study staff will make a final decision of whether a fall event occurred based on the provided information about the fall, and may include follow-up discussion with participant and study partner if applicable. Falls will only be monitored during the active 4mo intervention period.
  Validation: the falls calendar is intended for participants to use on their own, thus its administration does not differ as a function of face-to-face or remote assessments.

- **Mobility**. To further evaluate mobility, participants will be performing the one-minute sit to stand test (STST) while being assessed via video conferencing by a research team member[88].
  Validation: While the one-minute STST has been validated for use in face-to-face settings[89], there are no validations to our knowledge of its use in remote settings.

6.4.10 Biological Markers: Polygenic Hazard Score (PHS)

PHS will be collected via saliva samples that participants will self-collect at any point in time throughout the trial. That is, participants will be mailed an unopened saliva sample collection kit from DNA Genotek© (a Canadian bio sample collection company). Participants will be monitored and assisted during the sample collection process by a research team member. There are specific instructions that must be adhered during saliva collection (such as the requirement that the sample is collected in the morning prior to consuming any food or brushing one's teeth). These instructions will be shared with participants and they will be coached via video conferencing on how to collect, store, and ship their sample. Participants will be notified that providing a saliva sample is optional and they may refuse to do so and still continue their participation throughout the trial. Once collected, participants will be instructed to mail the unidentified sample in a mailing kit with a UNB return address to the lab in which analyses will take place. Samples will be sent to the Clinical Genomics Centre in the Mount Sinai Hospital, 600 University Ave, Toronto, ON M5G 1X5, Canada and will be processed under the guidance of Dr. Kathy Siminovitch.

The saliva sample will measure the following:

- **Biomarkers of ADRDs**: Polygenic Hazard Score (PHS). PHS is derived from a panel of 31single nucleotide polymorphisms (SNPs) and has been shown to robustly predict the 10 year odds ratio of ADRDs[50].

The genetic content known as DNA, or deoxyribonucleic acid, will be analyzed in order to learn about genetic information that may increase a person's risk for developing dementia. This test is part of the overall outcome measure and is not a diagnostic test.

Study participants will not receive results of this test. This test is not currently a standard of normal clinical care and is still under research to determine its utility in clinical practice.

7. STUDY INTERVENTIONS

7.1 INTERVENTION DESCRIPTION

All participants will participate in home-based intervention sessions of 90 minutes per session three times per week for 16 weeks (48 sessions), while in communication with the research team via *Zoom for Healthcare*©. This period of time for combined interventions of exercise and cognitive training has been conducted in previous studies in a clinical environment with significant and promising results[90,91], but has yet to be tested with a home-based delivery approach. Each session will last approximately 90 minutes and will consist of 20-25 minutes cognitive training (NEUROPEAK©) or the cognitive training control followed by approximately 60 minutes of combined exercise intervention (AE and RT) or BAT control exercise.

Cognitive interventions: Active (NEUROPEAK™) or Control (Website searching/video watching (WS+V)) will be set up remotely by the research team for the participant, allowing the participant to complete the cognitive training on her/his own. There will be a research assistant available online to assist with technical questions during this testing.

Exercise interventions: Active (Aerobic Exercise + Resistance Training (AE+RT)) or Control (Balance and Toning (BAT)) will be conducted under the direct supervision and coaching of a certified exercise physiologist with certification from the Canadian Society for Exercise Physiology (CSEP; or equivalent certification). These certified trainers will administer the exercise interventions in a one trainer to one participant ratio. All arms will have an equal volume and frequency of contact over the entire duration of the study. To avoid potential imbalances in exposure time, control conditions for exercise and cognitive training will have the same duration as the active interventions.

7.2 INTERVENTIONS

7.2.1 Active Exercise Intervention: Aerobic Exercise + Resistance Training (AE+RT)

The combined aerobic exercise and resistance training intervention (AE+RT) will be home-based and held three times per week between Monday and Saturday, ensuring that it is not on three consecutive days. Whenever possible, the research coordinator will ensure that the days of the week in which interventions occur are consistent within participants (i.e., a given participant may have a training schedule of Mondays, Wednesdays, and Fridays every week, or alternatively Tuesdays, Thursdays and Saturdays). Staff trained and certified in exercise training will supervise all sessions on a one-to-one trainer to participant ratio remotely. Trainers will connect virtually using video conferencing with participants and will coach them throughout the entire session for all sessions.

Difficulty of aerobic and resistance exercise will be tailored to their individual functioning level, with constant monitoring by the trainers. For this reason the intervention RA will be required to review the participant's Get Active Questionnaire completed at the screening assessment.

The exercise program described here has been developed by a trained and certified Kinesiologist. As such, it adheres to all safety guidelines and precautions necessary in developing such programs. 3 (below) presents a general overview of the active exercise intervention (AE+RT) regimen structure with the approximate time taken to complete each portion.

Table 3. General overview of active intervention exercise regimen structure.

Section	Type of Exercise	Duration (min)
Warm Up	Marching in one place with arm swings for 1 minute	1
	Dynamic Hamstring Stretching: 15 per side	1
	Shoulder Circles: 15 per direction	1
	15 Arm Reaches	0.5
	Torso Twists: 15 per direction	1
	Ankle Circles: 15 per direction per side	2
	Side Stepping for 1 minute	1

Section	Type of Exercise	Duration (min)
	15 Quarter Squats	1
	Total Warm Up Duration	8
Break		1
7 Strength Training Exercises	Chest	5
	Upper Back	5
	Bicep Curls	2.5
	Abdominals	2.5
	Mid/Lower Back	5
	Quadriceps	5
	Hamstrings	5
	Total Strength Training Duration	30
Break		3
Aerobic Exercise	Alternating Video for Participants	15
	Total Aerobic Exercise Duration	15
Break		3
Cool Down	Quadriceps Stretch	0.5
	Hamstring Stretch	0.5
	Calf Stretch	0.5
	2 Hip Stretches	0.5
	Static Torso Rotation	0.5
	Seated Side Bend	0.5
	Back and Shoulder Stretch	0.5
	Chest Stretch	0.5
	Triceps Stretch	0.5
	Neck Stretch	0.5
	Total Cool Down Duration	5
Total Time		**Approx. 65**

Warm Up. The first 5-10 minutes of the intervention exercise session will consist of a general warm-up using dynamic stretches, which include marching in place, various stretching warm up exercises, and quarter squats.

Strength training. Following the general warm-up, participants will execute the strength-training portion by performing progressive strengthening exercises (including pushes and pulls using resistance bands, and chair stands). Participants will complete 7

exercises which target major muscles, including quadriceps, hamstrings, chest, back, abdominals, and synergists such as biceps and triceps. Exercise dose characteristics will be structured to elicit the greatest muscular fitness benefits with a general starting regimen consisting of 1-2 sets of high repetition, low resistance training for the first 1 to 5 weeks of the intervention. Following this, weeks 6 to 10 will consist of 2 sets of moderate repetition, moderate resistance training. And finally, weeks 11 to 16 will consist of 1-2 sets of low repetition, high resistance training. For a visual depiction of the strength training progression across the 16 weeks, please see Table 4 (below).

Table 4. Example progression of strength training guideline across intervention.

Weeks	Sets	Repetitions	Resistance Bands
1 to 5	1	15 to 20	*Band Intensity will increase throughout the trial*
6 to 10	2	10 to 15	
11 to 16	3	8 to 12	

Table 4 presents a general guideline demonstrating the overall progression goals of the intervention. However, realistically there are significant individual differences in starting ability and mobility levels. Therefore, while the exercise physiologist will aim to follow the progression guideline of Table 4—individualized and tailored progressive training regimens may be necessary. Therefore, the certified exercise physiologist who developed the exercise program for SYNERGIC@Home has also recommended a series of progressions across the intervention that are tailored to suit individuals at varying levels of ability. These ability levels will be assessed by the site exercise physiologist at the outset of the study. Three main progressions will be offered for each muscle group to increase challenge throughout the training period for individuals of each starting mobility and exercise ability level. All participants will be instructed to rest 30-60 seconds between sets. Training prescription for all exercises was made in accordance to the ACSM guidelines for strength development in older adults (ACSM, 1998). For details pertaining to the tailored training prescription by baseline ability, please see Table 5 (below).

Table 5. Tailored resistance training prescription by mobility and exercise ability.

Low Fitness/Mobility Ability			
Muscle Group	**Starting Exercise**	**Moderate Progression**	**High Progression**
Quadriceps	Seated leg press with resistance band	Add resistance	Progress to sit-to-stand
Chest	Seated chest press (light band)/chest fly (light band)	Add Resistance	Lengthen rep time (count 3 down, 3 up)
Hamstrings	Standing hamstring curl/hip raise	Lengthen rep time (count 3 down, 3 up) + (hip raise)	Add resistance
Upper Back	Scapular squeeze/scapular wall hold	Seated resistance tube row/seated reverse fly (light band)	Add resistance
Mid/Low Back	Reverse Snow angels	Include legs simultaneously	Progress to pullover
Abdominals	Bird Dog variation (arms/legs separate)/dead bug variation	Progress to include simultaneous movements of limbs	Longer hold
Average Fitness/Mobility Ability			
Muscle Group	**Starting Exercise**	**Moderate Progression**	**High Progression**
Quadriceps	Squat/wall squat (knee pain)	Add resistance (either with normal bands or thigh bands to activate glutes)	Lengthen rep time (count 3 down, 3 up)/pulse
Chest	Counter Push-Up (incline approximately 45)/chest fly (mod band)	Reduce incline (shorter surface)	Lengthen rep time (count 3 down, 3 up)
Hamstrings	Resistance Tube Hamstring Curl/single-leg hip raise	Add resistance/Lengthen rep time (count 3 down, 3 up)	Change surface of planted foot (e.g. foam, bosu, etc.)
Upper Back	Standing Resistance Tube Row/Reverse Fly (mod band)	Add resistance	Lengthen rep time (count 3 out, 3 in)
Mid/Low Back	Resistance Tube Lat Pullover	Add resistance	Lengthen rep time (count 3 out, 3 in)
Abdominals	Incline Plank/bird dog progressions (simultaneous legs/arms)/dead bug progressions	Reduce incline towards horizontal)/banded bird dog/deadbug	Longer hold
High Fitness/Mobility Ability			
Muscle Group	**Starting Exercise**	**Moderate Progression**	**High Progression**
Quadriceps	Split Squat/lunges/walking lunges	Add resistance/change footing	Lengthen rep time (count 3 down, 3 up)/pulse

Chest	Floor Push-Ups (from knees or feet)/chest fly (hard band)	Lengthen rep time (count 3 down, 3 up)	Add resistance band/change hand positioning
Hamstrings	Romanian deadlift	Lengthen rep time (count 3 down, 3 up)/add resistance	Single Leg Romanian deadlift
Upper Back	Standing single arm resistance tube row/single arm reverse fly (at reasonable resistance)	Add resistance	Lengthen rep time (count 3 out, 3 in)
Mid/Low Back	Resistance Tube Lat Pulldown (high anchor, seated, kneeling, standing depending on set-up)	Add resistance	Lengthen rep time (count 3 out, 3 in), change arm position/grip
Abdominals	Forearm Plank/Hollow Hold	Hand plank/lower legs	Dynamic plank

Aerobic Exercise. The aerobic training portion will consist of 10-20 minutes of moderate intensity activity. Participants will be given one of two instructional, at home, exercise videos specifically designed for aerobic and cardiac fitness for older adults to complete via YouTube. Each video is approximately 15 minutes in length and participants will be encouraged to pause or slow down as needed; thus we expect the aerobic training to take approximately 20 minutes to complete. All participants will be monitored via video conferencing by a certified exercise physiologist while partaking in the YouTube home-based exercise. Participants will alternate between the following two videos in order to reduce boredom and maintain their interest.

Video 1: *https://www.youtube.com/watch?v=aVilzXtqi8c&t=167s*

Video 2: *https://www.youtube.com/watch?v=afvTMIT_ZTc*

French adaptations for Francophone participants are as follows:

French Video 1: https://youtu.be/nk0LcCl_UJQ

French Video 2: https://youtu.be/5MI5QWHc7II

Intensity will be set using the talk-test, whereby participants state in short sentences and Ratings of Perceived Exertion (RPE; 4-6 on Borg's 10-point scale). This intensity score will allow us to individually tailor and modify exercises based on the participant's rating.

Cool Down. Each session will end with a five-minute cool down, which will consist of the following stretches (each held for 20-30 seconds); quadriceps stretch, hamstring stretch, calf stretch, 2 hip stretches, static torso rotation, seated side bend, back and shoulder stretch, chest stretch, triceps stretch, and neck stretch.

7.2.2 Control Exercise Intervention: Balance and Toning (BAT)

Participants assigned to the BAT control exercise condition will take part in home-based balance and toning exercises, while supervised by a trainer through the video conferencing platform as outlined for the intervention exercise group.[92-97] The format of the control exercises including the duration of activities and the amount of coaching devoted will mirror that of the intervention condition. However, in the control condition, exercises will be devoted to improving muscle tone and flexibility, without improving strength, and cardiorespiratory capacity. Resistant load and number of repetitions will not progress across exercise sessions, unless participants were unable to complete required repetitions at the beginning of the intervention. All BAT sessions will include a simple stretching mat (rather than progressive resistance bands) that will be sent to participants at the study outset. For a general overview of the BAT program, please see Table 6 (below).

Table 6. General overview of control BAT regimen structure.

Section	Type of Exercise	Duration (min)
Warm Up	Marching in one place with arm swings for 1 minute	1
	Dynamic Hamstring Stretching: 15 per side	1
	Shoulder Circles: 15 per direction	1
	15 Arm Reaches	0.5
	Torso Twists: 15 per direction	1
	Ankle Circles: 15 per direction per side	2
	Side Stepping for 1 minute	1
	15 Quarter Squats	1

Section	Type of Exercise	Duration (min)
	Total Warm Up Duration	8
Break		1
7 Balance and Toning Activities	Standing with Feet Together + Tandem + Single Leg Stand	10
	Core Contractions + Core & Arm Raises	8
	Shoulder Retractions	3
	Isometric Quadriceps Strength	3
	Seated Hamstring Curls	3
	Seated Arm Shake	3
	Total Balance and Toning Duration	30
Break		3
Stretching Exercise	Alternating Video for Participants	15
	Total Stretching Duration	15
Break		3
Cool Down	Quadriceps Stretch	0.5
	Hamstring Stretch	0.5
	Calf Stretch	0.5
	2 Hip Stretches	0.5
	Static Torso Rotation	0.5
	Seated Side Bend	0.5
	Back and Shoulder Stretch	0.5
	Chest Stretch	0.5
	Triceps Stretch	0.5
	Neck Stretch	0.5
	Total Cool Down Duration	5
Total Time		**Approx. 65**

Warm Up. The session will start with the same 5-10-minute warm-up completed in the combined AE and RT group.

Balance and Toning. This will be followed by a variety of balance and toning exercises that will target the entire body. These activities are designed to match the intervention condition with respect to the time and duration—but they are not intended to physically challenge participants or progress in any way across the trial.

Stretching. Like the intervention condition, participants will alternate between two Youtube videos—but rather than an aerobic portion, the video will consist of a stretching

session geared toward older adults. The following are the two videos that participants in the control condition will be presented with in alternating order.

Video 1: https://www.youtube.com/watch?v=eHXbj2Uq8mM

Video 2: https://www.youtube.com/watch?v=zVCqkiqsz4I

Cool Down. All participants in the BAT condition will end with cool down stretching that is identical to the active intervention condition.

7.2.3 Cognitive Training: NEUROPEAK™

The cognitive training intervention will take place remotely using a tablet or computer-based multimodal and multi-domain dual-task training with memory load. Participants will be instructed on how to access the program from their home computer and will be asked to complete the cognitive training program called NEUROPEAK™ on their home computer prior to each exercise training session. Specifically, participants will be assisted by research staff in connecting to the platform from their home computer/tablet. The research assistant will connect with the participant via *Zoom for Healthcare*© in order to assist with the technical questions and offer technical assistance. NEUROPEAK™ has several cognitive training modules but for this study the custom-written program consists of a dual-task training program developed at University of Western Ontario for neurorehabilitation, which has been used in previous Canadian studies[98-100]. The cognitive training includes dual-task training that requires participants to maintain and prepare for many response alternatives (working memory) and to share attention between two concurrent tasks (divided attention). Difficulty of cognitive training is tailored to their individual functioning level. The training uses a custom-written program developed for neuro-rehabilitation and has been used in previous research trials for cognitive[82,83] and mobility outcomes[39]. Cognitive training will take 30 minutes at maximum to complete, and each participant will perform the cognitive training in their own home with no assistance for the cognitive training tasks, but will have the opportunity to ask for help on setting up the program or technical questions. The participant will be asked to do this training in a quiet room within their home to reduce any potential distractions.

During each cognitive training session, participants will perform one of two different visuo-motor tasks, which include sets of visual stimuli (e.g., letters, numbers, animals, vehicles, fruits, celestial bodies) and respective hand-button correspondences (i.e., keys that are to be tapped on either the right or the left side of the screen). Participants are instructed to perform these tasks as fast as possible, while maintaining accuracy. Tasks will be performed both separately and concurrently so that task-set cost and dual-task cost can be isolated, allowing us to determine the rate at which accuracy decreases when task demands are high. At each session, task combination for the sets of stimuli will change (from a total 18 combinations). Training will also include online feedback as well as a histogram of daily performance (a simple graph showing progression but without specific numbers) to encourage improvement.

7.2.4 Control Cognitive Training: Web Search and Video (WS+V)

The cognitive training control home-based sessions will last a maximum of 20-25 minutes to align with the same time frame as the cognitive training group. Participants will alternate between 2 different tasks (touristic searching using internet and video watching) completed using the same method as the intervention cognitive training (i.e., on a computer within a quiet room in their home). In the first session, participants will receive a short introductory lesson on how to navigate the internet. For the touristic searching using internet, participants will be required to find 3 hotels, 3 touristic places, and 3 restaurants of their own preference in a city assigned by the instructor (a new city will be selected each session). They will also need to include the respective addresses of those places on their log sheet.

For the video watching task, participants will watch a National Geographic video on YouTube selected by the instructor with a different video selected for each session. They will watch the video for 20 minutes and during the remaining 5 minutes they will answer the following questions on their log sheet: 1) What is the video about? 2) What is the most important information in your opinion? 3) Create a question based on the video and answer your own question. Regardless of whether or not participants have completed the above control cognitive training tasks, they will be stopped at 25 minutes.

7.3 RANDOMIZATION

Upon completion of the baseline assessments (T0), participants will be randomly allocated to one of the four study arms (as shown in Figure 1). Randomization will be completed by Nellie Kamkar, the study Research Coordinator located at Lawson Research Health Institute in Parkwood Hospital, London Ontario, who will distribute randomization codes (using a random number generator) to determine the treatment arm to which each participant is allocated. Assessors and Research Assistants administering the interventions will be blinded and as such, only Nellie Kamkar and Andrew Sexton (the project manager at the University of New Brunswick) will have access to the randomization lists.

7.3.1 Method

The randomization sequence of the participants will be generated centrally using a simple excel formula that generates a random number within a sequence. A block randomization by four will be applied to ensure an appropriate balance of the participants between each arm. Permuted blocks will be employed to ensure balance over time. This trial includes 4 possible treatment arms: 1) AE+RT and NEUROPEAK™; 2) AE+RT and WS+V; 3) BAT and NEUROPEAK™; 4) BAT and WS+V. Simple randomization will not necessarily ensure that an equal number of participants will be allocated to each group (for example, we may randomly have a large proportion of participants in one group and very few or none in another). Block randomization ensures that this does not occur. Every four participants will be put into a block. For example, the first block (Block A), will consist of our first participant whose treatment arm allocation will be determined using a random number ranging from 1 to 4 (each representing the respective arms listed). Let's assume that this number happened to be 3 (BAT and NEUROPEAK™). Then, for the next participant in the block, a random number ranging from 1 to 3 will be generated (with all treatment arms *except* the BAT and NEUROPEAK™). Now, the number 1 represents AE+RT and NEUROPEAK™ (like before), the number 2 represents AE+RT and WS+V (also like before). But the number 3 represents BAT and WS+V (what used to be arm 4). This ensures that the second participant will be randomly allocated to a different arm than the first participant. The

third participant in Block A will be randomly assigned to one of the two remaining arms and the fourth participant will be assigned to the last remaining arm.

7.3.2 Procedure

Each participant will have an allocated sequential randomization number. After the baseline assessment, the SYNERGIC@Home Research Coordinator at UNB (not involved in measurement or intervention) will access the randomization list to determine the arm allocation for the participant. The Research Coordinator will maintain a separate file stored in SharePoint (accessible only by the Coordinators and PI's) that links the participant's ID with their treatment group allocation.

7.4 BLINDING

In order to minimize a source of bias, this is a double-blinded study. Research personnel performing the outcome assessments will be blinded to group allocation. Participants will be blinded to the intervention received and study hypotheses.

7.4.1 Maintaining Blinding

Only the designated Research Assistants (RAs) delivering the interventions will know the treatment group that participants belong to. As part of the training for RAs during on-boarding (in our trial SoP), they will be informed of the importance of blinding and instructed to avoid conversing with participants in a way that could reveal their group membership.

Participants will be informed at consent and reminded at enrollment of the importance of blinding and that they should refrain from discussing their treatment program with friends and family and especially with others they may know that are participating in the study.

7.4.2 Unblinding

If it is medically necessary to un-blind a participant during the trial, the RA assigned to doing the assessments or interventions will contact the study Physician and Principal Investigators to discuss the reason for the code to be broken. If it is deemed relevant to unblind the participant the study Physician will contact the Research Coordinator to break the blinding. The participant will then withdraw from the study.

7.4.3 Debriefing

At the end of the trial (immediately after participants complete their T10 assessment), participants will be unblinded such that a research assistant divulges the exact condition that the participant was randomly allocated to. During this debriefing session, participants will have an opportunity to ask questions and to give feedback.

7.5 EARLY WITHDRAWAL

Participants will be withdrawn from the study if: 1) they no longer wish to continue their participation in the study (voluntary withdrawal), or 2) in the opinion of one of the study physicians, it is medically necessary to withdraw the participant (medically necessary withdrawal).

Voluntary withdrawal

Participants who inform their Intervention Research Assistant (RA) that they wish to voluntarily withdraw will be asked by the Intervention Coordinator (to protect blinding) if they would be willing to continue their participation in either intervention on its own and return for their follow-up assessments. For example, a participant who indicates that s/he would like to withdraw from the exercise intervention will subsequently be asked if s/he would be willing to continue with the cognitive training intervention on its own, and to return for T4 and T10 assessments. Or if they wish to discontinue both interventions, s/he would be asked if they would agree to return for T4 and T10 assessments.

If the participant remains in the study with either of these scenarios, they will not be withdrawn from the study provided they agreed to at least the T4 assessment. Voluntary non-adherence will be captured by entering 0 values in their intervention logs for the remainder of the weekly session(s) they withdrew from. These participants will also be considered eligible for the one-on-one interviews planned after the T10 assessment.

If the participant wishes to completely withdraw from the study, s/he will be asked to complete the Exit Survey (which will be mailed out to them) and will subsequently be withdrawn from the study. Voluntary non-adherence will be captured by entering 0 values in their intervention logs for the remainder of the weekly session(s) they withdrew from, and intention-to-treat applied to imputing follow-up assessment scores.

Medically necessary withdrawal

Medically necessary withdrawals may be required if participants experience unanticipated AEs or SAEs that cannot be readily ameliorated and would, in the judgement of a study physician, place the participant at risk of harm if they continued to participate in the study. Changes in medication or health status during the course of the study are other reasons for consideration of medically necessary withdrawal.

Upon first recognition of a medical issue being experienced by a participant, the Intervention RA will immediately notify the Intervention Coordinator, Clinical Research Coordinator/ Nurse, and the Lead Study Physician, who will provide direction to the Intervention Coordinator as to the whether or not the intervention should continue, be modified or stopped within 24 hours of receiving the information. A follow up telephone or videoconference session will be arranged as soon as possible (24-48 hours during the week) to review the situation , which may or may not involve the participant. The purpose of this meeting will be to arrive at a decision related to withdrawal of the participant to protect their health and welfare and to ensure that participant is receiving appropriate care.

If it is deemed medically necessary to withdraw the participant, the Clinical Research Coordinator/Nurse and/or Study Physician will meet with the participant (if not already) to follow up with the participant and review the reasons for withdrawal and to inquire about the elements of the study that may have led to their change in health status. If willing, the participant will be asked to complete the Exit Survey either verbally during that meeting or have it mailed out to them for them to return to the Clinical Coordinator and will subsequently be withdrawn from the study. These participants adherence will be measured relative to their time in the study, and intention-to-treat applied to imputing follow-up assessment scores.

7.6 MIXED METHODS DESIGN: EXPERIENCE OF STUDY PARTICIPANTS

One of the secondary feasibility objectives as described at the outset aims to measure the experience of study participants who have participated in this intervention trial being conducted in home-based, on-line settings using *Zoom for Healthcare*©. Using key concepts such as satisfaction, knowledge gained, motivation/commitment, adherence,

and benefits, and challenges, we will collect data about the feasibility of conducting a home-based, on-line intervention trial with an older, community-dwelling population.

7.6.1 Mixed Methods Design

An explanatory sequential mixed methods design will be used[101] where qualitative data will be collected to explore quantitative findings. This design is implemented in two phases where initially data collected using a quantitative instrument in the first phase is followed by a qualitative phase. Using mixed methods enables the quantitative results to be "sequentially" explored in more detail through this phase two qualitative approach.

A questionnaire (Appendix D) will be administered to the 64 study participants upon completion of the study intervention (T4). Semi-structured interviews will be conducted with study participants using the guide in Appendix E following the completion of their six month post-intervention follow-up assessment (T10).

7.6.2 Data Collection Instruments

Questions developed for both the quantitative and qualitative instruments were constructed using Kirkpatrick's (1975) framework—a four-level model that has been used to assess participants' benefits and experiences with different types of programs[4]. This framework consists of four dimensions as illustrated in Table 7 and has been used in numerous settings to conduct a process-focused program evaluation.

Table 7. Kirkpatrick's Framework for Evaluation of Participant Experience

Kirkpatrick's Framework for Evaluation	
Dimension	**Possible Areas for Exploration**
Reaction (to research study)	• How did participants feel about components of the study? • Were participants satisfied with the research team members implementing the intervention(s)?

Kirkpatrick's Framework for Evaluation	
Dimension	**Possible Areas for Exploration**
Learning (new knowledge / skills; what knowledge / skills unlearned)	• What new knowledge and skills were learned? Any new knowledge about how to improve thinking and memory? • Did participants become aware of new evidence-informed practices that required them to 'unlearn' skills? For example, was there new learning with respect to physical exercise?
Behaviour (change in behaviour as a result of participating in the research study)	• What does the participant identify as changes in behaviours as a result of participating in the study? • What new skills were learned? • What were motivators to change?
Results (Measurable outcomes)	• Benefits identified by participants

7.6.3 Participant Exit Questionnaire

The purpose of using a quantitative instrument (Appendix D) is to obtain a snapshot of the study circumstances and logistics from the participants' perspective. Upon completing the study intervention (at T4) each participant will be sent a one-page, short-form questionnaire via email. This questionnaire consists of 19 closed-ended questions using a 5 point Likert scale and one open-ended question. The questions consist of alternating positive and negative statements which collect participants' impressions about their experience and satisfaction with various elements of this study; i.e., such as using a computer or video-conferencing to complete the intervention and assessments. Study participants will either return the scanned questionnaire by email or mail a completed hard copy to the research coordinator using a stamped, self-addressed envelope.

7.6.3.1 Quantitative Data Analysis

The results of these questionnaires will be analyzed using a standard statistics software program such as SPSS. Descriptive statistics for the anonymized questionnaires will be compiled such as the number of responses, the percentages for each question, and the group mean and standard deviation.

7.6.4 Participant Semi-Structured Interview

A semi-structured interview guide has been developed (Appendix E) consisting of question that ask participants to comment on their study experiences. For example, the benefits of this research approach for exercise and cognitive training programs including their reaction to the type of training they completed, their user satisfaction, the ease of participation in a virtual setting, the quality of information received; and support provided by research team members and the extent of burden and fatigued from completing the assessments will be explored.

7.6.4.1 Qualitative Data Analysis

Transcribed data from the interviews will be uploaded into NVivo, a qualitative software program used for data analysis by the team's qualitative researchers. Transcripts will be divided amongst the qualitative researchers. These team members will code the interview data, initially independently, and then meet as a group to arrive at a consensus of codes. Following coding of the data, through thematic analysis, themes and sub-themes will be generated to identify participants' perspectives of the feasibility, experience and satisfaction with this type of virtually delivered study. Study participants will be invited to review and validate the themes generated; this validation adds rigor to analysis, which ensures that the researchers "got it right".

7.6.5 Triangulation

The mixed methods design promotes methodical rigor. For this aspect of the study, triangulation of the findings takes place from two perspectives. Collecting both quantitative and qualitative data gives more insight than any one method will provide. In addition, having more than one member of the research team conduct the semi-structured interviews can significantly enhance the credibility of the findings and is particularly important for decreasing bias in gathering, analyzing data and/or reporting study findings.

7.7 COMPENSATION

In recognition for the participant's time commitment they will be given $50.00 after the immediate post-intervention follow-up (T4) assessment and $50.00 the 6-month post-intervention follow-up (T10), for a total amount of $100. Compensation will be in the

form of gift cards to local grocers (Sobeys and Atlantic Superstore) and gas stations (Irving Circle K and Ultramar) of the individual's choice, or equivalent cash value paid by cheque.

8. STATISTICAL CONSIDERATIONS

8.1 SAMPLE SIZE AND POWER ANALYSIS

A total of 64 participants will be enrolled in the SYNERGIC@Home study. Participants will be randomly allocated to each of the four arms with 16 participants per arm. Power analysis was calculated a-priori using G*Power 3.1 based on our primary analytic goal of assessing the relationship between intervention preference and subsequent adherence. Specifically, we plan on examining correlations among continuous variables with a final total sample size needed of 48 (25% loss) and with one-tailed analyses at α = .05 for two correlation tests (equivalent to a two-tailed test at α = .1), thus we will have 96% power to detect a moderate to large effect size (of .5 or larger) and 82% power to detect an effect size of .4 or larger. For any r greater than .6, power will be well over 99%, meaning that we will have greater than 99% power to explain a minimum of 36% of the variability in our dependent variable.

8.2 PLANNED DATA ANALYSIS

Descriptive statistics for demographic and baseline characteristics will be provided with means and standard deviations, or medians and the interquartile range where appropriate, for continuous characteristics, and frequencies and percentages for categorical variables. Analysis will be conducted as intention-to-treat (ITT) and as per-protocol analysis (PPA).

8.2.1 Primary Feasibility Outcomes

Adherence to the interventions will be analyzed using a one-sample t-test that will test the hypothesis that participants complete at least 36 of the 48 (75%) scheduled interventions sessions. This test will be used to determine of the adherence is similar to hypothesize, better than hypothesized or worse than hypothesized.

8.2.2 Secondary Feasibility Outcomes

Enrollment recruitment target of 75% will be tested using a Chi-square goodness-of-fit test (α=.05) of actual distribution (# eligible and # screen fails) versus hypothesized distribution (75% and 25% of N). This test will be used to determine if the achieved distribution of eligible participants is similar to that hypothesized, significantly better than that hypothesized, or significantly lower than that hypothesized.

To answer the research questions pertaining to trial retention, we will examine proportions reaching our 75% enrollment retention target at the immediate post-intervention follow-up (T4) assessment and the 75% follow-up retention target at the 6-month post-intervention follow-up (T10) assessment with 95% confidence intervals (when possible). In addition, Chi-square good-of-fit test will also be used to quantify the significance of the difference between the observed and hypothesized proportions.

Assessment tolerability will use descriptive statistics (counts) to describe how many and under what circumstances (documented in CRF notes) that participants decided to drop out of the trial, not because of the interventions, but because of the extensive battery of testing they must undergo in order to start the trial.

Descriptive statistics will be used to analyze the quantitative Exit survey to determine where on the spectrum of satisfaction (completely unsatisfied to completely satisfied) participants fall in terms of the trial components (see Appendix D). Data will be analyzed using a two-way ANOVA on exercise intervention (active and control) and cognitive intervention (active and control) to determine if there is a significant interaction effect induced by the combined active treatments.

Adverse events will be analyzed using a Chi-square cross-tabulation analysis between AE severity and AE relation-to-trial. We will use this analysis to test the hypothesis that there is a relationship between AE severity and being in the trial. Furthermore, we will stratify the sample by treatment arm and use a Chi-square goodness-of-fit test to determine if AEs are distributed differently across treatment arms against the null hypothesis of an even distribution (no relation to treatment arm).

8.2.3 Primary Analytic Outcomes

For primary analytic outcomes examining the relationship between interest level in and adherence to the interventions, we will correlate interest level (responses given on the Intervention Preference Questionnaire, See Appendix A) for each intervention with adherence rates calculated from trial logs, using Pearson's r. This analysis will tell us if adherence to the trial is related to participants' affinity for any one or more interventions.

- **Interest in the Interventions:** Question 1 on the survey rates their interest in each intervention independently, **INT_EX** and **INT_CT**, on a 0-10 scale.
- **Intervention Preference:** The second question rates their relative preference for either intervention. This will generate a single variable that gives the relative preference (-2 to 2 scale), **PR**, where low scores prefer exercise and high scores prefer cognitive training. Because we will administer preference survey at baseline and then at 4mo, we will have two measures **PR1**and **PR2**. The difference scores (**dPR**=**PR2**-**PR1**) would be negative if their preference moved toward exercise, and positive if it moved toward cognitive training.
- **Intervention Allocated:** The treatment arms can be represented by two dummy (0,1) variables **EX_ARM** and **CT_ARM**.
- **Adherence to Interventions:** Adherence to the interventions at the end of the trial, **AD_EX** and **AD_CT**, is a continuous scale variable (% exercise and cognitive training sessions attended, respectively).

8.2.3.1 Analysis Plan

What is the Relationship between Adherence and Intervention Interest? For each of the two interventions we will calculate the Pearson correlation coefficient ($\rho_{X,Y}$) with a one-tailed alpha of .05.

$$H0: \rho_{X,Y} = 0,\ \ H1: \rho_{X,Y} > 0, \text{ where X=}\mathbf{INT\_EX} \text{ and Y=}\mathbf{AD}$$

$$H0: \rho_{X,Y} = 0,\ \ H1: \rho_{X,Y} > 0, \text{ where X=}\mathbf{INT\_CT} \text{ and Y=}\mathbf{AD}$$

Rejection of the null hypothesis for either test will allow us to conclude that interest level in the intervention type prior to the trial explains a significant amount of variance in adherence to the trial. Failure to reject the null hypothesis would suggest that prior

attitudes about the interventions does not influence how well they adhere to the interventions.

8.2.3.2 Other Analyses

Which intervention type (physical exercise or cognitive training) do the majority of participants prefer over the other? To answer this question we will use a single-sample t-test to test if the mean **PR** is directionally biased from the middle score (no preference).

What proportion of participants have no particular preference for either intervention? To answer this question we will compute the proportion of participants that selected "Equal preference" response.

Do their attitudes change after completing the active interventions versus the control interventions? To answer this question we will calculate the mean preference change **dPR** and test whether it is different from zero using a single-sample t-test.

Do participants adhere better if they receive the active treatments they prefer?

Because some participants will be randomly assigned to the active intervention that matches their preference and others will not (will get the control version of the intervention), we will transform the preference score into a logical variable **PR_MET** (1=preference met, 0=preference not met).

if (**PR1**<3 and **EX_ARM**=1) or (**PR1**>3 and **CT_ARM**=1),

then **PR_MET**= 1, else **PR_MET**=0

We will test the hypothesis that

H0: $\rho_{X,Y} = 0$, H1: $\rho_{X,Y} \neq 0$, where X=**PR_MET** and Y=**AD**

Rejection of the null hypothesis (p<.05) will allow us to conclude that adherence to the interventions is significantly influenced by receiving the active intervention they prefer.

8.2.4 Secondary Analytic Outcomes

Clinical and activity assessments will yield a rich source of information for quantifying effect sizes of trial outcomes. We will calculate Cohen's d effect sizes (mean difference/standard deviation) for cognitive, mobility and lifestyle outcomes (e.g., diet and sleep) listed in Table 2.

All statistical tests will be two-tailed, and a p-value of less than 0.05 will be considered to indicate statistical significance. All calculations will be made using the Statistical Package for the Social Sciences (SPSS version 23.0, SPSS Inc., Chicago, IL) and Stata (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

8.3 FREQUENCY OF THE DATA ANALYSES

Preliminary analysis will be performed after finishing recruitment to ascertain descriptive characteristics at baseline assessment. Interim efficacy analyses will be performed when recruitment is reaching 50% of target sample (N = 32) and final efficacy analysis will be performed at the end of the trial (N = 64, but 48 are need for final analyses), as no safety issues are anticipated in this study.

9. ADVERSE EVENTS

9.1 DEFINITIONS

9.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject that may present itself during the conduct of a research study and which may or may not have a causal relationship with the study procedures. An AE can therefore be any unfavourable or unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with a study procedure. An AE may be a

new illness, worsening of a sign or symptom of a condition, or an effect from a study procedure.

9.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening, i.e., the subject was at immediate risk of death at the time of the event; it does not include any event which hypothetically might have caused death if it had occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalizations and/or surgical procedures that are scheduled to occur during the study period, for an illness or disease that existed before subject enrolment in the trial, will not be considered AEs provided the pre-existing condition did not deteriorate (e.g., surgery performed earlier than the planned date).
- Results in persistent or significant disability/incapacity

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate. In other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

9.2 CLASSIFICATION

9.2.1 Severity

Adverse events will be classified as mild, moderate or severe in severity as follows:

- **Mild**: Discomfort noticed but no disruption of normal daily activity.
- **Moderate**: Discomfort sufficient to reduce or affect normal daily activity.
- **Severe**: Incapacitating with inability to work or perform normal daily activity.

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the

same as “serious”, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.2.2 Attribution

The relationship of the AE to study procedure will be assessed by the investigator to be not related, unlikely, possible, probable or definite, as follows:

- **Not related**: No relationship between the AE and the study procedure, judged clearly and incontrovertibly due to extraneous causes such as concomitant medication(s) or the subject’s clinical state.
- **Unlikely**: The AE is more likely due to an alternative explanation such as concomitant medication(s), concomitant disease(s) and/or the time relationship suggests that a causal relationship is unlikely.
- **Possible**: The AE might be due to a study procedure. An alternative explanation such as concomitant medication(s), concomitant disease(s) is inconclusive. The time relationship is reasonable therefore the causal relationship cannot be excluded.
- **Probable**: The AE might be due to a study procedure. An alternative explanation such as concomitant medication(s), concomitant disease(s) is less likely. The time relationship is suggestive, i.e. it is confirmed by de-challenge.
- **Definite**: The AE cannot be reasonably explained by an alternative explanation such as concomitant medication(s), concomitant disease(s). The time relationship is very suggestive, i.e. it is confirmed by de-challenge and re-challenge.

For the purposes of safety analyses, all SAEs classified with a relationship to a study procedure of possible, probable or definite will be considered study-related events.

9.3 PROCEDURES FOR AE AND SAE REPORTING

9.3.1 Adverse Event (AE) Reporting

All AEs experienced by the subject between the signing of the Informed Consent and discontinuation of the study will be reported. All AEs must be recorded in the CRF. For

both serious and non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

9.3.2 Serious Adverse Event (SAE) Reporting

All SAEs will be recorded in the CRF starting from the time of the signing of the Informed Consent up to and including the end of study. All SAEs, regardless of the relationship to study procedures, must be reported within one working day of site personnel being notified of the occurrence of the event.

SAE forms will be provided to each study site. The initial SAE report should include at a minimum: subject number, a narrative description of the event, and an assessment by the investigator of the intensity of the event and relationship of the event to study drug. The initial SAE report received from the site should be complete as soon as possible. A complete follow-up SAE report must be submitted when the information, not available at the time of the initial report, becomes available. The sponsor (or designee) may request SAE follow-up information.

Any SAE that occurs at any time after completion of the study, which the investigator considers to be related to study procedures, must be recorded in the CRF.

All SAE will be submitted to the REB.

9.3.3 Period of Observation

All AEs should be monitored to determine the outcome or until the investigator considers it medically justifiable to terminate follow-up.

All SAEs should be monitored until resolved or until the SAE is clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

10. ETHICAL AND OPERATIONAL CONSIDERATIONS

This study is conducted in compliance with International Conference on Harmonization Good Clinical Practice (ICH-GCP) and all applicable regulatory requirements. This SYNERGIC@Home study will undergo review and approval from the Research Ethics Committees/Boards of Vitalité Health Network In Moncton, New Brunswick, Horizon

Health Network in Fredericton, New Brunswick, the University of New Brunswick in Fredericton New Brunswick, and Université de Moncton in Moncton, New Brunswick.

10.1 ETHICAL CONSIDERATIONS

10.1.1 Informed Consent

When potential participants have self-identified as being interested in learning more about the study to decide if they want to participate, the Clinical Research Coordinator/Nurse will contact the individual to discuss an overview of the study. If they are interested in pursuing more information the informed consent will be emailed or mailed to them for their review. Potential participants will be given a copy of the informed consent form in their language of choice.

After the potential participant agrees to be considered for recruitment the clinical research coordinator/nurse will arrange a time for a more detailed videoconference meeting for the Screening Visit. Opportunity for discussion of the study and Informed consent will be provided and all questions will be answered. The informed consent will be completed and signed prior to beginning any study related assessments/procedures. Signing of the consent will be done via videoconference and then returned by mail using a stamped, self-addressed envelope to the clinical research coordinator/nurse who will then sign it and file the original with the participant research documents. A final signed copy of the informed consent will be provided to the participant either by email or mail depending on their choice.

Optionally, the participant will be asked to show the clinical research coordinator/nurse their signed informed consent form over the video-call so that they can ascertain and verify that the form has been signed in all the appropriate locations. Once verified, the clinical research coordinator/nurse will consider the participant to be consented for the study and will proceed with scheduling the study assessments and procedures and will not be required to wait until the returned mailed consent form is received before proceeding with the study.

10.1.2 Confidentiality and Privacy

Participants' private and identifiable information will be held in strict confidence and will not be shared outside the research team, with the exception of enforcement of applicable civil or federal laws. Research team members will only have access to private and identifiable information on a need-to-know basis or as necessary for carrying out their study tasks.

Due to the COVID-19 pandemic, many research team members will be working from a home environment. All RAs involved in assessing or delivering interventions to study participants will be provided a secure UNB laptop administered by the study Project Manager. The study laptop may only be used for study related activities and must be used for all videoconferencing activity and data storage. All research coordinators in the Health Network will be working within their institutions or from a home environment. They will be provided a secure Health authority laptop administered by Service New Brunswick. All connection will be protected behind the institution firewall. Research team members and investigators will be prohibited from discussing participant cases or sharing of private and identifiable information by email or non-secure videoconferencing.

10.1.3 Biospecimen Collection Privacy

To ensure participant privacy and confidentiality in biospecimen collection, storage, shipment, participants will be instructed to print their study ID number on their saliva sample box (rather than their name) and to ensure that their name or any personally identifiable information is *not* indicated on their sample box. They will be given mailing materials to pack their sample in and will be given instructions on how to mail the sample back for analysis. This is in accordance with standard operating procedures for storing, shipping, and handling of bio-samples for research purposes.

10.2 STUDY SAFETY AND MONITORING COMMITTEE

There will be a Study Safety and Monitoring Committee that will consist of all NB-PALM principal investigators and site physicians, project manager and research coordinator(s), as well as a physician not associated with the study (TBD) and a community member (TBD). This committee will be responsible to receive all reports of AEs and SAEs

reported for any participant as well as to monitor the overall operations of the entire research project. A log of these reports will be kept and reviewed regularly to monitor the safety of the clinical trial.

10.3 RISK MANAGEMENT AND SAFETY MONITORING PLAN

All participants will be monitored by trained research staff, and should any adverse events arise, the research team directly working with the participant will notify the Clinical Research Coordinator/Nurse, who will gather and document the appropriate information and will contact the Physician Principal Investigator and/or Study Physician. Adverse events will be documented as described above in Section 10.

Participants will be given a phone number and e-mail address to contact if there is an adverse event, or they may report AEs at the start of their training session with the RAs delivering their interventions. There will be a member from the research team available to assist with this Monday to Friday 0800-1600 (excluding statutory holidays). All participants will be encouraged to use the contact information provided to them to ask any non-urgent questions and address their concerns throughout the entirety of the study trial.

In order to ensure that participant safety is the utmost focus of the research project, we have put forth the following plan and answered the following risk management and safety monitoring questions:

10.3.1 Safety Monitoring

Participant safety will be regularly monitored during each assessment and intervention session using an ongoing paper log. This log will be filled out by the study assessor conducting the intervention session and she/he will insert detailed session notes pertaining to the events that transpired during each event. This log will be reviewed by the clinical research coordinator/nurse and if there are any concerns it will be reported to the physician principal investigator and/study physician. These will be reported to the Safety and Monitoring Committee on a monthly basis.

10.3.2 Withdrawal for Safety Reasons

During their intervention sessions which occur three times per week, participants will be monitored the Research Assistant administering the intervention. Any concerns that are medical in nature will be communicated to the Clinical Research Coordinator/nurse. Further information will be collected from the patient by the nurse and the physician principal investigator/study physician will be notified. Follow up on any medical matters will be done by the nurse and/or physician as required. If further medical care is needed the participant will be referred to their primary care physician/provider for follow up. A decision regarding early withdrawal from the study will be made by the principal investigator/study physician and all the appropriate document will be completed.

10.3.3 Study-wide Stopping Rules

In light of the fact that this intervention program has been implemented previously in the SYNERGIC trial, it is unlikely that this study would be required to stop early due to safety concerns. However, SYNERGIC@Home will be conducted remotely so it is possible that adverse events may arise that are not anticipated requiring the entire study to stop. The decision to stop the study early will rest with Study Safety and Monitoring Committee.

10.4 INCIDENTAL FINDINGS

Incidental findings include any previously undiagnosed medical finding observed throughout the trial, identified purely accidentally within the research trial. Any incidental findings observed throughout the trial will be addressed by the Clinical Research Coordinators/Nurse and Physician Principal Investigator/Study Physician. All incidental findings will be appropriately documented. Depending on the finding the participants' primary care physician/provider will be contacted so that appropriate follow up and care if necessary is received. All findings and their follow-up actions will be documented and monitored until it has been resolved or as long as the participant remains in the study.

10.5 PROTOCOL DEVIATIONS

A protocol deviation occurs when the activities of the study deviate from that which is detailed in the study protocol. All research staff will make it their priority to ensure that

the protocol is abided by as closely as possible. However, in the event that a participant deviates from the protocol, a protocol deviation form (see Appendix I) will be filed and details pertaining to the deviation will be noted in a hard copy stored in locked cabinets on the UNB campus. Attempts will be made to return to study procedure as outlined in the protocol as much as possible and as swiftly as possible.

10.6 DATA MANAGEMENT AND STORAGE

10.6.1 Primary Source Data

Primary source data will be stored using SharePoint, a secure platform through the University of New Brunswick to which only designated research staff have access. Primary source data are defined as the copies of the original hard copy assessment forms completed by the research team member conducting the assessments along with any hard copy self-report questionnaires and other study document sent by a participant of collected by the site research coordinators. Hard copies of any data collection forms will be stored in locked cabinets located at the workplaces of study research staff and accessible only by study staff.

10.6.2 Secondary Source Data

Upon completion of the study, all data collected in paper form with the unique identification numbers will be uploaded to the Longitudinal Online Research and Imaging System (LORIS) system (https://ccna.loris.ca/) at the McGill Centre for Integrative Neuroscience, McGill University, Montreal, Quebec. The LORIS is an OPEN SOURCE toolset framework for storing and processing behavioural, clinical, neuroimaging and genetic data. LORIS is designed to simplify management of large datasets acquired over time in a longitudinal study, and at different locations in a multi-site study. It provides a secure web-based access to data validation and quality control modules, as well as visualization and basic statistical tools. The LORIS servers in which the data is stored are physically located on the McGill University campus, in a secure data facility. Study staff will enter data into LORIS via web-portal.

10.6.3 Video and Audio Recording

All study procedures including intervention sessions (physical activity and cognitive training) will occur via Video Conferencing using *Zoom for Healthcare*©. The screening

and baseline (T0), immediate post-intervention follow-up (T4), and 6-month post-intervention follow-up (T10) assessments will be video and audio recorded. In addition, a subset of 3 intervention sessions will be selected to be video recorded per participant for quality control. Anytime during which participants will be video recorded, they will be told ahead of time that their session will be video recorded.

The audio and video recordings will only be accessed by members of the research team to verify the data that is needed for populating the assessment forms. Once scores are verified from video and audio recordings, they will be transferred to the Case Report Forms and data will be input into a data collection sheet (Appendix F) for input to LORIS as described in section 11.6.2. Data will only be linked to each study participant's unique study identification number. The audio and video recordings, will be stored at UNB on a secure Sharepoint server and discarded after the data has been transferred. Recordings will never be shared, uploaded or distributed to any individuals or organizations outside of the research team. Data obtained from the ActiGraph GT9X devices (i.e., gait parameters, heart rate, and sleep cycle data) will also be stored at UNB on a secure Sharepoint server and discarded after it has been transferred.

Participant names will not be associated with their video recording and participants will be asked to set their *Zoom for Healthcare*© user password as their initials. Video and audio recordings will be discarded after their data has been extracted.

10.7 FUTURE USE OF STORED SPECIMENS AND DATA

Biological samples will be stored at the Clinical Genomics Centre in the Mount Sinai Hospital, 600 University Ave, Toronto, ON M5G 1X5, Canada and will be processed under the guidance of Dr. Kathy Siminovitch. Approximately half of the samples will be used for planned analyses (polygenic hazard score (PHS) testing). The rest may be available for investigators who wish to perform further analyses on the whole cohort or a subset. Participants will be asked if they are willing to be contacted at a later date to be asked whether or not they consent to have their sample biobanked for future research use. Only participants who consent being contacted at the later date, and then consent to biobanking their sample for future studies will have their sample analyzed for other purposes, the samples form patients who didn't agree for this biobanking will be

destroyed. Access to these samples will be regulated by the Biological Sample Access Committee which is made up of members of CCNA (members list available on request). Requests for access will be assessed for feasibility, scientific rigour, and alignment with the consent of the participants. In order to be granted access to samples, investigators must agree that the data they generate from the samples will be included in the larger CCNA database on LORIS within 2 years of sample batch receipt. Samples will be shared within Canada only for a period of 3 years after the last sample has been collected. After that 3-year period, they will be available to international researchers, if not already depleted. The full Biological Sample Access policy document is under development and will be made available upon its finalization.

PHS testing is still in its early embryonic stages in terms of clinical development and while it holds great promise for clinical utility in the future, it is not currently a validated diagnostic tool used in medical practice.[102] Thus, the research team will be entirely transparent with participants and inform them at the study outset that their results will not be shared with them or their healthcare professional—as it is not currently a diagnostic tool. Any and all published work from the data will only include group statistics (and not individual trends) and will always include de-identified participant identification numbers (and not participant names).

10.8 PUBLICATION AND DATA SHARING POLICY

10.8.1 Dissemination of Study Findings

Prior to submission for publication or for presentation of any data or results obtained in this study, notification of the study Investigators (Principal and Co-Principal Investigators) is required. Draft manuscripts, abstracts and presentations should be submitted to the study Investigators for review and approval well in advance of applicable submission deadlines.

10.8.2 Authorship

Authorship of publications resulting from this study should accurately reflect the academic contribution of individuals to the design and implementation of the trial, analysis of the data and preparation of the manuscript. No researcher shall include identifiable personal health information in any publication or presentation.

10.8.3 Data Ownership

The University of New Brunswick will retain the ownership of the data obtained in this study. All publications that arise from the use of data will give acknowledgement, attribution, or co-authorship as appropriate in accordance with the International Committee of Medication Journal Editors (ICMJE) standards.

11. DISCUSSION

Older adults at risk for ADRDs have incident rates of related syndromes several times higher than their cognitively healthy counterparts[103]. Additionally, these populations of individuals at risk for ADRDs have an increased risk of falling and mobility decline[104,105]. Physical exercise, and cognitive training are emerging and promising non-pharmacological interventions to enhance mobility and cognitive functioning in older adults, especially in pre-dementia states prior to onset. These interventions have been tested separately, with positive results for physical exercise and cognitive training in improving cognitive function[30,32,35,42,46]. To our knowledge, this is the first study establishing the feasibility of conducting an entirely home-based combined exercise and cognitive training intervention program for older adults at risk for ADRDs.

11.1 SIGNIFICANCE OF ESTABLISHING FEASIBILITY

The goal of establishing the feasibility of conducting a home-based combined intervention program is critical, as it has the potential to inform other researchers on the logistics of designing remote intervention programs. In addition, in light of the physical distancing procedures implemented worldwide after the 2020 COVID-19 pandemic—many older adults have been further isolated in their homes. The SYNERGIC@Home trial is one of the first studies that has adapted to these unique times, allowing older adults to take part in various intervention and assessment procedures from the safety and comfort of their homes. If successful, the methodology and procedures tested in this feasibility trial will set the standard for a new platform in which participants are no longer restricted to intervention studies conducted in a physical laboratory.

11.2 SIGNIFICANCE OF EXAMINING INTERVENTION PREFERENCE

To address our primary analytic goal of assessing participant's intervention preference, we will examine the potential relationship between preference given for an intervention and the subsequent efficacy of it. We will assess participant's preference both prior to and after the intervention and correlate these values with their adherence to the intervention that they were randomized to receive. If we find that preferences given prior to intervention are strongly related to subsequent intervention compliance/adherence—then our data will provide unique insights on factors related to the success of lifestyle modification trials with community-dwelling older adults. We may find that strong preferences are weakly correlated with our measures of intervention fidelity. This will suggest that subsequent intervention trials will not benefit from the added complexity and cost associated with formally estimating preference effects in randomized control trials of future intervention studies. Therefore, regardless of the results of our primary analyses, we believe that the SYNERGIC@Home trial will provide unique insights the relationship between intervention preference and subsequent fidelity.

11.3 SIGNIFICANCE OF SECONDARY OUTCOMES

We believe that the two combined interventions of physical activity and cognitive training used in conjunction will lead to a cascade of improvements on our secondary outcomes, such that those in the combined intervention groups will outperform the control groups on tests of cognitive functioning. We further believe that, if successful, the combined intervention will further demonstrate a delay in their progression to dementia. The reasons why each of the interventions will pose benefits to cognitive, neurological, physical, and psychological health are delineated below.

11.4 BENEFITS OF INTERVENTIONS

11.4.1 Benefits of Exercise

Mechanistically, AE and RT exercises can provoke a cascade of biochemical, physiological, and structural changes in the brain including increases in blood flow, neurotrophic factor release, neurogenesis, immune system efficacy and metabolism. These effects of exercise could combat inflammatory processes and the atrophy of brain structures both often associated with aging and ADRDs[32,34]. Interventions using

RT exercises have found substantial improvements in high-order cognition (e.g. executive functions), whereas low-order cognition (e.g. attention, processing speed) is less benefited[34]. The reason for this selective improvement in cognition is unknown, but it is hypothesized that areas in the brain that modulate executive functions are more susceptible to both aging and physical exercises interventions. Mechanisms suggested involve modulation of insulin-like growth factor-1 and insulin sensitivity, decreasing inflammation, enhancing release of brain-derived neurotrophic factor pathways, and even decrease brain amyloid load.[35,106,107] Combined exercise interventions have also shown increased brain volume and muscle mass in older adults.[93]

11.4.2 Benefits of Cognitive Training

Cognitive training can also improve cognition through enhancing brain functioning. Individuals who practiced monitoring of two tasks at the same time (i.e. dual-task training) on computer devices have presented with improved connectivity between prefrontal and temporal cortices, areas known to be important for executive functioning and memory, when compared to control participants.[40] Furthermore, imaging in these participants showed increased activity in these cortical areas during resting state, as shown by increased blood flow. With this, implementing a dual-task cognitive training program in older adults has the potential to selectively improve high-order cognitive functioning through brain plasticity and improved activation.

11.5 STRENGTHS AND CONCLUDING REMARKS

To our knowledge, this feasibility randomized control trial is the first to test the feasibility of implementing a combined physical aerobic exercise and resistance training program with cognitive training program at home to improve cognition in a sample of community-dwelling older adults at risk for ADRDs. We also believe this is one of the first home-based intervention trials for older adults, in which all aspects of the study protocol are being administered remotely. With this study, we will build capacity in implementing a multifaceted home-based intervention to delay dementia in a sample of community-dwelling older adults. We will also establish the extent to which measuring participant preference for a given intervention is related to subsequent adherence and compliance to the intervention treatment. We believe that this will inform other researchers and scholars alike on whether or not the costs and efforts associated with tailoring

interventions in future studies to match participant preferences are a worthwhile endeavor.

Furthermore, we are collaborating with a team of expert engineers and scientists to collect and examine a wealth of data from the actigraphy devices (ActiGraph GT9X). This collaboration with an engineering team will allow us to collect and analyze a large subset of objective measures of sleep and wake cycles, cardiovascular measures including heart rate, and mobility and gait parameters on a continuous basis.

In conclusion, SYNERGIC@Home will build capacity for future research RCT design using home-based interventions in older adults at risk for ADRDs.

12. RESEARCH TIMELINE

We wish to begin this project in January 2021. This study will be completed within two years of its start date: end date estimated for October 31, 2022. It is anticipated that patient recruitment will occur over at least a 10-month period and could be extended beyond this time depending on the results obtained.

13. LIST OF ABBREVIATIONS

AD: Alzheimer's Disease

ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive

ADCS-ADL: Alzheimer Disease Cooperative Study Activities of Daily Living

ADNI: Alzheimer's Disease Neuroimaging Initiative

ADRD: Alzheimer's Disease and Related Dementia

AE: Aerobic exercise

ANCOVA: Analysis of Covariance

Aβ: amyloid-β

BAT: Balance and Toning

BDNF: Brain-Derived Neurotrophic Factor

BHSP: Brain Health Support Program

BNT: Boston Naming Test

CCNA: Canadian Consortium in Neurodegeneration and Aging

CDR: Clinical Dementia Rating

CFC 2: Cognitive Functional Composite

CI: Cognitively Intact

COMPASS-ND: The Comprehensive Assessment of Neurodegeneration and Dementia

CV: Coefficient of Variation

FACETS: Functional Assessment of Currently Employed Technology Scale

GAD 7: Generalized Anxiety Disorder 7

GDS-30: Geriatric Depression Scale

IADL: Instrumental Activities of Daily Living

ICH-GCP: International Conference on Harmonization Good Clinical Practice

ITT: Intention-To-Treat

LSQ: Life Space Questionnaire

MCI: Mild Cognitive Impairment

MDA-14: Mediterranean Diet Assessment 14-items

MoCA: Montreal Cognitive Assessment

NTB: Neuropsychological Test Battery

PASE: Physical Activity Scale for the Elderly

PSQI-18: Pittsburgh Sleep Quality Index 18-items

PPA: Per-Protocol Analysis

RT: Resistance training

SCI: Subjective Cognitive Impairment

SF-36: Short Form quality of life questionnaire

SPSS: The Statistical Package for the Social Sciences

STOFHLA: Short Test of Functional Health Literacy

STST: One Minute Sit to Stand Test

SYNERGIC: SYNchronizing Exercises, Remedies in GaIt and Cognition

TCOGS: Telephone Cognitive Screening

TMT: Trail-Making Test

VBM: Voxel-Based Morphometry

VEGF: Vascular Endothelial Growth Factor

VRF = Vascular Risk Factors

WMHs: White Matter Hyper-intensities

14. DECLARATIONS

This study is conducted in compliance with International Conference on Harmonization Good Clinical Practice (ICH-GCP) and all applicable regulatory and ethical requirements. All authors and research staff have no declarations, financial or otherwise, to disclose.

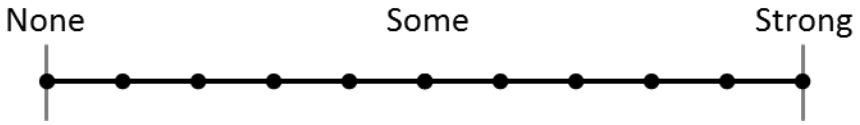
15. APPENDICES

APPENDIX A: INTERVENTION PREFERENCE QUESTIONNAIRE

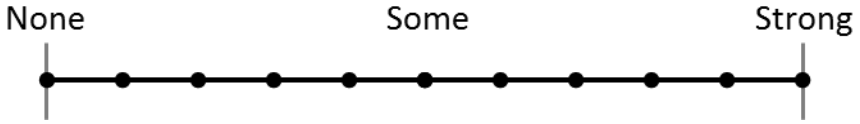
Participant ID # _____
Date (dd-mm-yyyy) _____

1. Given what you know *at this point in time*, please indicate how interested you are in each of the following interventions, by placing a mark along the line between no interest and strong interest.

Rate your level of interest in **physical exercise** as a way to improve your brain health



Rate your level of interest in **brain exercise** as a way to improve your brain health



2. Please rate your preference between physical exercise and brain exercise training. Select the response below that best describes your preference at this point in time.

   ☐ Strong preference for **physical exercise**
   ☐ Slight preference for **physical exercise**
   ☐ No preference
   ☐ Slight preference for **brain exercise**
   ☐ Strong preference for **brain exercise**

3. If you have selected that you prefer one of the interventions over the other, please indicate *why* you prefer it. If you have an equal preference, then you may skip this question.

4. Are there other interventions (besides physical exercise and cognitive training) that you would prefer? If so, please describe them below:

5. Please indicate if you have any additional comments pertaining to the interventions in this study below:

APPENDIX B: MATERIALS GIVEN TO PARTICIPANTS

The following items will be given to participants.

1. An ActiGraph GT9X Activity Monitor
2. A blood pressure cuff and monitor
3. A set of colourful exercise resistance bands for individuals in the AE+RT exercise condition.
4. An exercise mat for individuals in the BAT exercise condition.
5. A standard roll of measuring tape
6. A saliva kit

APPENDIX C: RECRUITMENT PLAN AND MATERIALS

SYNERGIC@Home RECRUITMENT PLAN	
Target Organization / Group / Provider / Platform	**Methods**
NB-PALM website	• Promote SYNERGIC@Home study through email synergic@unb.ca
Horizon Health Research Registry Patient Database	• Identify potential research participants who have joined the Research Registry and have volunteered to be included in brain health related studies.
Social Media	• Materials will be specifically developed with messages appropriate for posting on Facebook and other platforms popular with community dwelling older adults
Senior Goodwill Ambassador Program **Go Ahead Seniors/Aînés en Marche**	• Trained community volunteers who promote exercise and healthy living throughout NB • Email and flyers will be provided to the volunteer leaders of these programs for distribution to participants
Provincial Anglophone and Francophone Seniors' Organizations **Seniors and Healthy Aging Secretariat**	• Email and flyers to numerous seniors' organizations for posting on website and / or distribution to members • Association francophone des aîné(e)s du Nouveau-Brunswick • NB Senior Citizen's Federation • Association des universités du 3e âge du Nouveau-Brunswick T
NB Alzheimer's Society	• Distribute flyer to facilitators/ coordinators of care giver and patient support groups • Post flyer on website • Possible e-blast using generic email
Senior Centres	• Distribute flyer for posting • Have centre distribute if membership list is available • Seniors' Information Centre – Moncton • Seniors' Resource Centre – Saint John • Stepping Stone Senior Centre - Fredericton • Johnston Avenue Senior Centre – Fredericton • Université de troisieme Age Nord Ouest • Third Age Centre, St. Thomas University

SYNERGIC@Home RECRUITMENT PLAN	
Target Organization / Group / Provider / Platform	**Methods**
Targeted Provincial Special Interest/Membership Organizations	• Use list from Seniors and Healthy Aging Secretariat to distribute flyers, email • Distribute flyer for publication in seniors' newsletters, website • NB Society of Retired Teachers • Société des Enseignantes et des Enseignants Retraités Francophones du Nouveau-Brunswick • Email to UNB, U du M. Mt A alumni associations
Geriatric Clinics	• Provide Information Sheet to Geriatricians • Distribute flyer for posting
Primary Care Physician/Providers	• Provide Information Sheet for physicians and NPs • Distribute flyer for posting in office locations
Community Health Centres and Community Mental Health Centres	• Distribute flyer for posting
Community Developers	• Community Developers to distribute generic email, flyers to networks and organizations they work with
Print media	• Newspaper advertisements in Fredericton, Moncton, Saint John • Advertise in selected rural papers
Community-based businesses	• Flyers in selected physical locations where community dwelling older adults congregate i.e., libraries, recreation centres

RECRUITMENT FLYER (Image Based)

NB-PAVA

SYNERGIE-Chez soi

Projet de recherche

Vous avez entre 60 et 90 ans ?

Vous voulez entraîner votre corps et votre cerveau dans le confort de votre maison ou résidence ?

Vous avez accès à l'internet chez vous ?

Participation de 12 mois

- *4 mois d'exercices pour le corps et le cerveau, 3 fois par semaine*
- *6 séances d'évaluation*

Informations :

Site web : www.nbpalm.ca

Courriel : synergic@unb.ca

Téléphone : (506) 453-5137

Offert en français et en anglais

Cerveaux en santé du **N**ouveau-**B**runswick: **P**révenir l'**A**lzheimer en **V**ivant **A**utrement

Comités d'éthique de la recherche : UNB #2020-168, UdeM #2021-049, HHN #2020-2954, VHN

UNB EST. 1785 UNIVERSITY OF NEW BRUNSWICK · Réseau de santé Horizon Health Network · Réseau de santé Vitalité Health Network · Université de Moncton · CCNA Canadian Consortium on Neurodegeneration in Aging · CCNV Consortium canadien en neurodégénérescence associée au vieillissement · CAN Thumbs Up · Western · Healthy Seniors Pilot Project · Projet pilote sur les aînés en santé

Version 8.0, Feb 20th, 2022

SYNERGIC@Home

SYNchronizing Exercises, **R**emedies in **Ga**l**t** and **C**ognition **at Home**: Feasibility of a home- based double-blind randomized controlled trial to improve gait and cognition in individuals at riskfor dementia

SYNERGIC@Home is a research project assessing if it is possible to virtually deliver a home-based physical exercise and cognitive training program to older adults in New Brunswick. The hope is that this intervention will have a positive impact on memory for those at risk of developing dementia.

RESEARCH STUDY INVESTIGATORS

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Schulich School of Medicine & Dentistry, London, Ontario, Canada;
Departments of Medicine (Geriatrics) and of Epidemiology and Biostatistics,
University of Western Ontario, London, Ontario,Canada

INTRODUCTION AND BACKGROUND

A study called SYNERGIC taking place in Canada, is showing promising results that exercise and cognitive training can be beneficial for older adults who are experiencing early problems with their memory. This study—**SYNERGIC@Home**— is an extension of the SYNERGIC trial. This study will engage older adults at risk of developing memory problems in a home-based program that will use an online virtual platform called Zoom.

This study is also part of the *New Brunswick Brain Health Initiative: Preventing Alzheimer's through Lifestyle Modification* (NB-PALM), funded by the HealthySeniors Pilot Projects, Public Health Agency of Canada, Province of New Brunswick.

POPULATION UNDER STUDY

We are looking for interested older adults living in New Brunswick who are at risk for developing dementia between the age of 60 and 90 years.

You may be eligible to participate if you have:

1. **No Memory Problems** but have <u>two or more of the following risk factors:</u>
   - ☐ Overweight
   - ☐ Hypertension/High blood pressure
   - ☐ Diabetes
   - ☐ Cardiovascular disease
   - ☐ Physical inactivity
   - ☐ First-degree family history of dementia (parents, children, siblings)
   - ☐ High cholesterol
   - ☐ Poor sleep
   - ☐ Poor diet
2. Been diagnosed by a physician or nurse practitioner as having **Subjective Cognitive** Impairment or **Mild Cognitive Impairment.**

DESCRIPTION OF STUDY

This study will take place over 10 months and includes an initial general health questionnaire, memory tests, and mobility assessments. Assessments will occur before the start of the physical exercise and cognitive training, immediately after the training intervention and again at 10 months follow-up. The training intervention will take place over 4 months. The physical exercise and cognitive training sessions will be done virtually over a computer or tablet with a research assistant who is a personal trainer, 3 times per week. Each session will take about 90 minutes.

You are encouraged to have someone close to you who can assist you during the study, but this is not mandatory for everyone.

IF YOU HAVE FURTHER QUESTIONS REGARDING PARTICIPATION OR ARE INTERESTED IN HEARING MORE ABOUT THIS PLEASE CONTACT:

Research Coordinator
Alana Gullison
Phone: 1 (506) 453-5137
email: synergic@unb.ca

Research Assistant
Molly Gallibois
Phone: 1 (506) 447-3197
email: synergic@unb.ca

RECRUITMENT FLYER

RECRUITING PARTICIPANTS FOR ONLINE EXERCISE AND MEMORY STUDY TO TAKE PLACE IN YOUR OWN HOME!

Researchers at the University of New Brunswick, Université de Moncton, Horizon Health Network, and Vitalité Health Network are inviting your to participate in *SYNERGIC@Home, a* study about the role of exercise and cognitive training in delaying the onset of dementia and Alzheimer's disease.

WHO?

We want to hear from community dwelling older adults living in Anglophone and Francophone communities throughout New Brunswick who may be otherwise healthy, but feel their memory is worsening or have received a medical diagnosis of Mild Cognitive Impairment. If you are between the ages of 60 and 90 years, and meet the following criteria please contact us at synergicinfo@nb-palm.ca

- Have access to a computer in your home that is connected to high-speed Internet,
- Capable of sending and receiving emails,
- Can read/write/speak in either English or French, and
- Able to walk 10 meters (about 32 feet) independently, with/without a walking aid.
- Have a spouse, relative, or close friend interested in being a study care partner (an exception will be made if a study partner cannot be found)

WHERE?

*Research act*ivities usually done in an exercise lab or hospital setting, will be completed in your own home. This study will help us learn how practical it is to conduct research using video-conferencing to train participants and collect data. Participants' activity and sleep patterns will be monitored using a wrist-watch like device called an activity monitor.

WHAT?

Participants will be enrolled for a total of 10 months. You will be assigned an exercise and cognitive training program delivered in 3 – 90 minute sessions per week over 16 weeks. Sessions consist of both prescribed cognitive training and exercises. A research assistant trained in exercise science will guide participants through the exercises.

Questionnaires and assessments will be completed at various time points such as: screening for enrollment, baseline, and two follow-up sessions. Your medical history and cognitive functioning will be assessed and information collected about your lifestyle habits (e.g., how much exercise and physical activity you do, how well you sleep, your diet, and mental health)

STUDY CONTACT INFORMATION: Synergic@Home Study Research Coordinator email: synergic@unb.ca	

Initial Recruitment Email

PROCEDURE:

Following REB approval, this email along the flyer will be sent to organizations that post on their website and do an eblast to members and others including:

- Seniors organizations to include on website and newsletters
- Senior Ambassadors through Healthy Aging and Seniors Secretariat
- Community developers with HHN and VHN

Email Subject Line: Take part in a new virtual study called **SYNERGIC@Home!**

Email Content:

NB PARTICIPANTS WANTED FOR AN ONLINE EXERCISE AND MEMORY STUDY IN YOUR OWN HOME!

You are invited to take part in *SYNERGIC@Home – a research project studying how exercise a*nd cognitive training may delay the onset of dementia and Alzheimer's disease. We want to hear from community dwelling older adults living in Anglophone and Francophone communities throughout New Brunswick who may be otherwise healthy, but feel their memory is worsening or they have a medical diagnosis of Mild Cognitive Impairment. If you are between the ages of 60 and 90 years and meet the following criteria, we would like to hear from you:

- Have access to a computer in your home that is connected to the high-speed Internet,
- Capable of sending and receiving emails,
- Can read/write/speak in either English or French, and
- Able to walk 10 meters (about 32 feet) independently, with or without a walking aid.
- Have a spouse, relative, or close friend interested in being a study care partner (an exception will be made if a study partner cannot be found)

You are INELIGIBLE for our study if you have received a medical diagnosis of dementia or Alzheimer's disease by your family or specialist physician.

Promising Canadian research has shown that older adults who are at risk can benefit from participating in physical exercise and cognitive training. *We want to learn if s*tudy activities usually done in an exercise laboratory setting can be virtually completed in a participant's home. We also want to find out how practical it is to collect data from participants' about their activity levels and sleep patterns using a wrist-watch like device called an activity monitor.

For further information, please email: synergicinfo@nb-palm.ca

SYNERGIC@Home is *conducted by researchers at University of New Brunswick, Université de Moncton, Horizon and* Vitalité Health Networks *as well the University of Western Ontario. It is* part of the project *New Brunswick Brain Health Initiative: Preventing Alzheimer's through Lifestyle Modification* NB-PALM, which is funded by the Healthy Seniors Pilot Project (NB government) and the Canadian Consortium of Neurodegeneration on Aging. We are always looking for additional participants. If you think someone you know may be interested in taking part in this SYNERGIC@Home, please forward them this email.

Thank you for your interest!

Synergic@Home Study Research Coordinator

Email: synergic@unb.ca

Recruitment Newspaper Advertisement

Recruitment Newspaper Advertisement Content as follows:

SYNERGIC@Home Newspaper Advertisement

Procedure

- To advertise in selected NB newspapers assuming budget is available; i.e., Telegraph Journal (Saint John, Fredericton, Moncton issues)
- To advertise in selected rural newspapers assuming budget availability.

RECRUITING PARTICIPANTS FOR AN ONLINE EXERCISE AND MEMORY STUDY IN YOUR OWN HOME!

Feeling as if your memory is worsening?

Have you received a medical diagnosis of Mild Cognitive Impairment?

If so, you may be eligible to be a participant in

SYNERGIC@Home

A home-based virtual exercise and cognitive training research study for community living older adults residing in Anglophone and Francophone communities at risk of developing dementia and Alzheimer's Disease

For more information contact us at synergic@unb.ca

Follow-up Email

Dear****

I am a Study Research Coordinator with the SYNERGIC@Home study. I understand that you are interested in learning about our study.

I have enclosed a copy of the consent forms that provides detailed information on this project including the requirements of your participation.

I will follow up with you in a few weeks to see if you might be interested in participating.

In the meantime, if you have any questions, please email or call me as per the information below.

Thank you for your interest!

Synergic@Home Study Research Coordinator

Email: synergic@unb.ca

Version 8.0, Feb 20th, 2022

Study Information for Physicians / Providers

We are inviting you to discuss the following opportunity with your patients.

SYNERGIC@Home

An online exercise and cognitive training program taking place in the participant's own home

What is the Synergic@Home study?

SYNERGIC@Home, is a provincial study taking place throughout New Brunswick and will involve 64 participants from rural and urban locations who will "virtually" participate.

The study goals are twofold. The first is to learn about the role of exercise and cognitive training in preventing or delaying the onset of dementia and Alzheimer's disease; while the second goal is to find out how practical it is to conduct this research in a participant's home.

By participating in this study your patients will be making a valuable contribution about how to conduct research in a home environment that previously was conducted in hospital and university settings.

What is expected of participants?

Study participants must meet detailed inclusion and exclusion criteria which will be provide to you. A brief overview is as follows:

- Have access to a home computer that is connected to the high-speed Internet
- Capable of sending and receiving emails,
- Can read/write/speak in either English or French
- Able to walk 10 meters (about 32 feet) independently, with or without a walking aid
- Have a spouse, relative, or close friend interested in being a study care partner (an exception will be made if a study partner cannot be found)

Study participants will be randomly assigned to one of four exercise and cognitive training groups and asked to participate via Zoom. as outlined below:

The following table contains details of the study procedures /activities that you may wish to share/discuss with your patient.

Details of Research Study Assessments and Intervention		
Participant Activities	**When does this happen? How long will this take?**	**Description**
Consent & Clinical / Cognitive Screening	At consent: 2 hours	Screening is what you take part in to see if you are eligible to enter our study. The study team will review the Informed Consent Form with you to answer your questions about the study. After you sign the consent, the study team will ask questions about your: ▪ Personal and demographic information ▪ Health, family medical history, medications The study team will also test your memory and thinking skills.
Mobility & Lifestyle Screening	After giving your consent: 2 hours	You will be asked to questions about your lifestyle, physical activity, sleep patterns, and diet. You will be asked to perform tests to assess your walking speed and mobility. The study team will assist via you in taking measurements such blood pressure and waist size.
Physician & Participant Conference	After giving your consent: 1 hour	You will meet with a research physician who will review your medical history and discuss any specific concerns or questions related to your eligibility for participation in our study.
Activity Monitoring	Before the intervention begins: 10 days	You will wear an activity monitoring device similar to a wristwatch for 24 hours each day. This device records information about your activities and hours of sleep. This equipment will be sent to you via a secure courier and you will return it to the study team at the end of the 10 days.
Activity Assessment	Before the intervention begins: 2 hours	You will be asked to perform tests to assess your mobility and walking speed.
Cognitive Assessment	Before the Intervention begins: 2 hours	The study team will conduct tests to assess your memory, language, attention span, and problem-solving abilities.
Study Intervention	After you are enrolled: 96 hours	The research team will assign to a study group. You will follow exercise and cognitive training programs via Zoom for 2 hours per day, 3 times

Details of Research Study Assessments and Intervention		
Participant Activities	**When does this happen? How long will this take?**	**Description**
		per week for 16 weeks. A research assistant will be present during each of the exercise sessions.
Activity Monitoring	After completing the intervention: 10 days	About four months after you began your exercise and cognitive training program, you will once again wear an activity monitoring device for a period of 10 days. This equipment will be sent to you via a secure courier and you will return it after 10 days.
Activity Assessment	After completing the intervention: 2 hours	You will be asked to perform tests to assess your mobility and walking speed.
Cognitive Assessment	After completing the intervention: 2 hours	The study team will conduct tests to assess your memory, language, attention span, and problem-solving abilities.
Activity Monitoring	10 months after beginning the study: 10 days	For the final time, you will wear an activity monitoring device. Equipment will be provided as before and you will return it after 10 days.
Activity Assessment	10 months after beginning the study: 2 hours	You will be asked to perform tests to assess your mobility and walking speed.
Cognitive Assessment	10 months after beginning the study: 2 hours	The study team will perform tests to assess your memory, language, attention span, and problem-solving abilities.
Semi-structured interview	10 months after beginning the study: 30-45 minutes	A member of the study team will arrange a time for you to be interviewed via Zoom. You will be asked questions about your experience as a study participant.

If you have questions about this study or would like to send along a referral, please contact the Synergic@Home Study Research Coordinator.

Email: synergic@unb.ca

Recruitment Discussion Guide for Obtaining Consent

PROCEDURE

- Following REB approval, this discussion guide will be used by the Research Coordinators at HHN and VHN to review the consent form with the prospective participant and obtain consent.

INTRODUCTION

Hi my name is [*insert name*]. I am a Research coordinator with [*insert name]* which is one of our study sites.

I'm calling about the research study called Synergic@Home. I understand that you contacted us to say you were interested in becoming a participant. You indicated you saw the flyer in [insert if this information is known]. The reason I am calling is to discuss the study and proceed with obtaining your consent to participate in our study if you are ready to make that decision today.

Before we start, I'd like to [confirm or obtain] some basic personal information.

Name of Potential Study Participant:

_____

Email: _____

Phone number:_____

Home address:_____

Age:_____

Next, I'd like to carefully go over different sections of our form to make sure you understand what's involved and your role as a study participant.

So if you're okay to start, let's begin.

Did you receive the consent form that we recently mailed to you or sent via email?

- You did receive it – that's terrific.

Have you had an opportunity to read through it in detail?

- You did – that's wonderful.

As you were reading through it, did you make notes by any sections or sentences that you want to discuss with me? Or that you want me in explain or clarify?

RESPONSE 1:

- The form was very informative and I am ready to sign it.

If that's the case, then before we sign it, I'd like to go over some particular sections of the form. It's my role to make sure that you fully understand and are informed about your rights as a study participant.

RESPONSE 2:

- Answer the specific questions.

Then move on to reviewing the sections of the form that were not addressed by the questions. "It's my role to make sure that you fully understand and are informed about your rights as a study participant. I noticed that there are some sections of the form that you didn't have any questions about, so before we sign it, I'd like to go over some particular sections of the form".

BEGIN TO REVIEW THE SPECIFIC SECTIONS OF THE CONSENT FORM

Let's start with you answering a FEW KEY QUESTIONS and then we'll walk through other sections of the consent. Here's the first question:

Have you discussed your participation with your any family members, friends or your family physician?

- Yes or no

Do you understand that your participation in Synergic @ Home is your decision?

- Yes or no

Are you aware that your participation in Synergic @ Home is entirely voluntary?

- Yes or no

I want to stress that you can withdraw from the study at any time

- Understood or not

Finally, will you be having a study care partner? A study care partner is a spouse or family member or friend who will be asked information about your health behaviors at various time as well as provide you with support and encouragement throughout the study.

- Yes – I have a study partner.
    - Who is going to be your study partner?
    - What is their relationship?
    - I will need contact information as this person will also need to sign a consent form.
- No study partner.

RESEARCH PURPOSE AND BACKGROUND:

Do you have any questions about why we are doing this study?

- Yes - no

We are pleased to be offering the SYNERGIC@Home feasibility trial to NB residents. We are used to doing this research in a laboratory setting at a university or health center. So, since we can no longer bring people in during the pandemic, we decided to conduct a study about exercise and cognitive training in a participant's home using video-conferencing. Your participation will help us learn about the practicalities of doing this type of research remotely.

STUDY PROCEDURES

The consent describes the study activities in various sections. When you become a participant, you will be enrolled in an exercise and cognitive training program that you take part in for three sessions each week over 16 weeks. Each of these weekly sessions will consist of both cognitive training and exercises and will last about an hour and one-half. During each of these sessions a research coordinator who is trained in exercise science will guide you through your program.

Do you have any questions about the amount of time needed to participate each week?

As a participant in our study there are numerous questionnaires you will be asked to complete along with assessments that research coordinators such as myself will be conducting with you [and your study partner].

Now as you saw in the different sections describing the study activities, there are various times during the study when we will collect information from you [and your study partner if available]. This is when we will ask you questions about your medical history as well as assess your cognitive functioning. We do this by asking you questions that test your memory and thinking skills. We also use questionnaires that ask your lifestyle habits such as how much exercise and physical activity you do, how well you sleep, your diet as well your mental health.

Any questions about the assessments and questionnaires?

In order to complete the study exercise activities you will need some equipment which we will send to your home for you to sue throughout the study. Some examples are an activity monitor, exercise mat, blood pressure cuff, and so on. If you are familiar with a Fitbit – this is what the activity monitor looks like and you wear it like a wristwatch such as shown in the picture. It records information about your activity and sleep levels and you will return this to us at various times throughout the study. We will also get you to take your blood pressure and certain other measurements.

I imagine this is a lot of information to take in, however there will always be someone guiding you on the video-conference while you are using this equipment. Some of the equipment you will be able to keep, while others like the activity monitor and blood pressure cuff you will return at the end of the study.

Do you have any questions about the equipment?

You may be wondering about our sanitation procedures. Each time after you return the equipment, it will be thoroughly cleaned and sanitized prior to mailing it back to you.

We will also be sending you a manual that will contain easy to read instructions about various aspects of the study. And remember that someone will always be available by phone, video-conference, or email if you have any questions.

It's important for you to understand that before you can become a participant, we will need to collect information during a screening visit that will help us determine if you meet the study eligibility criteria. Do you have any questions about this aspect?

It will no doubt be me that will meet with you [and your study partner] to complete this assessment. There may also be another nurse who has a background in research who will interview you. Between the two of us, we will gather information to help us decide about your suitability for our study.

RISKS AND DISCOMFORTS

Do you have any questions about the section in the form that described the risks and discomforts?

As I previously mentioned, we will be giving your cognitive training tests and exercises to do three times a week. And, depending on how much exercise you are used to doing, you may experience some discomfort while you are performing the exercises. If you do, you can stop at any time. And our research coordinator will be watching you as you exercise. S/he will ask you to stop if you are experiencing shortness of breath, chest pain, dizziness, or unsteadiness.

During the cognitive training part of each session you may experience some frustration as you complete the tasks. Also, you may feel a bit of discomfort if you are not used to wearing a wrist watch but hopefully that won't happen!

Finally, you know that we have various questions and assessments that will take some time to complete. We know this can be frustrating for some people. And we know from our experience that some questions may trigger an unpleasant memory or distressing feelings. We will watch closely for your reactions and will suggest taking a break. And as always, you can ask to take a break at any time.

We are not aware of any side effects from wearing the activity monitor.

I also want to stress that it's your right to stop your participation in the study at any time and there is no judgement or penalty if you decide to do so. Also you don't need to give a written note notifying your withdrawal. Okay?

COST/BENEFIT

There is no direct cost for you to participate. We will provide everything you need except of course your computer or laptop and the internet connection.

In relation to benefits, so far some of our participants have mentioned they are pleased to be taking part in a NB study that will help researchers learn more about how to do this type of research in a participant's own home.

Are there any questions about this section?

PRIVACY AND CONFIDENTIALITY

The section on privacy and confidentiality is quite detailed.

Do you have any questions about the procedures we described about how your personal information including your name, email, phone number, address, medical conditions and so on will be protected and kept private throughout the study?

- If yes, answer the questions…..

I know we also described numerous ways about how your personal research data will be stored. Do you have any concerns about the information that is included in this section of the form?

- If yes, answer the questions.

Now if you're ready, I'm going to ask if you would like to participate in this study?

- If no - thank you very much for your time.

- If yes – let's proceed to the section of the form where I need to obtain your consent.

Direction: Proceed to review the different sections where you need to obtain consent. I.e., get initials in each box or sentence pertaining to the various study components.

After finalizing the consent form, provide directions as to how to return the form.

- If returned by email they will need to scan the original and email it to you.
- If returned by mail, the research coordinator will need to make a copy which is then returned by email or mail to the participant.

Now before I finish our call, I'd like to get the contact information for your study partner [if one is participating]

Name of Potential Study Partner:

_____

Email: _____

Phone number:_____

Home address:_____

Thank you for taking the time to review the form and agreeing to participate. I will be in touch with you to confirm a time when we will conduct the screening assessment. In the meantime, you have my contact information [provide email and phone number]. If you have any questions don't hesitate to be in touch. Good bye for now.

APPENDIX D: EXIT QUESTIONNAIRE

SYNERGIC@Home Exit Questionnaire

Rate how much you agree or disagree with each statement	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1. *Zoom* was easy to use in completing my exercise program.	○	○	○	○	○
2. Wearing the activity monitor was not a problem for me.	○	○	○	○	○
3. I did not like using my own computer/laptop to participate.	○	○	○	○	○
4. I did not like having a research assistant supervise my exercises.	○	○	○	○	○
5. Taking part in the program 3 days per week was the right amount of time for me.	○	○	○	○	○
6. Exercising in my own home was convenient.	○	○	○	○	○
7. I encountered many problems with my internet connection.	○	○	○	○	○
8. The research assistant was helpful in assisting me to complete my exercises.	○	○	○	○	○
9. I was frustrated because the exercises were too difficult to complete in my home.	○	○	○	○	○
10, I did not enjoy completing the assessments and testing on *Zoom.*	○	○	○	○	○
11. Each week I looked forward to my cognitive training program.	○	○	○	○	○
12. Participating took too much time away from my other activities.	○	○	○	○	○

13. Wearing the activity monitor interfered with my sleep and other activities.	○	○	○	○	○
14. I was able to form a positive relationship with the research assistant.	○	○	○	○	○
15. I would have preferred exercising with a group of my peers.	○	○	○	○	○
16. I felt anxious when I was asked questions that tested my memory.	○	○	○	○	○
17. I enjoyed doing the cognitive exercises.	○	○	○	○	○
18. I would have preferred having one of my peers or someone who is my age assist with my exercises.	○	○	○	○	○

19. There were 4 intervention groups participating in the SYNERGIC@Home research study. Of the four groups listed below, which one do you think you were assigned to?

- ☐ Active exercises and active cognitive training
- ☐ Active exercises and limited cognitive training
- ☐ Limited exercises and active cognitive training
- ☐ Limited exercises and limited cognitive training

20. We are interested in hearing about what motivated you to complete the interventions. Please describe the factors or reasons that influenced your decision.

_____

_____

_____

_____

_____

APPENDIX E: SEMI-STRUCTURED INTERVIEW GUIDE

Semi-Structured Interview Guide	
Dimension	**Questions**
Reaction to Participation in Research Study	**Overarching Questions:** How satisfied were you with the study? How was the support you received during the study? **Probing Questions:** What was your experience: ▪ Doing this study over the Internet? ▪ With the equipment you used? What are your thoughts about the assessments that took place? How can this study be improved?
Learning That Occurred During the Research Study	**Overarching Questions:** What knowledge or information about exercise did you learn from your participation? What did you learn from your involvement with cognitive training? **Probing Questions:**

Semi-Structured Interview Guide	
	Were there any areas that you had to "unlearn"? For example, did you find out that you had been doing exercises inappropriately? Have you identified any differences in your memory or concentration?
Behaviour Changes That Occurred During the Research Study	**Overarching Questions:** Have you modified your behaviour as a result of participating in the study? If yes, what are they? Can you identify any motivators that helped you to change or modify your behaviours?
Results Identified by the Participants	**Overarching Questions** What have been the greatest results for you?
Concluding Questions / Comments Is there anything that has not been asked that needs to be brought forward? Are there any comments you would like to add?	

APPENDIX F: CASE REPORT FORMS

APPENDIX G BUDGET SUMMARY

Budget Summary for Synergic@Home Study

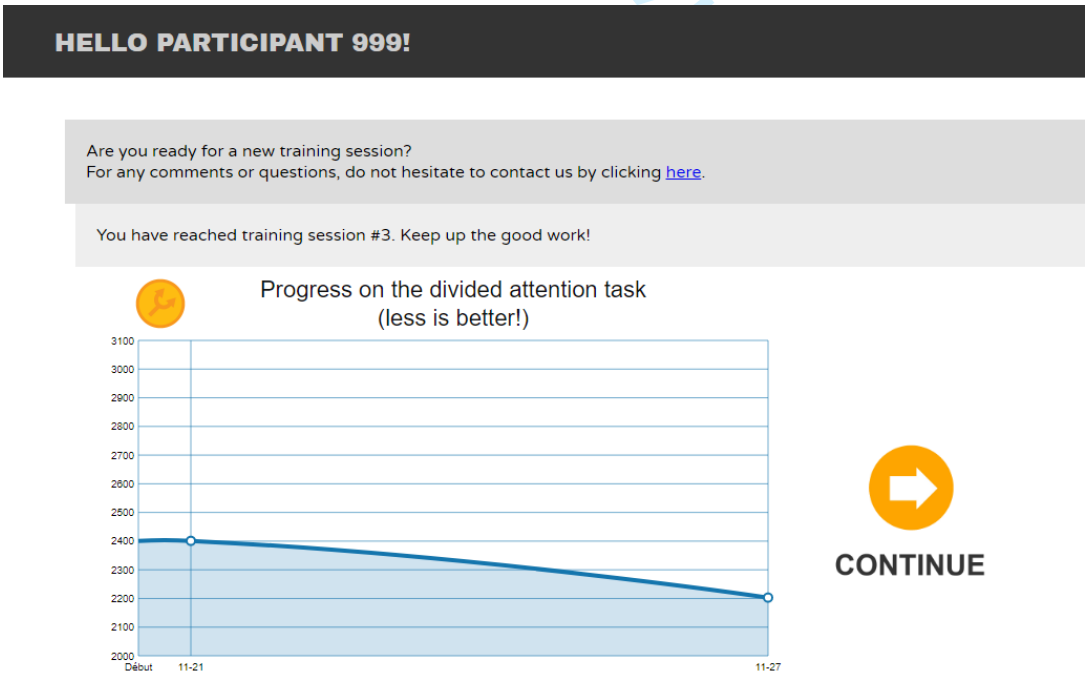
Funding Source:	Health Seniors Pilot Project (HSPP)
Project Title:	The New Brunswick Brain Health Initiative: Preventing Alzheimer's by Lessening Modifiable risk (NB-PALM)
Project Award Amount:	$2.69M
Study Title:	SYNERGIC@Home/SYNERGIE~Chez soi
Study Budget Amount:	$559,049.69

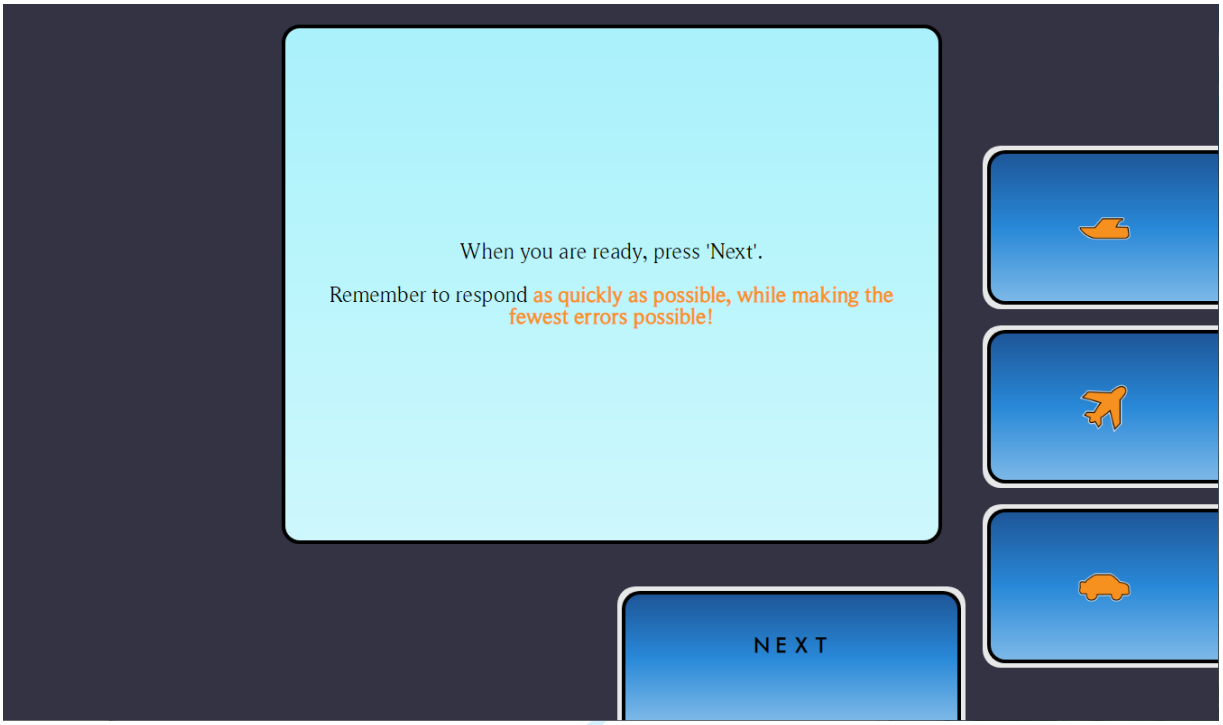
Synergic@Home Study Budget	**Study Budget Nov 2020 to end Oct 2022**
A) Personnel (include 20% benefits)	
HHN Clinical Research Coordinator	$ 149,760.00
VHN Clinical Research Coordinator	$ 140,400.00
UNB Study Research Coordinator	$ 112,589.28
(4) Intervention Research Assistants	$ 119,172.41
Subtotal	$ 521,921.69
B) Evaluation	
Community Consultations	
Focus Groups	
Surveys	
Venues	$ -
Software	
Subtotal	$ -
C) Travel	
Transportation	
Accomodation	
Meals and Incidentals	
Meeting Space	$ -
Subtotal	$ -
D) Materials	
Office Supplies	

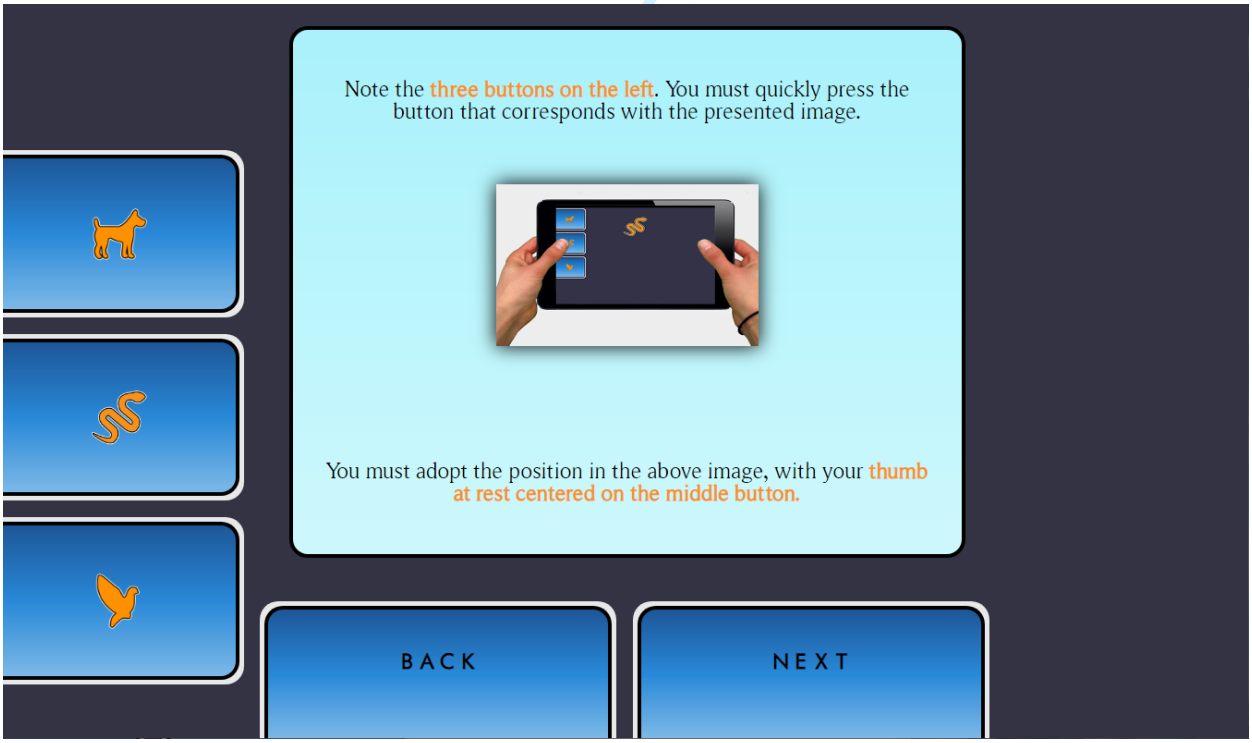
Project Materials		
Printing	$	1,000.00
Postage	$	1,000.00
Other	$	-
Subtotal	$	2,000.00
E) Equipment		
Office Equipment	$	1,000.00
Computer	$	10,500.00
Furniture	$	1,000.00
Special Equipment	$	22,628.00
Other		
Subtotal	$	35,128.00
F) Rent and Utilities		
Rent	$	-
Utilities	$	-
Subtotal	$	-
G) Other (specify)		
Training	$	-
Translation/ Interpretation Fees	$	-
Membership Fees	$	-
Subtotal	$	-
Total Cost		
Total Budget	**$**	**559,049.69**

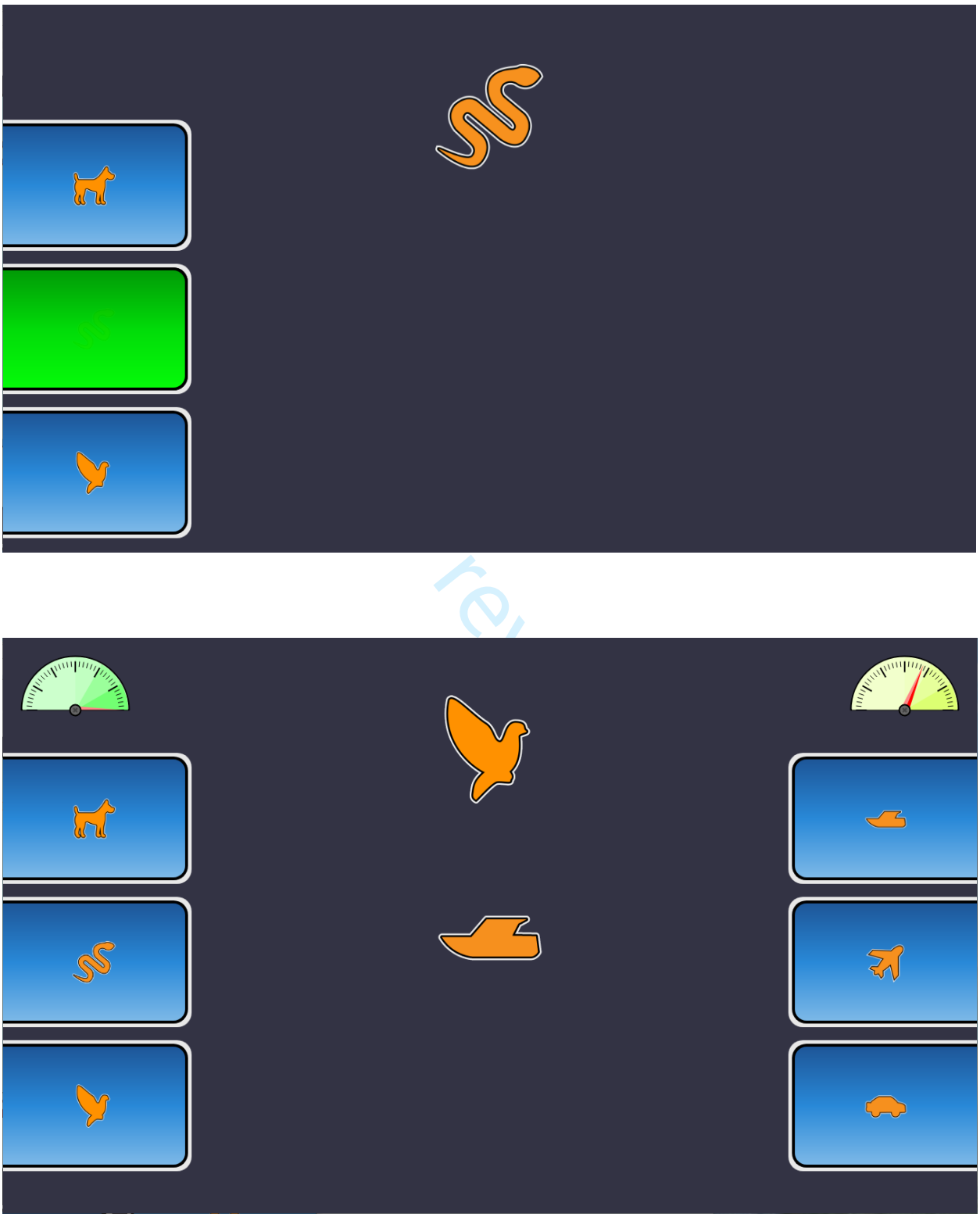
Version 8.0, Feb 20th, 2022

APPENDIX H: NEUROPEAK DUAL TASK SOFTWARE - SAMPLES









APPENDIX I: PROTOCOL DEVIATION FORMS

Protocol Deviations Log

Subject ID	Description of Protocol Deviation:	Deviation Category*	Deviation Code**	Date Deviation Occurred: (dd/mmm/yyyy)	Date REB Notified (if applicable):	Principal Investigator's Signature	Date Signed (dd/mmm/yyyy)

***DEVIATION CATEGORIES:**

A. Safety
B. Informed Consent
C. Eligibility
D. Protocol implementation
E. Other, specify in log

**DEVIATION CODES: Numbers listed by the sample protocol deviations

Safety (Category A)

1. Not reporting an SAE within 24 hours
2. Laboratory tests not done
3. AE/SAE is not reported to REB
4. Other, specify in log

Informed Consent (Category B)

10. Failure to obtain informed consent
11. Consent form used was not current REB-approved version
12. Consent form does not include updates or information required by REB
13. Consent form missing
14. Consent form not signed and dated by participant
15. Consent form does not contain all required signatures
16. Other, specify in log

Eligibility (Category C)

20. Participant did not meet eligibility criterion
21. Randomization of an ineligible participant
22. Participant randomized prior to completing Baseline Assessment, etc.
23. Randomization and/or treatment of participant prior to REB approval of protocol
24. Other, specify in log

Protocol implementation (Category D)

30. Failure to keep REB approval up to date
31. Participant receives wrong treatment
32. Participant seen outside visit window
33. Use of unallowable concomitant treatments
34. Prescribed dosing outside protocol guidelines
35. Missed assessment
36. Missed visit
37. Other, specify in log

Protocol Deviation Form (Descriptive)

Subject ID:		**Date:**	mm / dd / yyyy
Description of Protocol Deviation:			
This form completed by:			

***Study Title**: SYNERGIC@Home*

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____1_____
	2b	All items from the World Health Organization Trial Registration Data Set	___n/a_____
Protocol version	3	Date and version identifier	____1_____
Funding	4	Sources and types of financial, material, and other support	____16_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1,16____
	5b	Name and contact information for the trial sponsor	___n/a_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___n/a_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___n/a_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8,9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10,11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11,12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11,12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix C & D
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Appendix A, D & E

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.