Computerised Cognitive Training for MCI with Sleep Disturbance

CONFIDENTIAL

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).

PROTOCOL SIGNATURE PAGE

Protocol Title: **Computerised Cognitive Training for MCI with Sleep Disturbance**

Protocol Number: 2018/669

Protocol Version/ Date: Version 4.1: 7/3/2019

Sponsor Name: University of Sydney

Declaration of Investigator

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, The National Statement on Ethical Conduct in Human Research (2007) (National Statement (2007)), The Australian Code for the Responsible Conduct of Research (the Code) and the moral, ethical and scientific principles that justify clinical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of patients.

I agree to adhere to the protocol as approved by the HREC in all circumstances other than where necessary to protect the well-being of the participant.

Principal Investigator Name: Professor Michael Valenzuela

Principal Investigator Signature: _____

Date: _____

PROTOCOL MODIFICATIONS

Comparison	Changes	By Whom	Notes	Signed
V3 vs V4	• Added 2 personnel (Section 1.2 page 9) • Changed Version number in footnotes • Added protocol changes (page 2) • Changed typo (section 11 page 28) • Formatted header for consistency	PB PB PB PB PB PB		
V2 vs V3	• Corrected age in selection criteria from 55 to 50 (page 5) • Changed discontinuous font (section 11.2 page 29) • Changed destruction of hard copies from 15 to 20 years (section 11.2 page 29)	PB PB PB PB		
V1 vs V2	• Changed discontinuous font on page 29 • Changed destruction of hard copies from 20 to 15 years (section 11.2 page 29) • Changed destruction of hard copies from 15 to 20 years (section 11.4 page 29) • Added in ANZCRT trial registration and formatted text to be continuous (Section 12 page 29) • Added ICTRP UTN number (Section 12page 29) • Added HREC approval number (Section 12.1 page 29) • Changed Version number in footnotes	PB PB PB PB PB PB PB		

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PROTOCOL SYNOPSIS

Title	Computerised Cognitive Training for MCI with Sleep Disturbance
Objectives	Primary: Assess the effect of CCT versus waiting list control on global cognition in multi-domain MCI with sleep disturbance. Global cognition definition: pre-specified summary z-score composite across 5 cognitive domains of: memory, attention, executive function, processing speed, language. Secondary: 1. Does the immediate therapeutic cognitive effect differ if training commenced immediately or 3-months later? 2. Does the cognitive state 9-months after entering the trial differ if CCT was commenced immediately or 3-months later? 3. Change in individual cognitive domains measured in separate summary z-score composites 4. Change in daily functional: ADCS-ADL-Prevention Questionnaire 5. Change in quality of life: WHOQOL 6. Change in mood and mental-health symptoms: 15-Item GDS 7. Change in sleep-wake patterns: Sleep diary, actigraphy, PSQI 8. Change in risk-perception: Economic Decision Making Competency tool 9. Predictors of cognitive response to CCT: APOE 3/4 and BDNF ValMet polymorphism and baseline cognitive profile.
Study Design	Randomised, controlled, double-blinded, clinical trial
Planned Sample Size	62
Selection Criteria	Older adults (aged 50 or older) with amnestic multi-domain MCI with sleep disturbance:
Study Procedures	The trial is divided into three 3-month phases with three separate objectives (see **Figure 3**) Phase I is a 12-week randomised, double-blinded, wait-list controlled trial that will follow CONSORT[1] and SPIRIT[2] guidelines and follow Good Clinical Practice recommendations[3].

	Subjects will be randomly allocated in a 1:1 ratio to either 3-months of supervised, centre-based, multidomain CCT (ARM A) or wait-list control. The main endpoint from Phase I will be to determine whether CCT is effective for improving overall cognition for those with multidomain MCI with sleep disturbance. This is the trial's primary outcome. The Phase II endpoint is to assess whether the magnitude of therapeutic effect is dependent on the onset of treatment. Arm A started CCT 3-months prior and will transition to no-contact follow-up for 3-months, whilst Arm B that was on-hold for 3-months will commence the identical CCT intervention that Arm A completed in Phase I. The endpoint for Phase III is to determine whether delayed start of CCT matters after a period of no-contact follow up. The trajectory of cognitive function following early intervention verses delayed intervention will be examined. Both groups will receive no intervention for a further 3 months, with the main difference being that Arm A halted CCT 3-month previously whilst Arm B started CCT 3-months later. In order to assess the effect of delayed start separately from waning of benefits, Arm A at the end of Phase I will be compared to Arm B at the end of Phase II. Arm A at the end of Phase II will also be compared to Arm B at the end of Phase III to investigate the effect of delayed start on longevity of the intervention. Cognitive assessment will be completed at baseline and at the end of each phase.
Statistical Procedures Sample Size Calculation: Analysis Plan:	• **Phase I:** An *intention-to-treat* approach using recommended Linear Mixed Modelling[4] will evaluate a model including main effects for Group (Arm A vs Arm B), Time (BL vs FU1) and the main interaction term of interest: Group X Time. Covariates will only be added if baseline differences are noted between groups. • **Phase II** Linear Mixed Modelling[4] will evaluate a model including main effects for Group (Arm A vs Arm B), Time (Arm A BL vs FU1, Arm B **FU1 vs FU2**) and the main interaction term of interest: Group X Time

	• **Phase III**: T-test between Arm A vs Arm B at FU3. • **Clinical Response Prediction** will be addressed by multiple regression examining relationships between baseline predictor variables (i.e; cognitive profile) and cognitive change scores. • **Sample Size and Power** This study is powered on the basis of a relative effect size (RES) on Global Cognition of 0.44 at the end of the Phase I RCT (based on average from our Timecourse Trial[5] and NHMRC SMART trial[6]). Designate power of 0.80 controlling α at 0.05 translates to a required sample size of N=52 (calculated using G*Power 3.1 based on ANOVA repeated measures within-between interaction test, 2 groups, 2 time-points, within subject autocorrelation =0.4, equivalent effect size of [v]=0.22). A sample of N=62 (rounded up from 61) will be recruited to allow for 15% overall attrition (as per Timecourse Trial extrapolated to 9-months).
Duration of the study	3 years

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
CCT	Computerised Cognitive Training
MCI	Mild Cognitive Impairment
BTS	NHMRC Maintain Your Brain Trial Brain Training System
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living
WHOQOL	World Health Organisation Quality of Life
GDS	Geriatric Depression Scale
PSQI	Pittsburgh Sleep Quality Index
APOE 4	Apolipoprotein E 4
BDNF	Brain-derived neurotrophic factor

1. STUDY MANAGEMENT

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1.4 Internal Trial Committees

Researchers: Prof Valenzuela, Prof Naismith, Statistician: Dr Nancy Briggs, Co-ordinator: Dr Polly Barr

1.5 Independent Safety and Data Monitoring Committee: not applicable as intervention is entirely safe. There has never been an adverse event incident in any of the cognitive training trials that CI Valenzuela has led or been associated with and none reported in meta-analyses or individual studies (more than 75 trials to date).

1.6 Sponsor

University of Sydney NSW 2006

1.7 Funding and Resources

Funded by an NHMRC Project Grant (ID1084880, CIA Valenzuela), $715,764

2. INTRODUCTION AND BACKGROUND

2.1 Background information

Dementia and Alzheimer's: a global priority

Dementia is a disorder with huge global economic burden as currently, 47 million people suffer from it and the prevalence is expected to increase to more than 131 million by 2050. The 2016 total estimated worldwide cost of dementia is USD 818 billion, approaching a trillion-dollar disease by 2018[7]. There are no effective treatments as yet, to combat or alter the course of dementia. It is therefore highlighted from the G7-led Global Action on Dementia that the development of such treatments is an inter-governmentally agreed global public health priority[8].

Clinicians have long delineated a prodromal condition with cognitive symptoms prior to the onset of dementia and Alzheimer's disease (AD). This condition is known as Mild Cognitive Impairment (MCI). Individuals in this clinical staging present with subjective cognitive complaints and/ or objective evidence of abnormal cognitive testing with no functional deficits associated with cognitive impairment. Whilst not all rigorously defined MCI patients progress into dementia or AD and can revert back to normal, the rate of progression to AD is highest, while the rate of reversion is lowest[9].

Modifiable risk factors for prevention

Cognitive inactivity is estimated to be the most prevalent modifiable dementia risk factor worldwide[10]. CI Valenzuela has hence advanced a research program around an active cognitive lifestyle, characterised by a lifelong pattern of engagement in complex mental activities such as advanced and ongoing education, participation in mentally-challenging occupations, maintenance and development of social networks and pursuit of cognitively-loaded hobbies and pastimes [11]. Our meta-analysis of 18 prospective longitudinal studies found high levels of complex mental activity was associated with a 46% decreased risk of incident dementia[12]. Similarly, a systematic review based on aggregated data of 47,000 individuals followed for an average of 5 years revealed that lifespan complex mental activity slows the rate of cognitive decline in otherwise healthy older individuals[13].

MCI has been associated with comorbid neuropsychiatric conditions similar to that of dementia and AD. Multiple studies have shown that depression, lack of motivation and anxiety are more prevalent in MCI individuals than in cognitively intact people. Further, both major depression and anxiety markedly increased the risk of MCI conversion into Dementia[14,15]. There is also increasing evidence to

suggest that sleep quality also plays an important role in cognitive health in ageing. A review has revealed that people with MCI are almost twice as likely to have sleep disturbance than those with normal cognition (18.3-45.5% compared to 10.9-23.3%, respectively)[16]. This study also provides evidence to suggest that sleep disturbance is predictive of cognitive decline in older adults and those with neurodegenerative disorders. It has been identified that changes in sleeping patterns occur in MCI in the form of poor sleep efficiency, fragmented sleep, increased frequency of daytime napping, propensity to fall asleep and wake up earlier, and decreased levels of slow wave sleep. In AD, there are the same alterations in sleeping patterns, but to a higher intensity. One positive aspect of these knowledge combined, is that these are modifiable and manageable risk factors that contribute to hastened cognitive decline.

Therefore, by treating these modifiable risk factors, we hypothesise that this may help prevent against the development of dementia and AD. One such intervention that is able to target these risk factors is Computerised Cognitive training (CCT)

CCT

CCT is a cognitive intervention that uses computerised platforms including audiovisual stimuli, videogames or virtual reality. It involves repeated exercises on one or multiple cognitive domains such memory, executive functions or processing speed. The advantages of using this intervention is that it is safe, scalable, versatile, adaptive, and relatively inexpensive.

In a meta-analysis of MCI trials conducted by our group [17], CCT was efficacious not only for global cognition (g=0.38, 95%CI: 0.14-0.68) but also for psychosocial functioning (g=0.52, 95%CI: 0.01-1.03; *k*=17 RCTs, N=686).

To date, an individual RCT has shown that CCT improved both sleep quality (sleep onset latency and sleep efficiency) and cognitive performance (memory, working memory, and attention) in cognitively-intact older adults with insomnia[18].

The timing of therapeutic gains in CCT is also of interest. In our Timecourse Trial[5], we revealed that CCT progresses through three distinct therapeutic phases: loading dose, where there is a rapid onset of therapeutic gains, plateau, where therapeutic gains begin to reduce with additional training and reach maxima, and maintenance, where after cessation of training therapeutic gains wane quickly but some residual benefits are maintained in the long term. Whilst these temporal characteristics have been described assuming all patients begin CCT at a given time, it is unknown what the impact delaying the start of treatment in MCI may have. This is particularly important given: a) cognitive decline is more rapid in MCI than in healthy elderly, suggesting that timely intervention is required, and b) there is a common practical resource barrier such that not all those with MCI may be able to access CCT at a given time (in effect creating a waiting-list). Accordingly, whether CCT therapeutic gains degrade over time in

MCI is clinically important, as is whether this matters over the longer term after the cessation of training.

In summary, there have not yet been any studies to test the efficacy of CCT in multi-domain MCI patients with concomitant sleep disturbance, and no studies have systematically investigated the impact of timing of onset of treatment.

2.2 Main Research Questions

a. What are the effects of CCT on global cognitive function in multi-domain MCI with sleep disturbance?
b. In this population, are delayed training effects equivalent to immediate training effects?
c. In this population, does starting training early compared to later change outcome after cessation of training?
d. In this population, does CCT help with sleep symptoms?
e. In this population, does CCT transfer to important functional outcomes such as IADLs, psychosocial state and decision making?
f. Is there a cognitive response phenotype?
g. Does APOE or BDNF ValMet polymorphisms influence cognitive responsivity?

2.3 Rationale for Current Study

This RCT will produce three main endpoints:

Firstly, it will determine whether CCT is effective for improving global cognition, thereby providing a potential intervention for the reversal of cognitive decline and prevention of developing dementia for those at high-risk.

The prevalence of MCI is even higher than that of dementia[19]. Small gains could have a major impact on prevention of disease burden: a 2-year delay in dementia presentation would for example reduce the prevalence of the disease by 20% by shifting symptom onset (at a population level) beyond natural mortality. With no current effective treatment for dementia and Alzheimer's disease, this endpoint therefore has major significance to human-health, particularly with respect to age-related disease burden.

Secondly, we will learn whether CCT produces secondary gains across a wide variety of important clinical outcomes, including day-to-day function, mood, and quality of life. In particular, assess the impact of CCT on sleep quality in those with sleep disturbance (the first time in MCI). This will also further support the RCT which found CCT improved sleep for participants with disturbed seep[18] (albeit without MCI). This endpoint will translate to clinically- and personally-relevant information.

Thirdly, this RCT will clarify if the timing of onset of CCT in this clinical population matters. This is of great pragmatic importance, as not all MCI patients can access in-person CCT at the same time.

Fourth, this RCT will examine for the first time in this population if there biological (genetic) or cognitive (profile) predictors of therapeutic response, of great significance for the more selective application of this treatment in MCI and for better resource allocation at a community level.

Accordingly, this endpoint will add fundamental new knowledge highly relevant to clinical practice. Flowing from these endpoints is the expectation of top-quality publications in international peer-reviewed journals, as well data that will directly inform future guidelines for the use of BT in the clinic and in the community. Overall, the outcomes from this project are suggested to be of international medical, scientific and community significance.

3. STUDY OBJECTIVES

3.1 **Primary Objective**

To assess the effect of CCT versus waiting list control on global cognition in multi-domain MCI with sleep disturbance.

Global cognition definition: pre-specified summary z-score composite across 5 cognitive domains of: memory, attention, executive functions, processing speed, language.

3.2 Secondary Objectives

Determine the following:

1. Does the therapeutic cognitive effect differ if training commenced immediately or 3-months later?
2. Does the cognitive state 9-months after entering the trial differ if CCT was commenced immediately or 3-months later?
3. Change in individual cognitive domains measured in separate summary z-score composites
4. Change in daily functional: Amsterdam IADL
5. Change in quality of life: WHOQOL
6. Change in mood and mental-health symptoms: 15-Item GDS
7. Change in sleep-wake patterns: Sleep diary, actigraphy, PSQI
8. Change in risk-perception: Economic Decision Making Competency tool
9. Predictors of cognitive response to CCT: APOE 3/4 and BDNF ValMet polymorphism and baseline cognitive profile.

3.3 Background Variables

The following variables will be tested at baseline for any systematic differences between randomisation groups as well as for associations with change in primary and secondary outcomes: age, sex, education, WTAR, physical activity (using CHAMPS questionnaire), SF-36 physical health, cardiovascular risk factors, cognitive lifestyle (using CIA Valenzuela's Lifetime of Experiences Questionnaire), PSQI[20], family history of dementia, APOE4 and BDNF status, new onset illness or new medication use.

4. STUDY DESIGN

4.1 Type of Study

This study is a 9-month randomised, double-blind, passive-controlled clinical trial that will explicitly follow CONSORT[1]and SPIRIT[2] guidelines and follow Good Clinical Practice recommendations[3].

4.2 Study Design

This clinical trial adheres to the conceptual and ethical framework for prevention trials articulated by Peters et al, in which long-term intervention in individuals at-risk for dementia should be correspondingly low-risk[21]. Our experience across four major longitudinal RCTs of CCT has been of no adverse events.

MCI clients that meet basic entry criteria will be recruited from the Healthy Brain Ageing (HBA) clinic, Brain and Mind Centre, University of Sydney (head: Prof Naismith) and the Memory Clinic of the Prince of Wales Hospital (head: Prof Brodaty). Any additional assessments required beyond clinic-based tests, and all intervention procedures, will take place at the Brain and Mind Centre, Sydney, Australia.

The study will consist of three phases and follow-up assessments designed to produce distinct outcomes (refer to **Figure 3**).

Subjects will be randomly allocated in a 1:1 ratio to either ARM A: immediate intervention or ARM B: delayed intervention. Those in ARM A will commence supervised, centre-based multi-domain CCT twice a week, 1 hour per session for 3 months. The main endpoint at the end of Phase I will be to determine whether CCT can improve cognitive function in comparison to a waitlist control. For ARM A, we hypothesize that CCT will lead to an improvement in global cognition. For ARM B, we hypothesise that there will be no change in cognition or measureable cognitive decline. On the basis of our previous work in the Timecourse Trial[5] and NHMRC-funded SMART Trial[38], our proposal is powered for Phase 1 (baseline-FU1) of the trial.

The endpoint of FU2 is designed to assess the magnitude of effect between immediate intervention versus delayed intervention (see Figure 3 and 4). That is, whether the effect size of CCT for ARM B is equivalent to the effect size of CCT for ARM A. We hypothesise that the effect size for those allocated in ARM A will

be greater than ARM B. This is because, as time progresses, the abnormality rates for cognition and other dementia and AD biomarkers increases, thereby making it more difficult to treat. (Figure 1,2)[39]

Figure 1

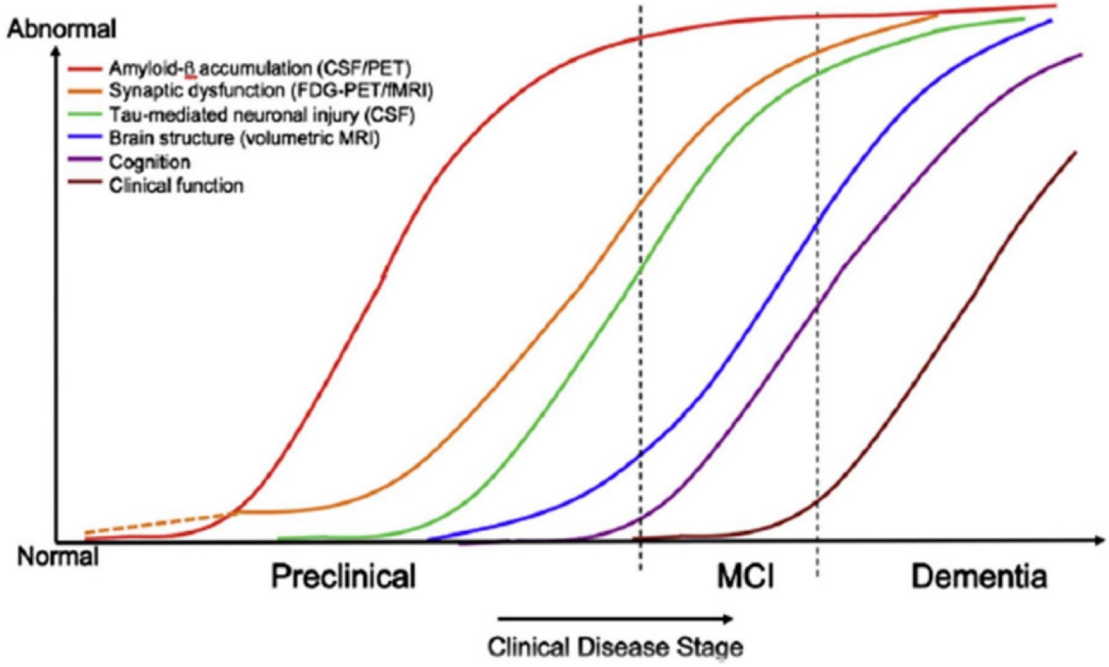
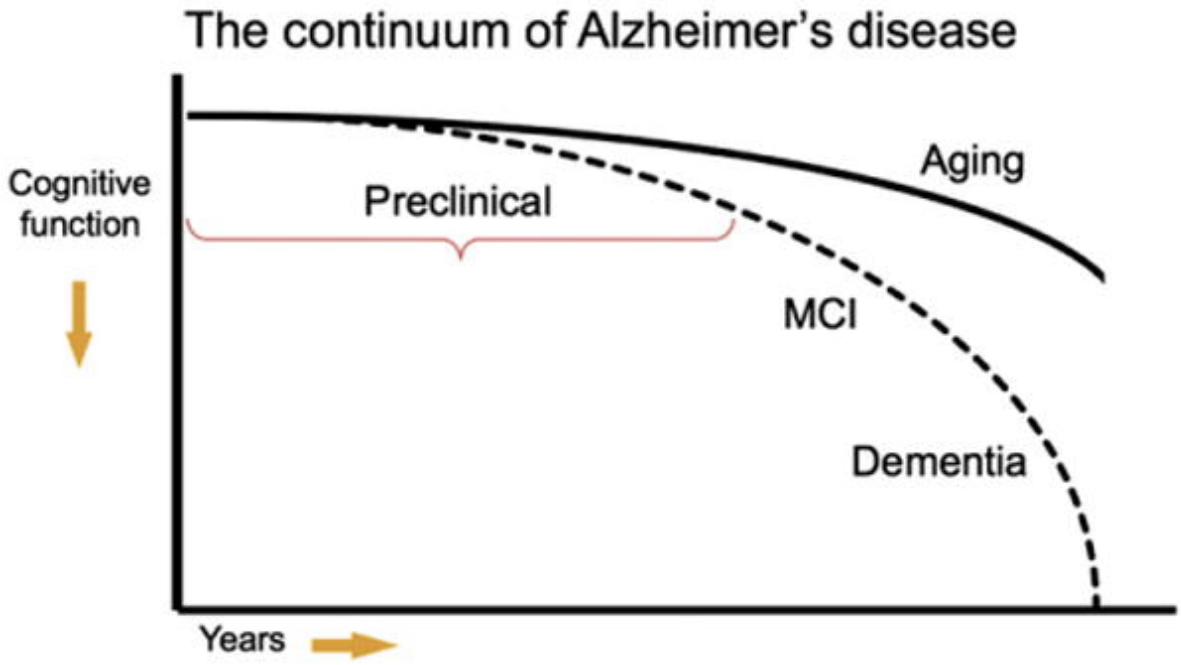
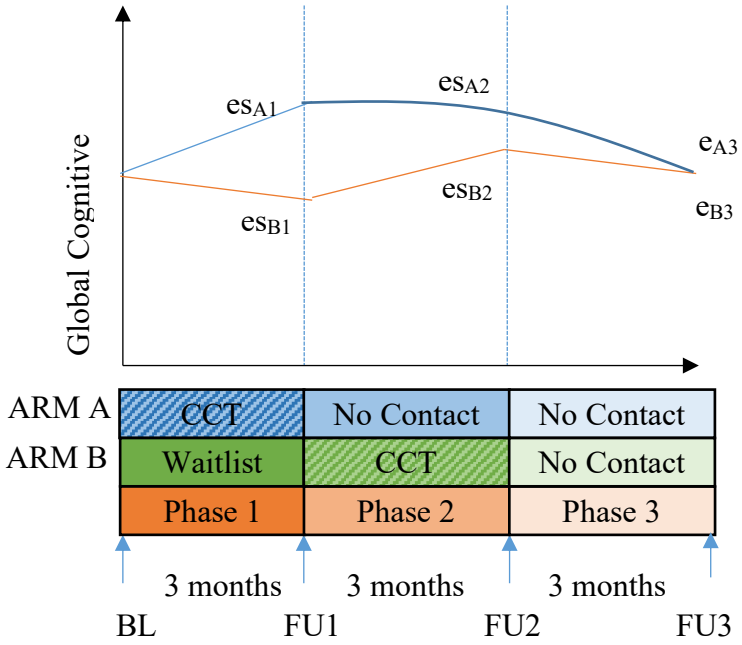


Figure 2



The endpoint of FU3 will assess the long-term implication of immediate compared to delayed intervention. If over a 9-month period the timing of a 3-month CCT intervention does not matter, i.e., both arms are cognitively equivalent at the end, then that may influence and inform the distribution of CCT resources in clinics and the community.

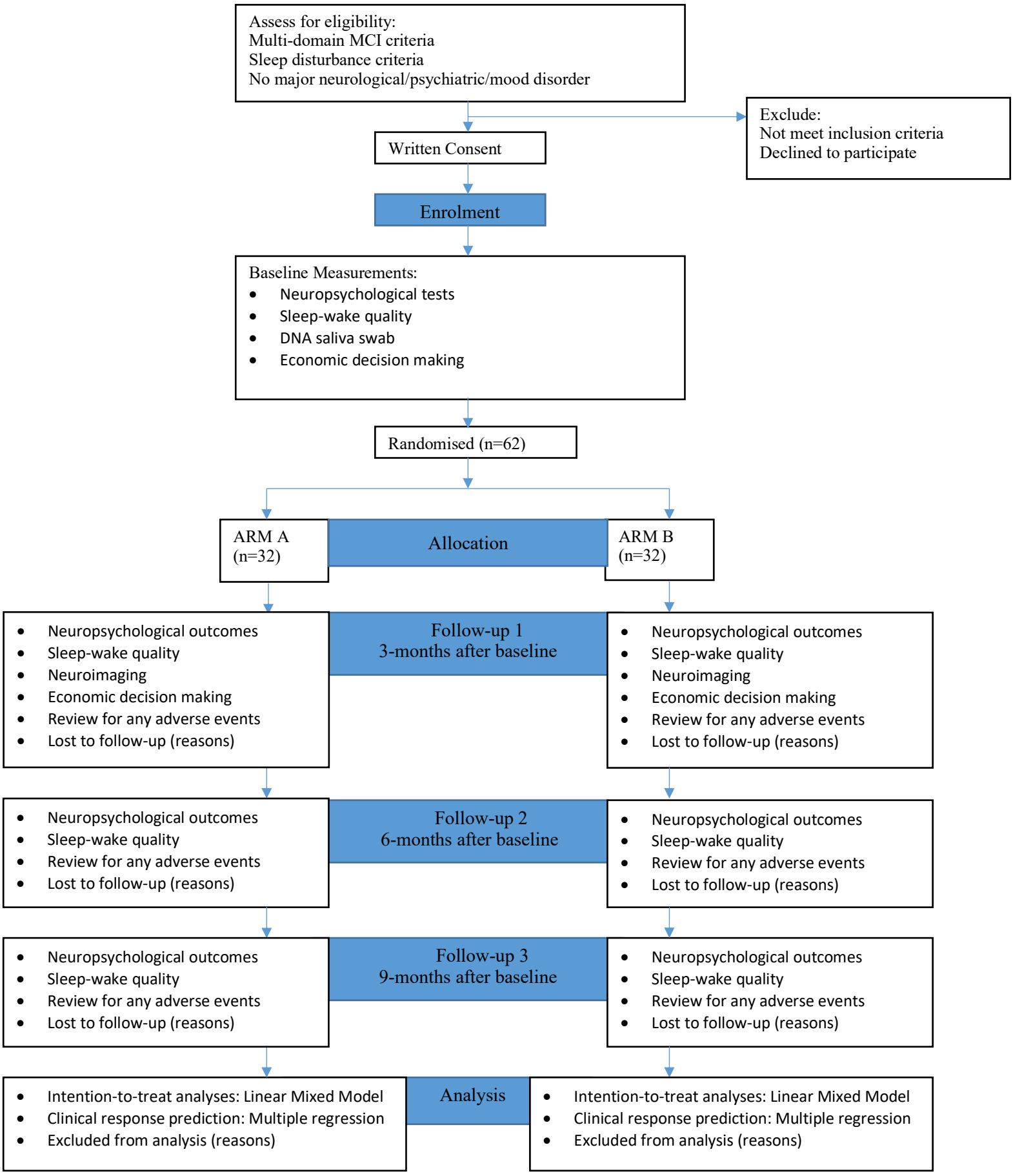
Figure 3: Study Hypotheses



Hypotheses
es = effect size
e = endpoint

Primary
Phase I: $es_{A1} > es_{B1}$

Secondary
Phase II: $es_{A1} > es_{B2}$
Phase III: $e_{A3} = e_{B3}$


Assess for eligibility:
Multi-domain MCI criteria
Sleep disturbance criteria
No major neurological/psychiatric/mood disorder
Exclude:
Not meet inclusion criteria
Declined to participate
Written Consent
Enrolment
Baseline Measurements:
Neuropsychological tests
Sleep-wake quality
DNA saliva swab
Economic decision making
Randomised (n=62)
ARM A (n=32)
Allocation
ARM B (n=32)
Neuropsychological outcomes
Sleep-wake quality
Neuroimaging
Economic decision making
Review for any adverse events
Lost to follow-up (reasons)
Follow-up 1 3-months after baseline
Neuropsychological outcomes
Sleep-wake quality
Neuroimaging
Economic decision making
Review for any adverse events
Lost to follow-up (reasons)
Neuropsychological outcomes
Sleep-wake quality
Review for any adverse events
Lost to follow-up (reasons)
Follow-up 2 6-months after baseline
Neuropsychological outcomes
Sleep-wake quality
Review for any adverse events
Lost to follow-up (reasons)
Neuropsychological outcomes
Sleep-wake quality
Review for any adverse events
Lost to follow-up (reasons)
Follow-up 3 9-months after baseline
Neuropsychological outcomes
Sleep-wake quality
Review for any adverse events
Lost to follow-up (reasons)
Intention-to-treat analyses: Linear Mixed Model
Clinical response prediction: Multiple regression
Excluded from analysis (reasons)
Analysis
Intention-to-treat analyses: Linear Mixed Model
Clinical response prediction: Multiple regression
Excluded from analysis (reasons)

Screening

MCI criteria

MCI is diagnosed according to the Winblad et al 2004 criteria[22] confirmed on the basis of consensus rating of multiple clinicians within the memory center. Typically, this includes a geriatrician or neurologist and two clinical neuropsychologists who review the individual's clinical profile and neuropsychological results.

The Winblad 2004[22] recommends the diagnosis of MCI to fulfil the following criteria: 1. The individual does not meet the criteria for a dementia syndrome in accordance to the DSM IV or ICD 10; 2. Functional activities of the person are mainly preserved; 3. Evidence of cognitive decline.

Objective cognitive impairment is defined as performance of more than or equal to 1.5 standard deviation below the patient's estimated level of premorbid general intellectual functioning (determined using the Wechsler Test of Adult Reading[23]).

Cognitive domains are defined based on the following:
Memory: Wechsler Adult Intelligence Scale (WAIS) Digit Span[24]; Rey Auditory Verbal Learning Test[25]; Wechsler Memory Scale-III Logical Memory I[26] and II[27],
Learning: Rey Complex Figure Test-3 minute Recall[28],
Speed of processing: Trails Making A[29]
Language: Controlled Oral Word Association Test[31]; Boston Naming Test[31]
Visuospatial skills: Rey Complex Figure Test-Copy2; Clock-drawing Test[33]
Executive functioning: Delis Kaplan Executive Functioning System[a] (STROOP)[34]; Trails Making B[29];
Daily function: Amsterdam IADL (informant-rated if available)[34], Global Deterioration Scale[35]; Global assessment of Functioning Scale[37]
Where possible, alternate forms are used between assessments to reduce retest effects.

Single domain MCI refers to MCI with impairment in only one domain; if more than one domain is affected, it is defined as **multi-domain MCI**. Amnestic MCI is defined here by an impairment in delayed recall (assessed as Logical Memory II total score or percent retention[27]; Rey Auditory Verbal Learning Test trial 7 total score or 7/5 percent retention[25]). In cases where only new learning is impaired but delayed recall is intact, the individual is categorised as non-amnestic MCI.

Sleep disturbance criteria

Sleep disturbance will be measured with the Pittsburg Sleep Quality Index (PSQI)[20]: Self Report Questionnaire. Patients with multi-domain MCI diagnosed with the above criteria and a score of >/= 5 in the PSQI; without any major neurological or psychiatric disorder, major depression, current alcohol abuse, will be eligible for the study.

[a] If this test data is not available/provided by the referal memory clinic we will conduct the test after consent and prior to commencement of the intervention

Randomisation
Randomisation will be by computer-generated sequence using small block sizes (n=2), administered by Dr Briggs. Allocation will be revealed to the Study Coordinator after the completion of each baseline assessments. A small block size will ensure that the immediate intervention will start relatively immediately.

4.3 Number of Participants
62

4.4 Expected Duration of Study
3 years

5. STUDY TREATMENTS

5.1 Treatment Arms
Following our meta-analysis of CCT in MCI, showing clear evidence of efficacy on general cognition and psychosocial function[17], clinical equipoise for CCT is shifting in favour of a general recommendation for this intervention (Neurology guidelines; US Taskforce). Accordingly, a purely inactive comparison group is no longer justifiable. Reflecting this, both our treatment arms include the same 3-month/24 session CCT prescription and dose, with only the timing of intervention distinct.

5.1.1 Description
CCT period
Will utilise the NHMRC-funded Maintain Your Brain Trial's "Brain Training System (BTS)", designed by CI Valenzuela that implements exercises from NeuroNation. BTS CCT involves online, guided, drill-and-practice standardised tests that load on specific cognitive processes. These cognitively challenging tasks usually are conducted without explicit instruction of problem-solving strategies. The exercises target either working memory, logic, attention and verbal skills or a combination. The BTS system is a personalised cognitive training program run as flash files meaning that the training regime is based on the participants' baseline cognitive profile and continues to evolve in response to within-training task performance. Performance across verbal executive, speed, verbal memory, visual executive, visual memory and visual attention are ranked in descending order. The training session will 'sandwich' the weaker cognitive abilities in the middle of the training session with the participants stronger cognitive task at the beginning and end of the session. Task difficulty and task type will be recalculated throughout the training depending on the participants' improvement. BTS is therefore designed to be automatically adaptive to a participant's baseline score and progress during training.

Participants will complete supervised, group- and centre-based BTS CCT twice a week, one hour each session, for a total of twelve weeks (24 sessions). It will be optional for participants to complete one session per week from home after completing successfully 6 supervised sessions. Each session is 45 minutes long and will comprise of 17 exercises.

Wait list control period
Will comprise of treatment as usual in our referring clinics which comprises psycho-education.

5.1.2 Dosage and Route of Administration
As above

5.1.3 Dosage modification
n/a

5.2 Preparation and administration of study drug
n/a

5.2.1 Dispensing and Product Accountability
n/a

5.3 Measurement of participant compliance
Automated logs of exercises performed by each participant will be created by the BTS after each session.

5.4 Excluded medications and treatments
Participants currently undertaking any 3rd generation antidepressants that are SSRIs or tricyclic antidepressants and with current symptoms of depression, and those currently undertaking other CCT program(s).

6. PARTICIPANT ENROLMENT AND RANDOMISATION

6.1 Recruitment
62 older adults diagnosed with multi-domain amnestic MCI with sleep disturbance will be recruited from the Healthy Brain Ageing Clinic, Brain and Mind Centre and POWH Memory Clinic in a rolling fashion. The clinics accept referrals from neurologists, geriatricians and psychiatrist as well as local GPs for aged individuals who report new onset cognitive problems. Most of the baseline tests will be taken as part of standard clinic assessment; accordingly, these data will need to have been collected within the last 6-months in order to be valid for study entry.

6.2 Eligibility Criteria
6.2.1 Inclusion Criteria
- Multi-domain amnestic MCI with sleep disturbance
- Amnestic features defined by impairment in recall tasks.
- Other cognitive domains impairment on representative neuropsychological tests

- Sleep disturbance as measured by the Pittsburgh Sleep Quality Index (PSQI) [20] score of ≥ 5
- If using Hypnotics, sedating antihistamines, antipsychotics etc for sleep medication, use must be stable for 3-months (any changes in sleep medication will be monitored during intervention and followup)

6.2.2 Exclusion Criteria

- History of dementia of any aetiology
- History of stroke in last 12 months
- Major neurological disorder requiring current treatment (e.g. epilepsy, Parkinson's disease)
- Major psychiatric disorder requiring current treatment (e.g. schizophrenia, bipolar disorder)
- Current major depression as measured by the 15-item Geriatric Depression Scale (score of ≥ 10) or the 17-item Hamilton Rating Scale for Depression (score of ≥ 12)
- Physical (sensory or motor) impairment that would restrain training
- Current alcohol dependence or abuse
- Currently undertaking external computerised cognitive training and unwilling to cease during trial engagement

6.3 Informed Consent Process

After a participant has been referred to us from a clinic a member of the study team will go through the participant information sheet in person and ensure we have obtained free, fully-informed written consent.

6.4 Enrolment and Randomisation Procedures

Following informed consent, the participant's baseline cognitive data from the referring clinic will be collated and checked for completion. Any additional baseline assessments that are not obtained from the referral clinic will be completed and after all baseline data has been collected the statistician will then inform randomisation status (Arm A or Arm B) to the study co-ordinator (by email) who will then book the participant for the appropriate training schedule.

6.5 Blinding Arrangements

This is a double-blind RCT. Subjects will be informed they will undertake a series of different combination of "brain exercises" of different intensities and will therefore be blind to study hypotheses; expectancies should therefore be well matched. We achieved equivalent insight as to effective treatment status in our NHMRC-funded SMART trial[26] between intervention and control groups using this approach. Assessors will be blinded to group status.

NB: As this is a behavioural intervention with no documented risk of adverse events, there are no pre-specified stopping rules or conditions.

6.6 Breaking of the Study Blind

6.6.1 On Study

The participant will continue in the trial as per normal. The person's data will be red-flagged on final analysis, with sensitivity analyses to determine whether they are influencing study outcomes. Please refer to 9.6 for un-blinding in the case of adverse events.

6.6.2 Following Completion of the Study

This will be documented but eventually will have no impact on the trial integrity or analysis

6.7 Participant Withdrawal

6.7.1 Reasons for withdrawal

In our experience across four RCTs, the main reasons for study withdrawal are: excessive time commitment, changes in personal circumstances (e.g., illness, relocation) and loss of interest in the program.

The only foreseeable circumstance for early termination of the entire study would be some major infrastructure failure at the study site. In this case, the Chief Investigator Prof Valenzuela will be responsible for informing participants, corresponding to HREC, compiling a final study report, and unbinding if applicable.

6.7.2 Handling of withdrawals and losses to follow-up

The trial co-ordinator (Dr Polly Barr) will be responsible for documenting withdrawals and losses to follow-up.

6.7.3 Replacements

There will be no replacements for withdrawals or loss to follow up.

6.8 Trial Closure

At the close of the trial there will be no ongoing follow-up of trial participants.

6.9 Continuation of therapy

We will provide all participants with advice on whether or not to engage in ongoing computerised cognitive training after the close of the trial, depending on the scientific results of the trial.

7. STUDY VISITS AND PROCEDURES SCHEDULE

List procedures	Enrolment	Baseline	Followup 1 (3 months)	Followup 2 (6 months)	Followup 3 (9 months) Final study visit
Informed consent	✓				

Inclusion/exclusion criteria	✓	✓			
Demographic data		✓			
Neuropsychological examination		✓	✓	✓	✓
Saliva sample		✓			
Actigraphy		✓	✓	✓	
Sleep diary		✓	✓	✓	✓
GARP (Tea and Cookies)		✓	✓		
WHO-QOL		✓	✓	✓	✓
GDS		✓	✓	✓	✓
Amsterdam IADL		✓	✓	✓	✓
Adverse event and serious adverse event logbook			✓	✓	✓

8. CLINICAL AND LABORATORY ASSESSMENTS

Primary Outcome Measure

Global Cognition as defined by pre-specified average of z-scores (referenced to baseline) across following weighted cognitive domains:

1. Memory (40%): Wechsler Adult Intelligence Scale (WAIS) Digit Span[24]; LOGOS; Wechsler Memory Scale-III Logical Memory I[26] and II[27], Rey Complex Figure Test-3 minute Recall[28].

2.Speed of processing (15%): Trails Making A[29].

3. Language (15%): Controlled Oral Word Association Test[31]

4. *Visuospatial skills (15%):* Rey Complex Figure Test-Copy[31]

5.Executive functioning (15%): Trails Making B[29]

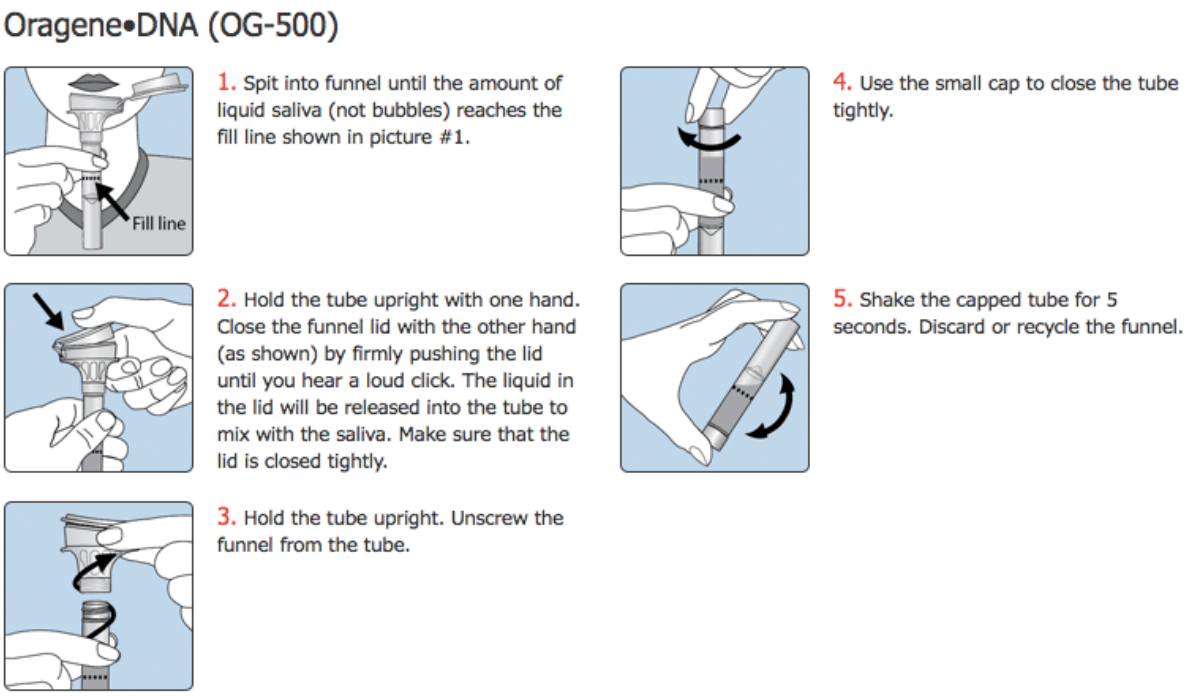
Secondary Outcome Measures

1. Individual cognitive domains measured in separate summary z-score composites
2. Daily functional: Amsterdam IADL
3. Quality of life: WHOQOL
4. Mood and mental-health symptoms: 15-Item GDS
5. Sleep-wake patterns: Sleep diary, actigraphy, PSQI
6. Generalised Axiom of Revealed Preferences (GARP[41])
7. Predictors of responsivity: APOE 3/4 and BDNF ValMet polymorphism, baseline cognitive profile and any other baseline descriptor.

Salival DNA Extraction Swabs Protocol

A saliva sample will be collected during baseline measurements to examine APOE4 and BDNF ValMet genotype status. DNA samples will be stored in Room 403, level 4, 94 Mallett Street, Camperdown and analyses will be conducted in Room 303 Level 3,

94 Mallett Street, Camperdown by AI AProf Kwok. BDNF Val/Met polymorphism (rs6265) will be analysed using the Taqman SNP BDNF-AS Assay (SNP ID: rs6265).



Sleep Actigraphy

An actigraphy watch will be used to measure sleep-wake patterns for one week at baseline, follow-up 1 and follow-up 2. Participants will also complete a sleep diary over this period. Data from Actiwatch systems (Philips, Respironics, USA) will be collected over 30-second epochs and sleep–wake detection scored using Actiware (Philips, Respironics) software. Data will be scored by visual inspection, in conjunction with information from sleep diaries. Wake after sleep onset (WASO) will be identified by epochs of limb movement (specifically non-dominant arm) during the nocturnal rest period, also with reference to light exposure where appropriate. The key variable of interest for this study will be WASO, as per our prior work[27]. However, we will also record mean sleep onset and sleep offset times, and total sleep time for descriptive purposes. This analysis will be conducted by AI Prof Naismith.

9. 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

9.1 Definitions

Device Adverse Events

An adverse event for devices is any undesirable clinical occurrence in a participant whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device.

For devices is any adverse medical occurrence that:

- led to a death;
- led to a serious deterioration in health of a patient user or other. This would
- include:
- a life threatening illness or injury;
- a permanent impairment of body function or permanent damage to a body
- structure;
- a condition requiring hospitalisation or increased length of existing
- hospitalisation;
- a condition requiring unnecessary medical or surgical intervention; or
- foetal distress, foetal death or a congenital abnormality/birth defect;
- might have led to death or a serious deterioration in health had suitable action or intervention not taken place.
- This includes: a malfunction of a device such that it has to be modified or temporarily/permanently taken out of service; or a factor (a deterioration in characteristics or performance) found on examination of the device.

9.2 Assessment and Documentation of Adverse Events

Adverse events can be reported by participants to the Trial Co-ordinator at any time. She will make an immediate determination whether it is a serious adverse event (SAE) or not. In the case of SAE these will be reported immediately to the Chief Investigator who will manage the event. Specific eliciting for adverse events will occur at each of the follow-up assessments (3 months, 6 months, 9 months). All elicited and non-elicited adverse events will be databased.

9.3 Eliciting Adverse Event Reporting

As noted above, eliciting of adverse event information will occur at each of the follow-up assessments (3 months, 6 months, 9 months).

9.4 Serious Adverse Event Reporting

9.4.1 SAEs

Definition of Serious adverse event (SAE)

An unforeseen medical event that occurs in the course of clinical research that:

- results in participant death
- is life-threatening to the participant

- requires the inpatient hospitalisation or prolongation of existing hospitalisation for the participant leads to the participant having a persistent or significant disability/incapacity.

9.4.2 SUSARs

Suspected Unexpected Serious Adverse Reaction (SUSAR)
Not relevant to this trial

9.5 Specific Safety Considerations (e.g. Radiation, toxicity)

Not relevant to this trial

9.6 Un-blinding procedures for adverse events

The code for any participant should only be broken by the chief investigator or authorised person if it is absolutely necessary to ascertain the type of treatment given. The code will be documented and held by the statistician, not to be provided beyond the study co-ordinator (who requires this in order to administer the interventions) until the completion of the trial, or if un-blinding is required. Cases/adverse events that are considered serious, unexpected and probably or definitely related to the treatment will by unblinded by Dr Briggs (an independent statistician and holder of the randomisation code). Blinding of all assessors who are in direct contact with the participants will be maintained.

Contact for unblinding:
Dr Nancy Briggs
Senior Statistical Consultant
Stats Central
Mark Wainwright Analytical Centre
UNSW Sydney NSW 2052
nancy.briggs@unsw.edu.au
m: +61 (0)435 579 173
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10. STATISTICAL METHODS

10.1 Sample Size Estimation

This study is powered on the basis of a relative effect size (RES) on Global Cognition of 0.44 at the end of the Phase I RCT (based on average from our Timecourse Trial[5] and NHMRC SMART trial[6]). Designate power of 0.80 controlling α at 0.05 translates to a required sample size of N=52 (calculated using G*Power 3.1 based on ANOVA repeated measures within-between interaction test, 2 groups, 2 time-points, within subject autocorrelation =0.4, equivalent effect size of [v]=0.22). A sample of N=62 (rounded up from 61) will be recruited to allow for 15% overall attrition (as per Timecourse Trial extrapolated to 9-months).

10.2 Population to be analysed

Clinic-referred older adults with multi-domain amnestic MCI with sleep disturbance.

10.3 Statistical Analysis Plan

Phase I: An *intention-to-treat* approach using recommended Linear Mixed Modelling[4] will evaluate a model including main effects for Group (Arm A vs Arm B), Time (BL vs FU1) and the main interaction term of interest: Group X Time. Covariates will only be added if baseline differences are noted between groups.

Phase II Linear Mixed Modelling[4] will evaluate a model including main effects for Group (Arm A vs Arm B), Time (Arm A BL vs FU1, Arm B **FU1 vs FU2**) and the main interaction term of interest: Group X Time. An additional covariate of initial global cognitive status will be added to this analysis to control for different potential starting points for the two arms at the different timepoints.

Phase III: Equivalence of the two arms at follow up III will be tested using a two one-sided test (TOST[42]) .

Clinical Response Prediction will be addressed by multiple regression examining relationships between baseline predictor variables (i.e; cognitive profile) and cognitive change scores.

10.4 Interim Analyses

None will be conducted.

11. DATA MANAGEMENT

11.1 Data Collection

The Healthy Brain Ageing Clinic: will provide baseline cognitive data in raw and normed scores format for each test and this will be emailed to Trial Co-ordinator.

Similarly, the POWH Memory Clinical will provide baseline cognitive data in raw and normed scores format for each test and this will be emailed to Trial Co-ordinator.

Additional cognitive tests: Amsterdam IADL and Risk Perception test will be administered by the Chief Investigator's team and collated by the Trial Co-ordinator. Composite z-scores for each cognitive domain and global cognition will also be computed by the trial co-ordinator.

DNA APOE information: the saliva DNA extraction kit results will be sent by Al Kwok to Trial Co-ordinator by email.

Sleep-related information (diary, actigraphy and PSQI) will be collected by Al Naismith's team and email to the Trial Co-ordinator.

All relevant information will be collated by the trial Co-ordinator onto a single password-protected file.

11.2 Data Storage

The data will be stored as hard copies and electronic copies. All hard copies will be stored in a locked filing cabernet at Prof Valenzuela's office, Room 408, Level 4 Bldg M02K. 94 Mallett Street, Camperdown NSW 2050. Electronic files will be saved on dedicated computers in locked room 401 Building K, 94 Mallett Street, Camperdown NSW 2050. LOGOS audio files will be stored in de-identifiable form on the secure MYB server under UNSW HREC (HC16252 titled Maintain Your Brain; MYB).
All hard copies will be shredded at the end of the 20-year period. An electronic file containing non-identifiable data will be kept in perpetuity.

11.3 Data Confidentiality

All data will be re-identifiable (Prof Valenzuela and Study Co-ordinator will be the only one with the re-identifying code to re-identify individual files) and kept on site at the Brain and Mind Centre. All data will be collected and stored in a locked room at the Brain and Mind Centre.

The data presented for publication and presentations at scientific conferences, will be in de-identified form.

11.4 Study Record Retention

All hard copies will be stored in a locked filing cabernet at Prof Valenzuela's office, Room 408, level 4, Bldg M02K. 94 Mallett Street, Camperdown NSW 2050.
Electronic data will be backed up and archived using the Research Data System (RDS) of Sydney University.
Since this is a clinical trial, the records will be stored for a minimum of 20 years post study completion or last publication.

12. ADMINISTRATIVE ASPECTS

This trial is registered with ANZCTR with ACTRN : ACTRN12618001126202p

The WHO International Clinical Trials Registry Platform (ICTRP), Universal Trial number (UTN) for this trial is: **U1111-1215-8784**

12.1 Independent HREC Approval

This trial has been approved by the University of Sydney's Human Research Ethics Committee (HREC): **2018/669.**

12.2 Amendments to the protocol

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

12.3 Protocol deviations

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

12.4 Participant Reimbursement

Participants time and travel will be reimbursed with $25 Coles/Myer vouchers for each follow up (i.e. $75 in total if no drop out)

12.5 Financial Disclosure and Conflicts of Interest

PI Valenzuela has no relevant financial disclosures or conflicts of interest.

As NeuroNation is providing software to support the intervention, they have a financial interest in the outcome of the trial, however, they will have no input or involvement in the design, analysis, interpretation, publication or dissemination of the findings.

13. USE OF DATA AND PUBLICATIONS POLICY

At the end of their involvement in the trial, (i.e. ~9 months after baseline) each participant will receive a report of their cognitive testing scores at all follow-ups. They will be offered possibility to discuss these results with a person from the study team.

In order to maximise transparency and foster value-added interrogation of this RCT data, the team will host all de-identified RCT data (i.e. demographic and clinical) on a publicly- accessible server (following login and verification of research credentials) after the completion of the study.

Following the great success of this approach in the ADNI collaboration[28], researchers will be able to download any or aspects of the data to investigate their own research questions and acknowledge authorship via the "TRAJECTORIES TEAM".

14. REFERENCES

1. Moher, D.*, et al.* CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Bmj* **340**, c869 (2010).
2. Chan, A.W.*, et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *Bmj* **346**, e7586 (2013).
3. Therapeutic Goods Administration. *The Australian Clinical Trial Handbook* (2006).
4. Gueorguieva, R. & Krystal, J.H. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Arch Gen Psychiatry* **61**, 310-317 (2004).
5. Lampit A*, et al.* The timecourse of global cognitive gains from supervised computer-assisted cognitive training: a randomised, active-controlled trial in elderly with multiple dementia risk factors. *Journal of Prevention of Alzheimer's Disease* **1**, 33-39.
6. Fiatarone Singh, M.A.*, et al.* The Study of Mental and Resistance Training (SMART) Study—Resistance Training and/or Cognitive Training in Mild Cognitive Impairment: A Randomized, Double-Blind, Double-Sham Controlled Trial. *Journal of the American Medical Directors Association* **15**, 873-880 (2014).
7. Prince, M., Comas-Herrera, A., Knapp, M., Guerchet, M. & Karagiannidou, M. World Alzheimer Report 2016. in *Improving Healthcare for People Living with Dementia;*

Coverage, Quality and Costs Now and In the Future (Alzheimer's Disease International: The global voice on dementia,, London, UK, 2016).
8. Council, T.W.D. The World Dementia Council's Year-On Report 2014/15. (UK, 2015).
9. Lopez, O., Kuller, L. & Becker, J. Incidence of Dementia in Mild Cognitive Impairment in the Cardiovascular Health Study Cognition Study. *Arch Neurol* **2007**, 416-420 (2007).
10. Barnes, D. & Yaffe, K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurology* **10**, 819-828 (2011).
11. Valenzuela, M.J. Cultivating a Cognitive Lifestyle: Implications for Healthy Brain Aging and Dementia Prevention. *Dementia:[Three Volumes]*, 99 (2011).
12. Valenzuela, M.J. & Sachdev, P. Brain reserve and dementia: a systematic review. *Psychological medicine* **36**, 441-454 (2006).
13. Valenzuela, M.J. & Sachdev, P. Brain reserve and cognitive decline: a non-parametric systematic review. *Psychol Med* **36**, 1065-1073 (2006).
14. Palmer, K., Berger, A. & R, M. Predictors of Progression from Mild Cognitive Impairment to Alzheimer's disease. *Neurology* **2007**, 1596-1602 (2007).
15. Modrego, P. & Ferrandez, J. Depression in patients with Mild Cognitive Impairment Increases the Risk of Developing Dementia of Alzheimer type: A Prospective Cohort Study. *Arch Neurol* **2004**, 1290-1293 (2004).
16. da Silva, R.A. Sleep disturbances and mild cognitive impairment: A review. *Sleep Sci* **8**, 36-41 (2015).
17. Hill, N.*, et al.* Computerized Cogntiive Training in Older Adults With Mild Cognitive Impairment or Dementia: A Systematic Review and Meta-Analysis. *The American Journal of Psychiatry* **174**, 329-340 (2016).
18. Haimov, I. & Shatil, E. Cognitive training improves sleep quality and cognitive function among older adults with insomnia. *PLoS One* **8**, e61390 (2013).
19. Rosenberg, P.B. & Lyketsos, C. Mild cognitive impairment: searching for the prodrome of Alzheimer's disease. *World Psychiatry* **7**, 72-78 (2008).
20. Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research*, *28*(2), 193-213.
21. Peters, K.R., Lynn Beattie, B., Feldman, H.H. & Illes, J. A conceptual framework and ethics analysis for prevention trials of Alzheimer Disease. *Prog Neurobiol* **110**, 114-123 (2013).
22. Winblad, B.*, et al.* Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* **256**, 240-246 (2004).
23. The Psychological Corporation. *Wechsler Test of Adult Reading*, (Harcourt Assessment, San Antonio TX, 2001).
24. Wechsler, D.A. Digit Span. in *Wechsler Adult Intelligence Scale* (The Psychological Corporation, San Antonio, TX, 1997).
25. Schmidt, M. *Rey Auditory Verbal Learning Test: A handbook*, (Western Psychological Services, Los Angeles, CA, 1996).
26. Wechsler, D.A. Logical Memory I. in *Wechsler Memory Scale-III* (The Psychological Corporation, San Antonio, TX, 1997).
27. Wechsler, D.A. Logical Memory II. in *Wechsler Memory Scale-III* (The Psychological Corporation, San Antonio, TX, 1997).

28. Meyers, J., & Meyers, K. . *Rey Complex Figure and Recognition Trial: Professional manual.*, (Psychological Assessment Resources, Odessa, FL, 1995).
29. Tombaugh, T.N., Rees, L. & McIntyre, N. Normative data for the Trail Making Test. Personal communication cited in Spreen and Strauss. in *A compendium of neuropsychological tests: Administration, norms and commentary* (Oxford University Press, New York, 1998).
30. Tombaugh, T.N., Kozak, J. & Rees, L. Normative data stratified by age and education for two measures of verbal fluency: FAS and Animal Naming. *Archives of Clinical Neuropsychology* **14**, 167-177.
31. Ivnik, R.J., Malec, J.F., Smith, G.E., Tangalos, E.G. & Petersen, R.C. Neuropsychological tests' norms above age 55: COWAT, BNT, MAE token, WRAT-R reading, AMNART, STROOP, TMT, and JLO. *The Clinical Neuropsychologist* **10**, 262-278 (1996).
32. Meyers, J., & Meyers, K. The Rey Complex Figure and the Recognition Trial under four different administration procedures. *The Clinical Neuropsychologist* **9**, 65-67 (1995).
33. Agrell, B. & Dehlin, O. The clock-drawing test. *Age and Ageing* **1998**, 399-403 (1998).
34. Delis, D.C., Kaplan, E. & Kramer, J.H. *Delis-Kaplan Executive Function System*, (Pearson, 2001).
35. Sikkes, S. A., Knol, D. L., Pijnenburg, Y. A., De Lange-de Klerk, E. S., Uitdehaag, B. M., & Scheltens, P. (2013). Validation of the Amsterdam IADL Questionnaire©, a new tool to measure instrumental activities of daily living in dementia. *Neuroepidemiology*, *41*(1), 35-41.
36. Reisberg, B., Ferris, S.H., de Leon, M.J. & Crook, T. The global deterioration scale for assessment of primary degenerative dementia. *American Journal of Psychiatry* **1982**, 1136-1139 (1982).
37. American Psychiatric Association. *Dianostic and Statistical Manual of Mental Disorders, Fouth Edition, Text Revision (DSM-IV-TR)*, (American Psychiatric Press, 2000).
38. Fiatarone Singh, M.A*., et al.* The Study of Mental and Resistance Training (SMART) study-resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. *Journal of the American Medical Directors Association* **15**, 873-880 (2014).
39. Sperling, R.A*., et al.* Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 280-292 (2011).
40. Wechsler, D. (2014). Block design in Wechsler adult intelligence scale–Fourth Edition (WAIS–IV). *San Antonio, Texas: Psychological Corporation*.
41. Chung, H. K., Tymula, A., & Glimcher, P. (2017). The Reduction of Ventrolateral Prefrontal Cortex Gray Matter Volume Correlates with Loss of Economic Rationality in Aging. *Journal of Neuroscience*, *37*(49), 12068-12077.
42. Walker, E. & Nowacki, A.S. (2011). Understanding equivalence and noninferiority testing. J. Gen Int Med, 26(2).