**FULL STUDY TITLE**

CogStep Phase 2.0: Evaluation of a 12-week combined home-based exercise and psycho-education program on dementia risk, mood, health knowledge, cognition, sleep, metabolic markers and brain connectivity in individuals with cognitive difficulties.

**SHORT STUDY TITLE**

CogStep Phase 2.0

**CONFIDENTIAL**

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# STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

Contents

STATEMENT OF COMPLIANCE 1

GLOSSARY OF ABBREVIATIONS 5

1. Study Management 5

2. INTRODUCTION AND BACKGROUND 7

3 STUDY OBJECTIVES 9

4. STUDY DESIGN 10

5. STUDY TREATMENTS 11

6. PARTICIPANT ENROLLMENT AND RANDOMISATION 12

6.3 Informed Consent Process 15

7. STUDY VISITS AND PROCEDURES SCHEDULE 20

Study Flow Chart 20

8. CLINICAL AND LABORATORY ASSESSMENTS 21

9. ADVERSE EVENT REPORTING 23

*Unexpected Adverse Event:* 24

10. STATISTICAL METHODS 26

11. DATA MANAGEMENT 27

12. ADMINISTRATIVE ASPECTS 28

13. USE OF DATA AND PUBLICATIONS POLICY 28

14. REFERENCES 28

# PROTOCOL SYNOPSIS

|  |  |
| --- | --- |
| Title | CogStep Phase 2.0: Evaluation of a 12-week combined psycho-education and home-based exercise program on dementia risk, mood, health knowledge, cognition, sleep, metabolic markers and brain connectivity in older adults with cognitive difficulties. |
| Objectives | Primary:  The primary objective of this study is to examine the effect of a 12-week combined psycho-education and exercise program (CogStep Phase 2.0) on Alzheimer’s disease risk index score in adults aged > 60 years with cognitive difficulties.  Secondary:  The secondary objectives of this study are to assess the effect of a the’CogStep Phase 2.0’ program on mood, health knowledge, cognition, sleep, metabolic markers and resting state functional connectivity.  In addition, this study aims to evaluate recruitment, compliance, uptake and effect size to facilitate accurate power and sample size calculations for future randomised controlled trials. |
| Study Design | Two arm, Pilot, Randomized Controlled Trial |
| Planned Sample Size | Planned: 25 subjects |
| Selection Criteria | To be eligible participants must:   * Have a Memory and Ageing Telephone Screen learning learning score between 13 and 19. * Be greater than 60 years old at time of assessment; * Be willing to attend baseline (Week 1) and follow-up (Week 13) assessments at the Brain and Mind Centre; * Be willing to undergo a Magnetic Resonance Imaging scan at baseline and follow-up at the Brain and Mind Centre; * If randomized to the intervention arm, be willing to receive monitoring phone calls and attend a clinical review at 6-weeks mid-intervention; * If randomized to the intervention arm, be willing to view the weekly psycho-education sessions and implement their prescribed exercises at home; * If randomised to the control arm, be willing to receive health information via text message, email or letter at weeks 2, 4, 6 and 9.   Participants will be excluded if they:   * Have insufficient English language skills for neuropsychological assessment; * Have a diagnosis of dementia or suspected dementia (MATS learning score <13 ); * Have a history of any other major neurological conditions (e.g. stroke, epilepsy); * Have current severe mood disturbance (K10 score > 30); * Have a history of head injury with loss of consciousness for greater than 30 minutes; * Have a medical condition known to affect cognition (e.g. cancer); * Have a high level of baseline physical activity at study commencement (i.e. meets minimum American College of Sport Medicine exercise guidelines); * Have any exercise contraindications (including unstable angina, uncontrolled cardiac failure, severe aortic stenosis, uncontrolled hypertension, symptomatic hypotension, resting tachycardia or arrhythmia, uncontrolled diabetes or acute illness/fever) * Have any contraindications for magnetic resonance imaging scanning (e.g. aneurysm clip, pacemaker etc); * Have started taking any new medications in the two months prior to commencement of the trial; and/or * Are the current recipient of a cognitive training intervention (therapist or internet-based). |
| Study Procedures | Information regarding the study will be circulated to general practitioners and specialists; disseminated via advertisements (with permission) in the Brain and Mind Centre, community centres and relevant public areas. We will also advertise via social media; presentations at seminars and/or forums; by emailing or posting study information to previous Healthy Brain Ageing Program study participants who have consented to be contacted about further research; and by word of mouth. Potential participants will be directed to complete an online screening questionnaire to determine provisional eligibility via RedCap. This questionnaire will be anonymous, however if eligible, participants will be given the option to request to be contacted by the study team, where we will offer further information about the study and complete the remaining screening assessment. Should the ‘CogStep Phase 2.0’ study team be contacted directly by interested participants, a member of the team will speak to the interested participant and conduct the eligibility screen via telephone. This phone call will include an overview of the study, informed verbal consent, an eligibility interview, and cognitive screening via the Minnesota Cognitive Acuity Screen. Eligible participants are then invited to the ‘CogStep Phase 2.0’ baseline assessment.  The baseline assessment is administered by trained clinicians at study commencement (Week 1), after which participants will be randomized to either the ‘CogStep Phase 2.0’ program or ‘Waitlist Control’ group. Immediately following the cessation of the intervention (Week 13), both groups will undergo a follow-up assessment.  Study assessments for participants will include:   * Alzheimer’s disease risk index (ANU-ADRI); * Self-Report Questionnaire (assessing mood, quality of life, cognition, sleep, physical activity, nutrition and diet, and psychological wellbeing); * Physical, Medical and Neuropsychological Assessments (assessing grip strength, balance, leg strength, gait, psychiatric history, global cognition, learning, memory, executive functioning and processing speed); * Blood Assessment (to examine markers of metabolic health); * Actigraphy (to measure sleep/wake and physical activity behaviour); * Magnetic Resonance Imaging (to assess brain structure, function and neurometabolite concentration); * Cardiovascular Assessment (to examine arterial stiffness and central aortic pressure). |
| Statistical Procedures,  Sample Size Calculation,  Analysis Plan: | No formal power analysis has been conducted as this study is a pilot study for the purposes of calculating sample and effect sizes needed. This study is exploratory in nature and the outcomes will be used to power a larger more rigorous randomized controlled trial and establish an adequate protocol to leverage future funding.  Group differences at baseline will be assessed using independent samples t-tests for continuous data and chi-squared tests for categorical data (such as gender). A repeated measures analysis of variance will be used to examine group differences in primary and secondary outcomes. |
| Duration of the study | 18 months |

# GLOSSARY OF ABBREVIATIONS

|  |  |
| --- | --- |
| **ABBREVIATION** | **TERM** |
| **AD** | Alzheimer’s Disease |
| **AE** | Adverse event |
| **GCP** | Good clinical practice |
| **GP** | General Practitioner |
| **HBA** | Healthy Brain Ageing |
| **HREC** | Human Research Ethics Committee |
| **MATS** | Memory and Aging Telephone Screen |
| **MCI** | Mild Cognitive Impairment |
| **MOCA** | Montreal Cognitive Assessment |
| **N** | Number |
| **NHMRC** | National Health and Medical Research Council |
| **SAE** | Serious adverse event |
| **TGA** | Therapeutic Goods Administration |

# STUDY MANAGEMENT

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The University of Sydney.

* 1. **Funding and resources**

This study is being funded by the KickStart Grant awarded to Dr. Kathryn Broadhouse by the Balnaves Foundation and Sydney Medical School partnership.

# INTRODUCTION AND BACKGROUND

* 1. **Background Information**

*Dementia Risk as a Target for Intervention*

With Australia’s ageing population, disease burden and health care costs associated with dementia, in particular Alzheimer’s Disease (AD), are increasing (1). This rapid increase in the prevalence of dementia will constitute a significant burden on health care provision, both from an institutional perspective, but also at a community, family and individual level. Although several pharmacological interventions provide symptomatic relief for the symptoms of dementia, no effective treatments exist currently. As such, the need to address dementia risk factors, slow cognitive decline, improve wellbeing and limit functional impairment in these groups is clear.

*Relationship Between Cognitive Difficulties and Dementia Risk*

There is increasing evidence that individuals with subjective cognitive complaints are at a much greater risk of meeting criteria for objective cognitive decline longitudinally. Indeed, a recent meta-analysis demonstrated that over a 4-year period, 40.7% of individuals with subjective memory complaints convert to either mild cognitive impairment (MCI) or dementia (2). This equates to an annual conversion rate of subjective memory complaint to dementia of 2.3%, with a relative risk of 2.1 compared to individuals without cognitive complaints. These findings are supported by a recent systematic review that further highlights the research and clinical significance of subjective memory complaints (3). Of nine studies included in the review, eight found that subjective cognitive complaints are associated with a higher risk of progression to MCI or dementia, with the remaining study showing a non-significant increase in MCI incidence after a 4-year follow-up period. As such, this represents an important period to intervene and address modifiable risk factors for cognitive decline and dementia.

*Relationship Between Exercise and Cognitive Functioning*

Members of this team have led international efforts in the development, implementation and research translation of successful exercise-based interventions for older people (4-7). Given that 83% of Australians aged >75 years are physically inactive (8), programs incorporating exercise into daily life are urgently required. Such programs need to incorporate a combination of aerobic, muscle strengthening and balance/flexibility exercises at least three times per week (9). Importantly, our work has shown that exercise programs can be easily delivered in the home environment and adherence is high (4-7, 9). Of great concern, inactivity is not only associated with functional decline, loss of independence and disease burden, but is also associated with a greater risk of dementia (9). A recent review of 24 randomised controlled trials and 21 prospective studies highlighted that older people who exercise have a 40% lower risk of AD, with benefits extending to mood, quality of life and activities of daily living (10). Indeed, reducing inactivity by 25% would prevent one million cases of dementia worldwide. In mild cognitive impairment, physical exercise has been shown to improve performance on executive function and memory tasks, and increase plasticity in temporal regions commonly affected by AD neuropathology, including the hippocampus (11).

*Sleep and Metabolic Dysfunction in Early AD*

Increasing evidence suggests that sleep-wake and metabolic dysfunction are also common in individuals with cognitive impairment. Importantly, our group has shown that a) over 60% of those with mild cognitive impairment report sleep disturbance (12) , b) sleep disturbance is associated with neuropsychological dysfunction (4, 13), and c) circadian phase advance is evident even in the early stages of disease manifestation and relates to overnight memory consolidation (5, 13). Additionally, obesity is recognised as an independent risk factor for AD, with recent research demonstrating that obesity induced hyperleptinaemia can accelerate tau pathology in mice (14). While the link between vascular risk factors and dementia risk is well established, the investigation of other markers such as arterial stiffness has been less well examined and may be an important marker of disease trajectory. Furthermore, the economic need to identify those who will benefit most from an intervention to develop targeted treatment plans for individuals is clear.

*Exercise as a Holistic Treatment in Early AD*

Unfortunately, many exercise programs require a health professional and/or trainer and are associated with high levels of face-to-face contact. Also, no programs have provided exercise in conjunction with a more holistic multi-disciplinary “Healthy Brain Ageing” program targeting modifiable risk factors such as mood, anxiety, sleep, and diet. Importantly, none have concurrently taught practical internal (i.e. mnemonics) and external (i.e. memory aides such as whiteboards, diaries) memory strategies. Our group has previously demonstrated that such multi-faceted “Healthy Brain Ageing” programs are not only associated with increased knowledge (15), but are also associated with improved memory, mood and sleep (16-18). We have delivered such programs to over 350 older people including those with late-life depression, mild cognitive impairment and Parkinson’s disease (12, 16-18). Importantly our data shows high acceptability and excellent attendance rates (>95%). More recently, we commenced a feasibility trial to examine the efficacy of the ‘CogStep’ combined home-based exercise and psychoeducation program in older adults with multi-domain MCI or early stage AD. This study will build upon the outcomes of this feasibility trial and aims to collect pilot data for future grant applications.

* 1. **Research Question**

This study aims to examine the effect of a 12-week combined psycho-education and exercise program, ‘CogStep Phase 2.0’ on dementia risk score (assessed via the Australian National University - Alzheimer’s Disease Risk Index) in adults aged > 60 years with cognitive difficulties.

* 1. **Rationale for Current Study**

Dementia prevalence in Australia is expected to triple to almost one million people by 2050. It is well recognized that provision of early intervention programs and strategies to prevent disease progression and increase the wellbeing of ‘at risk’ patients are required. However, currently few programs exist that can be easily incorporated into daily life.

Inactivity is not only associated with functional decline, loss of independence and disease burden, but is also associated with a greater risk of dementia. Many exercise programs require a health professional and/or trainer and are associated with high levels of face-to-face contact, making their functionality limited. Also, no programs have provided exercise in conjunction with a more holistic multi-disciplinary program targeting modifiable risk factors such as mood, anxiety, sleep and diet.

Neither the effect of psycho-education programs on functional outcomes, nor the combination of such programs with an evidence-based practical exercise intervention have been examined in individuals with cognitive difficulties who are ‘at-risk’ for dementia.

For these reasons, we previously conducted a feasibility study ‘CogStep’ (*HREC University of Sydney Protocol Number: 2015/815*) that aimed to investigate the feasibility and efficacy of a 12-week combined psycho-education and exercise program in older adults with early stage AD or multi-domain amnestic MCI. Here, participants were rated via consensus by a team of neuropsychologists and neurologists according to McKhann et al. (2011) criteria for early AD or multi-domain amnestic MCI (19).

We are currently analysing the quantitative data for this study. However, based on participant and carer feedback from the current sample, the capacity for participants to engage with the psycho-education content and to perform their prescribed exercises has been difficult in participants with early stage AD. This has therefore impacted compliance and the subsequent efficacy of the ‘CogStep’ intervention in this particular population. In addition, we identified that several of our outcome measures were not sensitive change in this population. Importantly, given that individuals with subjective memory complaints (i.e. those presenting with cognitive difficulties) are more likely to progress to more significant cognitive decline such as Mild Cognitive Impairment without intervention, implementation of modifiable intervention strategies such as the Cogstep Intervention program may be more beneficial in this subgroup (20).

For this reason, for the second ‘pilot’ phase of this study, we will exclude individuals with early stage dementia. Rather, we will seek to recruit individuals with subjective cognitive complaints who demonstrate objective cognitive decline as per a telephone screen (Memory and Aging Telephone Screen). The same screen will be used to identify and exclude participants who may be characteristic of a dementia diagnosis. These individuals will be referred to the Heathy Brain Ageing Clinic for further assessment.

Furthermore, we have experienced barriers with regard to the feasibility of our recruitment methodology in the feasibility phase of the CogStep study, whereby participants were required to first be assessed via the “Clinical Staging of Late-Life Mood and Cognitive Syndromes” research study (*Clinical Staging Study; HREC University of Sydney Protocol Number: 02-2011/13515*) through the Healthy Brain Ageing Clinic. These barriers related to time for consensus of diagnosis to be determined following assessment via the Clinical Staging Study, communication between separate research teams, and the low throughput of participants entering the Clinical Staging Study. It was imperative that participants in the Phase 1 study were screened via the Clinical Staging study as we were specifically recruiting individuals with early stage AD, and as such, we had to ensure that participants underwent thorough clinical and neuropsychological assessment to confirm they had capacity to consent to participate in research. However, the CogStep Phase 2.0 study aims to recruit individuals with cognitive difficulties and will be excluding individuals with dementia. Therefore, in the second phase of this study we will be eliminating the requirement for participants to first have an assessment via the Clinical Staging Study, and will instead be using the MATS as a cognitive screening tool to confirm study eligibility.

# STUDY OBJECTIVES

* 1. **Primary Objective**

The primary objective of this study is to examine the effect of a 12-week combined psycho-education and exercise program (CogStep Phase 2.0) on Alzheimer’s disease risk index in adults aged > 60 years with cognitive difficulties.

* 1. **Secondary Objectives**

The secondary objectives of this study are to assess the effect of the ‘CogStep Phase 2.0’ program on mood, health knowledge, cognition, sleep, metabolic markers and resting state functional connectivity.

In addition, this study aims to evaluate compliance, uptake and effect size to facilitate accurate power and sample size calculations for future randomised controlled trials.

# STUDY DESIGN

* 1. **Type of Study**

This study will be a two-arm pilot randomized controlled trial.

* 1. **Study Design**

Participants will be screened via telephone by a member of the ‘CogStep Phase 2.0’ team. Participants who meet eligibility criteria will then undertake a baseline assessment which will involve the characterization of their cognition, quality of life, physical health status, mood and other descriptives. Following baseline assessment, participants will be randomized to either the ‘CogStep Phase 2.0’ program or ‘Waitlist Control’. Baseline and follow-up assessments will be conducted in the week of commencement, and 1-week following the intervention. A summary of the time commitment required for participation and the study procedure is provided below:

* Initial Screening: Eligibility Assessment via telephone (including the Minnesota Cognitive Acuity Screen, K10 to screen for severe affective symptomatology, MRI safety screening, Adult Pre-Exercise Screening Tool), dissemination of the Participant Information Sheets and baseline assessment booking.
* Week 1 CogStep Phase 2.0: Baseline Assessment including blood/cardiovascular, mood and neuropsychological tests, as well as a brief physical assessment to outline exercise prescription to implement at home. Actigraphy data collection. If randomized to the intervention, the participant will be given the psycho-education video CD to begin week 1 at home.
* Weeks 2-12: Intervention Phase (described in detail below).
  + Week 6 (If in the intervention arm): Clinical Review at the Brain and Mind Centre with the Exercise Physiologist.
  + Weeks 2, 4 & 9: Monitoring calls will be made to participants in the exercise component of the study to ensure no adverse events have occurred. Participants in the control arm will be sent text messages or letters with health messages to match contact between groups.
* Weeks 13: Follow-up Assessment - Immediately post intervention/waitlist control.

(See Study Flow Diagram below).

* 1. **Number of Participants**

Twenty-five males and females greater than 60 years of age who have cognitive difficulties (determined using a score of between 42 and 52 on the Minnesota Cognitive Acuity Screening) will be recruited.

* 1. **Study sites**

Brain and Mind Centre, 100 Mallett Street, Camperdown NSW 2050.

* 1. **Expected Duration of Study**

The study is estimated to run for approximately one and a half years; from June 2018 – December 2019. Months 1-3: Design and methodology finalized, ethics approval, governance established. Months 4-11: Begin rolling recruitment, conduct baseline and follow up assessments. Months 12-18: Determine benefits, analyze and interpret findings, reporting and dissemination, publishing of results and project evaluation.

* 1. **Primary and Secondary Outcome Measures**

*Aims and Hypothesis*

This study aims to determine whether, in comparison to a control condition, a structured 12-week home based exercise and psycho-education program is associated with:

* A change in dementia risk as measured by the ANU-ADRI score.

The secondary outcomes of this study include exploring whether the ‘CogStep 2.0’ program is associated with:

* Change in clinician-rated apathy and other depressive symptoms as determined by the Apathy Evaluation Scale and Hamilton Rating Scale for Depression;
* Objective change in 6-minute Walk Test and 6-Metre Timed Walk Test measurements via the GAITRite software and walkway;
* Objective change in balance as determined by the Timed Single Leg Stand, 3-metre Timed Up and Go Test, and the Functional Reach Assessment;
* Objective change in hand grip strength;
* Change in functional connectivity and neurometabolite markers of oxidative stress and neuronal integrity assessed via resting state functional MRI and proton magnetic resonance spectroscopy, respectively.

The tertiary/exploratory outcomes of this study include:

* Change in self-reported psychological wellbeing (including apathy, depression and anxiety) as determined by the Apathy Evaluation Scale (Participant Version), 15-item Geriatric Depression Scale (GDS-15), 7-item Generalised Anxiety Disorder scale (GAD-7), 18-item Lubben Social Network Scale, and Social Adaptation Self-Evaluation Scale;
* Change in wake after sleep onset; sleep onset and offset variance; sleep efficient; and normalization of acrophase (via actigraphy monitoring);
* Change in self-reported sleep quality as determined by the Pittsburgh Sleep Quality Index and Healthy Brain Ageing Sleep Questionnaire;
* Change in blood LDL cholesterol and fasting blood glucose;
* Objective change in executive function, processing speed, learning, and visual, verbal and episodic memory, via the Cambridge Neuropsychological Test Automated Battery (CANTAB);
* Objective verbal learning and memory performance (California Verbal Learning Test);
* Changes in verbal fluency (Controlled Oral Word Association Task; COWAT);

# STUDY TREATMENTS

* 1. **Treatment Arms**
     1. **CogStep Phase 2.0 Intervention**

The ‘CogStep Phase 2.0’ Intervention will comprise a program of combined home based exercise and psycho-education for a period of 12 weeks. The treatment program comprises two distinct parts:

Exercise Prescription: Immediately following the baseline assessments, an Exercise Physiologist will prescribe six individually tailored strength, balance and/or flexibility exercises based on individual results on physical assessment. In addition, participants will be given aerobic exercise goals to achieve each week. This will be outlined with the participant and exercise barriers will be discussed to ensure adherence to the exercises at home. Participants will be provided with an exercise workbook including the prescribed exercises (images demonstrating the exercise, instructions for performing the exercise, options for progression or regression of difficulty, and prescribed volume of exercise), and an exercise tracking sheet for each exercise to monitor compliance. In accordance with standard clinical care, the exercise prescription will be reviewed by an Exercise Physiologist at Week 6 to ensure exercise prescription/intensity is appropriate for the duration of the trial.

Psycho-education sessions: Participants will also be given a video CD to take home with a total of 12 sessions, from which participants will be asked to sequentially view one session per week. These will be viewed alongside the implementation of the exercises prescribed. These psycho-education sessions will include 20-30 minute video talks provided by a range of clinicians including Neuropsychologists, Nurses, Clinical Psychologists, Sleep Psychologists, Exercise Physiologists and Nutritionists. Content from the sessions will also be provided in the form of a workbook that will be provided to the participant. Following the viewing of each session, participants will be encouraged to complete the corresponding activities and/or questions in the provided workbook. Participants will be able to clarify any questions during monitoring phone calls at weeks 2, 4 and 9, as well as at the week 6 clinical review.

* + 1. **Waitlist Control**

Participants randomized to the control condition will be on a waitlist for treatment and after the 12-week control period, an exercise workbook and psychoeducation workbook with accompanying video CD’s matching that of the ‘CogStep Phase2.0’ Intervention group, will be offered to them after the follow-up assessment. After randomization, participants will be provided with a handout containing generic exercise information. Mobile phone text messages consisting of general physical activity guidelines and health information will be sent to the waitlist control group on weeks 2, 4, 6 and 9 (to mirror contact time points with the intervention group). The messages will differ between weeks and will be managed via an automated electronic platform. Should the participant not have access to a device to receive these mobile phone text messages, a letter containing the same details will be mailed to the participant.

* 1. **Measurement of participant compliance**

Participants randomised to the intervention arm of the study will have their compliance monitored at the clinical review in Week 6 and follow-up assessment. Participants will be required to record their weekly exercise activity on the exercise tracking sheets provided in their exercise workbook, and will be asked to bring this exercise record to the clinical review in Week 6 and follow-up assessment. At the conclusion of the intervention period, the exercise record will be collected from study participants, and program compliance will be calculated for the 12-week period.

# PARTICIPANT ENROLLMENT AND RANDOMISATION

* 1. **Screening & Recruitment**

Information regarding the study will be circulated to general practitioners and specialists in order to inform them of the upcoming study and notify eligible participants if interested. Flyers and advertisements of the study will be placed in relevant public areas including the Brain and Mind Centre, Charles Perkins Centre, community centres, pharmacies and other relevant sites if given verbal approval by the practice manager or equivalent. Advertisements and relevant information about the study may also be disseminated via the Brain and Mind Centre, community centres, webpages and social media outlets e.g. facebook; and at information sessions, symposia or forums such as that of community centres or Dementia Australia. Interested participants may contact a member of the research team via the contact details (email and phone number) provided on the advertisements.

Potential participants will be directed to complete an online screening questionnaire to determine provisional eligibility via RedCap. This questionnaire is entirely voluntary and will be anonymous. If eligible, participants will be given the option to request they be contacted by the study team to offer further information about the study and complete the remaining screening assessment. Should the ‘CogStep Phase 2.0’ study team be contacted directly by interested participants, a member of the team will talk to the interested participant and conduct the eligibility screen via telephone. This phone call will include a verbal explanation of the study and what it will involve, informed verbal consent to complete an eligibility screen, an eligibility interview, and cognitive screening via the Minnesota Cognitive Acuity Screen. Participants who meet study inclusion criteria, will be invited to participate in the ‘CogStep Phase 2.0’ study, and an appointment for the Baseline assessment will be booked.

Should the participant require further information prior to providing consent to participate in the screening process, or being enrolled in the study, the Participant Information Statement will be provided to the participant and they will be re-contacted an agreeable time for both parties.

We do not anticipate any issues with study recruitment. As opposed to Phase 1 of this trial, we are recruiting individuals with cognitive difficulties rather than established, clinician diagnosed mild cognitive impairment or Alzheimer’s disease. In addition, as described in detail in Section 2.3, we will no longer be recruiting via the Healthy Brain Ageing clinic, with cognition screened via telephone interview instead. In essence, this means that we will be including a broader spectrum of individuals with cognitive difficulties, thus increasing the recruitment pool. At present we have access to approximately 800 current Healthy Brain Ageing program study participants we can invite to participate in the study in addition to the print, social media and poster based advertising we plan to complete.

Recruitment Flow Diagram

|  |
| --- |
| Advertisement and promotion of the ‘CogStep Phase 2.0’ study. |
|  |
| Interested participants contact a member of the ‘CogStep Phase 2.0’ study via email or telephone (as provided on the advertisements) AND/OR complete an online screen to assess provisional eligibility  The research team contact interested participants via telephone to explain details of the study and perform a screening interview which includes the Minnesota Cognitive Acuity Screen, Adult Pre-Exercise Screening Tool, K10 and MRI safety screening. |
|  |
| Participants who are interested and meet eligibility criteria are invited to participate in the ‘CogStep Phase 2.0’ study. |
|  |
| Eligible participants are provided with a Participant Information Statement and Consent Form, and are booked for the Baseline assessment. |
|  |
| Eligible participant undergo informed consent and are enrolled into the study. |

* 1. **Eligibility Criteria**
     1. **Inclusion Criteria**

To be eligible participants must:

* Have The Memory and Aging Telephone Screen: (MATS) score between 13 and 19;
* Be greater than 60 years old at time of assessment;
* Be willing to attend the baseline (Week 1) and follow-up (Week 13) assessments at the Brain and Mind Centre;
* Be willing to undergo Magnetic Resonance Imaging scanning at the Brain and Mind Centre;
* If randomized to the intervention arm, be willing to receive monitoring phone calls and attend a clinical review at 6-weeks mid-intervention;
* If randomized to the intervention arm, be willing to view the weekly psycho-education sessions at home and implement their prescribed exercises at home; and
* If randomised to the control arm, be willing to receive health information via text message, email or letter at weeks 2, 4, 6 and 9.
  + 1. **Exclusion Criteria**

Participants will be excluded if they:

* Have insufficient language skills for neuropsychological assessment;
* Have dementia or suspected dementia (MATS<13);
* Have a history of any other major neurological conditions (e.g. stroke, epilepsy);
* Have current severe mood disturbance (K10 score > 30);
* Have a history of head injury with loss of consciousness for greater than 30 minutes;
* Have a medical condition known to affect cognition (e.g. cancer);
* Have a high level of baseline physical activity at study commencement (i.e. meets minimum American College of Sport Medicine exercise guidelines);
* Have any exercise contraindications (including unstable angina, uncontrolled cardiac failure, severe aortic stenosis, uncontrolled hypertension, symptomatic hypotension, resting tachycardia or arrhythmia, uncontrolled diabetes or acute illness/fever)
* Have any contraindications for magnetic resonance imaging scanning (e.g. aneurysm clip, pacemaker etc);
* Have started taking any new medications in the two months prior to commencement of the trial; and/or
* Are the current recipient of a cognitive training intervention (therapist or internet-based).

## Informed Consent Process

Although participants in this study will have cognitive difficulties, this research will not include any individuals who are unable to provide informed consent.  All potential participants will be assessed for level of cognitive impairment via a telephone screen, the mMemory and Aging Telephone Screen (MATS).  The initial telephone interviews will be performed by trained and experienced clinicians of the ‘CogStep Phase 2.0’ research study, who are well equipped to complete this online screen and ascertain capacity to consent to participate in a research study. To further ensure that only those able to provide informed consent are involved in the ‘CogStep Phase 2.0’ study, the below additional steps are taken:

1. Participants with an MATS score <13 at the time of telephone screening, or with suspected MATS<13 at commencement of the study, will not be eligible to participate in the study.
2. Should the participant have an MATS score < 13, but the clinician suspects the participant may be having difficulty understanding the communication, the researcher may ask additional questions to ascertain the extent of the participant’s understanding of the information, reasoning, ability to express their wishes and ability to appreciate the relevance to their own circumstances (as set out in Lai & Karlawish, 2007, American Journal of Geriatric Psychiatry). Examples of these additional questions may include,
   * “Can you briefly repeat back to me what I have explained to you?”
   * “Do you have any questions, or is there anything you do not understand?”
   * “What do you think about participating in this research study?”
   * “Would you like to take some time to discuss this with a trusted family member / friend / your doctor before making a decision about whether to participate?”
3. If we believe that a participant lacks capacity to provide informed consent to participate, we will provide the participant with information about the Healthy Brain Ageing Clinic where a formal assessment of their memory and thinking skills will be completed. This assessment will be independent of the current study.

Delegated research staff will collect written consent from each participant before his/her participation in the study. Prior to this, research staff will contact interested and provisionally eligible participants to go through details of the study, i.e. objectives, possible benefits, risks and requirements of the study, with the participant. The participant will be provided with an information statement and consent form prior to their first study appointment. They will also be provided with a verbal explanation of the study and will have ample time to discuss details of the study with researchers, to decide whether or not to participate.

* 1. **Enrolment and Randomisation Procedures**

The participant will be enrolled into the study after the informed consent process has been completed and the participant has met all inclusion criteria and none of the exclusion criteria. The participant will receive a study enrolment number and this will be documented in the patient file and on all study documents.

Our randomisation procedure is based on variable length blocks and will be administered independently of personnel in day-to-day contact with participants via Redcap. As recruitment occurs, the delegated randomisation staff member, who has no direct contact with trial participants, will carry out the random allocation. Each individual will be randomly assigned a value of 1 or 2, corresponding to one of the intervention arms. Participants will be stratified according to cognitive and physical functioning. All assessors of the follow-up assessment will be blinded to treatment allocation.

* 1. **Blinding Arrangements**

As participants will be randomised to either the intervention or a waitlist control condition, study participants will not be blinded to treatment allocation. Members of the research team who are involved in the baseline assessment, exercise prescription, monitoring calls, 6-week clinical review, and booking of appointments, will also be unblinded. However, all assessors of the follow-up assessment will be blinded to randomisation outcomes to minimise measurement bias.

* 1. **Participant Withdrawal**

Participants will be free to withdraw at any point during the trial. They are not obliged to provide a reason as to why they withdraw. If participants experience any significant side effects, they will be assessed by the medical staff and treatment discontinued if these are judged by the medical staff or the participant to be a significant risk to health.

* + 1. **Reasons for withdrawal**

Criteria for mandatory discontinuation of treatment:

* Absence of written consent or consent withdrawal by the patient.
* Any serious adverse event related or unrelated to the treatment justifying the discontinuation of the treatment in the investigator’s or a co-investigator’s opinion. If the discontinuation is due to an adverse event, at least one visit or telephone interview must be organised with the participant to collect the information relating to outcome of the adverse event. This information will be reported in the part of the case report from concerning adverse events.

Other criteria for premature discontinuation of treatment:

* Any event or circumstances unrelated to treatment justifying the discontinuation of the treatment in the investigator’s opinion.
* Protocol deviation threatening the patient’s safety.
  + 1. **Handling of withdrawals and losses to follow-up**

*Participant lost to follow up*

In the case that the participant does not respond to follow up phone calls or letters, the investigator will attempt to make contact over a one month period with him/her via telephone or email to establish the reason for the non-contact, check the participant’s condition and ask the participant to attend a check-up/follow-up visit. If these phone calls fail to reach the participant, the investigators will send them a letter. If all reasonable attempts to contact over a reasonable period of time fail, the investigator may declare the participant “lost to follow up”.

*Withdrawal Reporting Procedure*

The investigator must record the reason(s) and the exact date and time of the premature discontinuation of treatment in the case report form. If more than one reason is given, the investigator must indicate the main reason.

* 1. **Trial Closure**

Participants will be involved in this study for a period of 13 weeks comprising baseline assessment, the intervention period and the post-intervention assessment. If an adverse event occurs, the investigator will ensure that follow up of the participant is relevant to the nature of the event, and that it continues until resolution irrespective of study period.

* 1. **Continuation of therapy**

The intervention is only scheduled to continue for the 12 week intervention period of the study, however, participants are welcome and encouraged to continue their prescribed exercises and re-watch the video CDs in consultation with their general practitioners. At present the research team is not able to offer continuation of the program after study completion. However, those individuals who are randomly allocated to the Waitlist Control condition will be invited to participate in the program once they have completed the follow-up study assessment.

# STUDY VISITS AND PROCEDURES SCHEDULE

## Study Flow Chart

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ‘CogStep Phase 2.0’ Phone Screening, Recruitment and Eligibility  (N=25) | | | | | | |
|  | |  | | |  | |
| Baseline Assessment  (Medical, Blood, Physical, MRI, Sleep and Activity Assessments) | | | | | | |
|  | |  | | |  | |
|  | | Randomisation | | |  | |
|  | |  |  | |
| Treatment | |  | Waitlist Control | |
|  | |  |  | |
| Home-based Psychoeducation and Exercise Intervention | |  | Treatment as usual | |
|  | |  |  | |
| Post-Intervention Follow up | |  | Post-Intervention Follow up | |
|  | |  |  | |
|  | |  | Participant offered ‘CogStep’ Intervention | |

Schedule of Observations and Procedures:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| List Interventions | Eligibility Screening & Recruitment | Baseline Assessment | Mid Intervention Clinical Review | Post Intervention Assessment |
| Week(s) | -2 to 0 | 1 | 6 | 13 |
| Informed Consent | ✓ | ✓ |  |  |
| Inclusion / Exclusion criteria | ✓ | ✓ |  |  |
| Self-Report Questionnaires |  | ✓ |  | ✓ |
| Medical Assessment |  | ✓ |  | ✓ |
| Physical Assessment |  | ✓ |  | ✓ |
| Neuropsychological Assessment |  | ✓ |  | ✓ |
| Cardiovascular Tests |  | ✓ |  | ✓ |
| MRI Assessment |  | ✓ |  | ✓ |
| Actigraphy Assessment |  | ✓ |  | ✓ |
| Blood Test |  | ✓ |  | ✓ |
| Exercise Compliance Assessment |  |  | ✓ | ✓ |
| Adverse Events |  | ✓ | ✓ | ✓ |

# CLINICAL AND LABORATORY ASSESSMENTS

Physical Assessment: All participants will undergo an assessment of physical function/activity at baseline, and week 13 (directly following intervention/waitlist control). Exercise assessments will comprise the 6 Minute Walk Test and 6-metre Timed Walk Test via the GAITRite software and pathway to assess gait and functional capacity; 30-second Sit-To-Stand Test to assess lower limb muscle strength; Hand Grip Strength test with a hand dynamometer, and the Timed single leg stand, 3-m Timed-Up-and-Go test and functional reach assessment to assess balance.

Neuropsychological Assessment: All participants will undergo a neuropsychological assessment of executive function, processing speed, learning, and visual, verbal and episodic memory (Cambridge Neuropsychological Test Automated Battery, and California Verbal Learning Test). Other cognitive tests will comprise: The Wechsler’s Test of Adult Reading to assess predicted IQ (baseline only); Montreal Cognitive Assessment (MoCA) to assess global cognition; and the Controlled Oral Word Association Test to assess verbal fluency.

Medical and Mood Assessment: All participants will undergo a brief assessment of their medical history, and exercise contraindications via the Adult Pre-Exercise Screening Tool at baseline only. If participants respond positively to any questions on the screen they will be asked to consult their General Practitioner before participating in the study. A trained clinician will also implement the Hamilton Rating Scale for Depression to assess the participants’ depressive symptoms, and the Apathy Evaluation Scale to assess levels of apathy. Participants will also be assessed for depression diagnostic criteria using the Mini Psychiatric Interview 6.0.

Cardiovascular Tests: Arterial stiffness will be measured using carotid-femoral pulse wave velocity. This is a non-invasive procedure that involves placing a blood pressure cuff around the participant’s upper thigh and a probe on the neck while the participant is lying down. The probe is not invasive and sits on top of the skin. Central aortic pressure will be measured using pulse wave analysis. This will be done by placing a traditional blood pressure cuff around the participant’s upper arm while the participant is lying down.

Blood Assessment: In the baseline assessment (Week 1) of the intervention/waitlist control period, and at week 13 (directly following intervention/waitlist control), a fasting blood sample will be collected from all participants to analyse blood glucose, cholesterol and triglyceride concentration. Blood will also be assessed for inflammatory and oxidative stress marker concentration.

Actigraphy: All participants will be asked to undertake actigraphy monitoring for seven consecutive days in the two weeks prior to or following the baseline and follow-up assessments. Sleep activity, daytime activity and activity levels will be recorded and analysed to determine habitual sleep onset/offset time, sleep efficiency and wake after sleep onset. In addition, acrophase and circadian rhythmicity will be determined by cosinor analysis. Participants will be asked questions regarding their sleep quality and habits on a daily basis for 7-days, and will be asked to record their responses on the ‘’CogStep Phase 2.0’ Activity and Sleep Diary’.

Magnetic Resonance Imaging: All participants will undergo an MRI scan at baseline and at the 13-week follow-up assessment. All MRI data will be acquired on a 3Tesla General Electric (Milwaukee, WI) 750w scanner at the Brain and Mind Centre, iMed Radiology with a 32 phase array head coil. Structural MRI data will provide regional and global grey, white and CFS volume change as well as a template to register the functional MRI data to aid in group comparisons during statistical analysis. Resting state functional MRI (rsfMRI) data will be acquired to characterize longitudinal changes to resting state brain activation patterns during an eyes closed procedure. Magnetic Resonance Spectroscopy acquired in both the Anterior Cingulate Cortex and the Posterior Cingulate Cortex will be acquired to quantify metabolite concentration changes in these regions. In addition, as part of the scan, participants weight and height will be collected to calibrate standard scan parameters. Participant information and data will only be used for the purposes outlined in the above project design and Participant Information Statement.

Self-Report Questionnaire: All participants will be asked to complete self-report measures at baseline, and week 13 (directly following intervention/waitlist control). These will include Alzheimer’s disease risk index as well as a series of questionnaires assessing general demographics, general health and wellbeing, medical history, cognition, sleep, physical activity, nutrition and diet, daily functioning, alcohol and drug use, and current medications. Outcome measures will include: Alzheimer’s Disease Risk Index (ANU-ADRI); Physical Activity (Active Australia Survey, and 2 questions regarding sedentary behaviour from the International Physical Activity Questionnaire); Memory (Everyday Memory Questionnaire, and Memory Compensation Questionnaire); Psychological Wellbeing (15-item Geriatric Depression Scale, Apathy Evaluation Scale, 18-item Lubben Social Network Scale, and Social Adaptation Self-Evaluation Scale); Quality of Life (World Health Organization - Quality of Life); Sleep (Pittsburgh Sleep Quality Index, and Healthy Brain Ageing Sleep Questionnaire); Diet and Nutrition (Healthy Brain Ageing Nutrition Questionnaire); Health Knowledge (Healthy Brain Ageing Knowledge Questionnaire); and, cognitively stimulating activities (HBA Cognitively Stimulating Activities Questionnaire).

# ADVERSE EVENT REPORTING

Adverse event reporting for clinical trials involving therapeutic products, must meet the requirements of the National Health and Medical Research Council, Australian Health Ethics Committee (AHEC) Position Statement “*Monitoring and reporting of safety for clinical trials involving therapeutic products*” (May 2009), which can be found at:

<http://www.nhmrc.gov.au/health_ethics/hrecs/reference/_files/090609_nhmrc_position_statement.pdf>

* 1. **Definitions**

*Adverse Event (AE):*

* Any untoward medical occurrence in a patient or clinical investigation subject who is administered with an intervention and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

*Serious Adverse Event (SAE):*

* Any event that suggests a significant hazard, contraindication, side effect, or precaution, whether or not it is considered to be associated with the trial intervention. An SAE is any event that meets any of the following criteria:
  + Results in death;
  + Is life-threatening;
  + Requires inpatient hospitalisation or prolongation of existing hospitalisation;
  + Results in persistent or significant disability/incapacity;
  + Is a congenital anomaly/birth defect, or;
  + Other important medical events that based upon appropriate medical judgment are thought to jeopardise the patient or subject and/or require medical or surgical intervention to prevent one of the outcomes defining a serious adverse event.

### *Unexpected Adverse Event:*

* Any experience not previously reported (in nature, severity or incidence) in the current Investigator’s or Intervention Brochure.
  1. **Assessment and Documentation of Adverse Events**

The investigator must therefore document as an adverse event:

* Any unfavourable and unintended sign, including an abnormal finding from an additional

examination (lab tests, X-rays, ECG, …) deemed clinically relevant by the investigator,

* Any symptom or intercurrent disease, any worsening during the study of a symptom or a disease already present when the participant entered the study (increase in frequency and/or intensity), and which:
  + is detected during a study visit or at an additional examination,
  + Occurred since the previous study visit and is notified by the participant, the investigator must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution. He/she must immediately inform the sponsor of any secondary worsening.

Any event meeting the above mentioned definitions must be reported on an adverse event form (Appendix 1.0) including details of severity, relationship to intervention and outcome.

*Follow up of AE*

The investigator must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution. He/she must immediately inform the sponsor of any secondary worsening.

Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported must be written up in a new complete evaluation of the event documented on the Adverse event page previously created for the event.

If the adverse event is not resolved at the participant's final visit in the study, the participant must be followed up suitably (phone contact, next visit not in the frame of the study) and any information on the outcome of the event will be noted on the Adverse Event page previously created for the event.

If the follow-up of the participant is not done by the investigator him/herself (hospitalisation, followed by a specialist or the participant's general practitioner), the investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of the participant, so as to have additional information and report it on the Adverse Event page previously created for the event.

* 1. **Eliciting Adverse Event Information**

All relevant event information, including diagnosis, signs and symptoms, severity, relationship with intervention and outcome of event will be reported on adverse event form. Certain sections of the Adverse Event form must always be completed; whether or not the event requires immediate notification. Further sections must be completed only when the event requires immediate notification.

* 1. **Serious Adverse Event Reporting**
     1. **SAEs**

Serious Adverse Event (SAE): Any event that suggests a significant hazard, contraindication, side effect, or precaution, whether or not it is considered to be associated with the trial intervention. An SAE is any event that meets any of the following criteria:

* Results in death;
* Is life-threatening;
* Requires inpatient hospitalisation or prolongation of existing hospitalisation;
* Results in persistent or significant disability/incapacity;
* Is a congenital anomaly/birth defect, or;
* Other important medical events that based upon appropriate medical judgment are thought to jeopardise the patient or subject and/or require medical or surgical intervention to prevent one of the outcomes defining a serious adverse event.

*Response to a Serious Adverse Event*

Any SAE must be documented on the ‘Serious Adverse Event’ form and reported to the HREC as soon as possible upon researchers becoming aware of the event. The investigator must provide details of the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the participant or a third person), as well as anonymised copies of supporting documents which provide additional useful information, such as hospital admission reports, reports of further consultations, laboratory test reports, reports of other examinations aiding diagnosis. The Chief Investigator must then determine if the seriousness of the event warrants the removal of the participant from the study or abandonment of the study.

# STATISTICAL METHODS

* 1. **Sample Size Estimation**

The total sample size for this study is 25, which allows for approx. 10 people per group for the comparison of the CogStep program to a waitlist control condition. Based on our work, we have allowed for ~20% attrition and expect a medium effect size improvement in the treatment group. However, this work is novel and within this pilot study we seek to determine the actual effect size difference between groups. The outcomes of this study will be used to power a larger more rigorous randomized controlled trial.

* 1. **Statistical Analysis Plan**

Group differences at baseline will be assessed using independent samples t-tests for continuous data and chi-squared tests for categorical data (such as gender). A repeated measures analysis of variance will be used to examine group differences in primary and secondary outcomes.

# DATA MANAGEMENT

* 1. **Data Collection**

Data collection will be conducted only by authorised members of the CogStep Research Team. An updated log of individuals responsible for data collection will be kept on record. Only sufficiently trained and supervised research staff will be engaged to enter and analyse data. An audit of data files over time to ensure completeness of data collection will be conducted on a routine basis. Two copies of most data (the original hard copy and electronic copy) will be held so that comparison is possible at any time.

Participants will be asked to complete screening and self-report questionnaires via the Research Electronic Data Capture platform; REDCap. Should participants not have access to the internet and/or a computer or tablet, they will be provided with pen and paper self-report questionnaire packs. Furthermore, where possible, data will be directly entered into the Research Electronic Data Capture (REDCap) platform during and/or following screening and other assessments. Physical and medical assessment data will be collected by clinicians using paper participant research files. Neuropsychological testing will be performed via the CANTAB platform on a laptop or tablet. Actigraphy data is collected via an actigraphy watch (worn by participants) and subsequently downloaded using appropriate software. Additional sleep, actigraphy and exercise data will be filled in by participants on pen and paper diaries. MRI data is collected through the MRI scanner located at the Brain and Mind Centre. All study data will be entered into REDCap and/or SPSS by trained and authorised research staff.

* 1. **Data Storage**

All clinical assessments will be performed at the Brain and Mind Centre. Clinicians will use REDCap software using an electronic tablet or given a paper-based participant research file, in which they record results and data. All research files will then be forwarded to the trial manager who will supervise data entry and storage of participant files. Paper-based self-report questionnaires (if used), and any other clinical information will be inserted into the participant research file. The individual assessment component scores will be summarised at the beginning of each section and a file audit will be carried about periodically to ensure that all required documents are present. Furthermore, where possible, data will be directly entered into the Research Electronic Data Capture (REDCap) platform and/or the Statistical Package for Social Sciences (SPSS) during and/or following screening and other assessments.

All identifiable information i.e. study consent forms will be held in a secure location (i.e. filing cabinet) at the Charles Perkins Centre. Data returned by participants e.g. questionnaires and research files, will be de-identified and kept in a separate locked filing cabinet in a secure office at the Charles Perkins Centre. All electronic information will be stored on a secure computer network maintained by the University of Sydney. Within this network, files are restricted to researchers and cannot be accessed without password permissions.

* 1. **Data Confidentiality**

Identifiable and de-identified study data and information will be stored separately within locked filing cabinets in secure locations at the Charles Perkins Centre. All study data will be de-identified i.e. questionnaires, research files, actigraphy and MRI data. Access to study materials will be restricted to research staff, who will have undertaken ARCS Good Clinical Practice training. Electronic data i.e. actigraphy and MRI data, will be stored on a secure university network server, with access only available to those relevant research staff.

* 1. **Study Record Retention**

As per State Records Authority of NSW, data will be retained for a minimum of twenty years as this is the appropriate duration of storage for study data from a clinical trial.

# ADMINISTRATIVE ASPECTS

The trial will be registered in a publicly accessible trials registry prior to enrolment of the first participant. Registration number will be provided when available.

* 1. **Amendments to the protocol**

Any amendments will be submitted to the HREC for review prior to implementation as per HREC guidelines.

* 1. **Protocol deviations**

Any protocol deviations will be submitted to the HREC for review.

* 1. **Participant reimbursement**

Participants will be given a total of $50 in reimbursement via a gift voucher to assist with the expenses incurred in travel to and from the Brain and Mind Centre for the follow-up assessment component of the study. This $50 voucher will be given to the participant at the conclusion of the post intervention follow-up at week 13 of the study.

# USE OF DATA AND PUBLICATIONS POLICY

When the overall results of the study are made available, a layperson summary in the form of a newsletter will be sent to all study participants.

Results of this study will be published in peer-reviewed journals and may be presented at both domestic and international scientific meetings.

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