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Determinants of Physical Activity Engagement and Physical Activity Intervention Adherence in Individuals with Mild Cognitive Impairment: A Mixed Methods Study

Volume Two (of Two)

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A thesis submitted to Trinity College Dublin in fulfilment of the degree of Doctor of Philosophy in the Department of Medical Gerontology

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List of Appendices

Appendix A: Quantitative critical appraisal checklist

CHECKLIST FOR ANALYTICAL CROSS-SECTIONAL STUDIES

Critical Appraisal tools for use in JBI Systematic Reviews

Introduction

JBI is an JBI is an international research organisation based in the Faculty of Health and Medical Sciences at the University of Adelaide, South Australia. JBI develops and delivers unique evidence-based information, software, education, and training designed to improve healthcare practice and health outcomes. With over 70 Collaborating Entities, servicing over 90 countries, JBI is a recognised global leader in evidence-based healthcare.

JBI Systematic Reviews

The core of evidence synthesis is the systematic review of literature of a particular intervention, condition or issue. The systematic review is essentially an analysis of the available literature (that is, evidence) and a judgment of the effectiveness or otherwise of a practice, involving a series of complex steps. JBI takes a particular view on what counts as evidence and the methods utilised to synthesise those different types of evidence. In line with this broader view of evidence, JBI has developed theories, methodologies and rigorous processes for the critical appraisal and synthesis of these diverse forms of evidence in order to aid in clinical decision-making in healthcare. There now exists JBI guidance for conducting reviews of effectiveness research, qualitative research, prevalence/incidence, etiology/risk, economic evaluations, text/opinion, diagnostic test accuracy,

mixed-methods, umbrella reviews and scoping reviews. Further information regarding JBI systematic reviews can be found in the JBI Evidence Synthesis Manual.

JBI Critical Appraisal Tools

All systematic reviews incorporate a process of critique or appraisal of the research evidence. The purpose of this appraisal is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. All papers selected for inclusion in the systematic review (that is – those that meet the inclusion criteria described in the protocol) need to be subjected to rigorous appraisal by two critical appraisers. The results of this appraisal can then be used to inform synthesis and interpretation of the results of the study. JBI Critical appraisal tools have been developed by the JBI and collaborators and approved by the JBI Scientific Committee following extensive peer review. Although designed for use in systematic reviews, JBI critical appraisal tools can also be used when creating Critically Appraised Topics (CAT), in journal clubs and as an educational tool.

JBI Critical Appraisal Checklist for

analytical cross sectional studies

Reviewer_____

Date_____

Author_____Record Number_____

	Yes	No	Unclear	Not applicable

Were the criteria for inclusion in the sample clearly defined?	□	□	□	□
Were the study subjects and the setting described in detail?	□	□	□	□
Was the exposure measured in a valid and reliable way?	□	□	□	□
Were objective, standard criteria used for measurement of the condition?	□	□	□	□
Were confounding factors identified?	□	□	□	x□
Were strategies to deal with confounding factors stated?	□	□	□	x□
Were the outcomes measured in a valid and reliable way?	□	□	□	□
Was appropriate statistical analysis used?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments (Including reason for exclusion)

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Explanation of analytical cross sectional studies critical appraisal

How to cite: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk . In: Aromataris E, Munn Z (Editors). *JBI Manual for Evidence Synthesis.* JBI, 2020. Available from https://synthesismanual.jbi.global

Analytical cross sectional studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. Were the criteria for inclusion in the sample clearly defined?

The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. Were the study subjects and the setting described in detail?

The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them. The authors should provide a clear description of the population from which the study participants were selected or recruited, including demographics, location, and time period.

3. Was the exposure measured in a valid and reliable way?

The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.

Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. Were objective, standard criteria used for measurement of the condition?

It is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. Characteristics are another useful approach to matching groups, and studies that did not use specified diagnostic methods or definitions should provide evidence on matching by key characteristics

5. Were confounding factors identified?

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

6. Were strategies to deal with confounding factors stated?

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured.

7. Were the outcomes measured in a valid and reliable way?

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer

is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

Having established the objectivity of the outcome measurement (e.g., lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g., radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

8. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured.

For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

Appendix B: Qualitative critical appraisal checklist

JBI Critical Appraisal Checklist for Qualitative Research

Reviewer_____Date_____

Author _____Year_____Record Number_____.

		Yes	No	Unclear	Not applicable
1.	Is there congruity between the stated philosophical perspective and the research methodology?	☐	☐	☐	☐
2.	Is there congruity between the research methodology and the research question or objectives?	☐	☐	☐	☐
3.	Is there congruity between the research methodology and the methods used to collect data?	☐	☐	☐	☐
4.	Is there congruity between the research methodology and the representation and analysis of data?	☐	☐	☐	☐
5.	Is there congruity between the research methodology and the interpretation of results?	☐	☐	☐	☐
6.	Is there a statement locating the researcher culturally or theoretically?	☐	☐	☐	☐
7.	Is the influence of the researcher on the research, and vice- versa, addressed?	☐	☐	☐	☐
8.	Are participants, and their voices, adequately represented?	☐	☐	☐	☐
9.	Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	☐	☐	☐	☐
10.	Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Appendix C: Data extraction table for quantitative findings

Table A1.

Data Extraction Table for Quantitative Studies

Author	Year	Journal	Study Design	Participants	Intervention	Independent Variable	Primary Outcome	Adherence Rates	Main Findings	Statistical Methods
Tak et al.	2012	Journal of Aging and Physical Activity	RCT	community-dwelling adults aged 70–80 years, mean age 75.1 (2.9), (n= 134)	Group based. 12-month duration. 60 minutes twice per week. Conditions were a moderate intensity walking programme and low intensity balance and flexibility exercise training.	Cognitive function demographics, PA	PA programme adherence	23% did not start the programme. Mean adherence was 49 % for the walking group, 55 % for the balance group and 53 % for total adherence.	Main reasons for non - adherence were having trouble with walking or moving and being ill or injured, and programme intensity (too vigorous). Adherence was not statistically different between groups	Student t test and chi squared MANOVA with repeated measure
Cox et al.	2013	Preventive Medicine	RCT.	Participants had MCI and SCI (n	6-month home - based	Cognitive function, Baseline PA	PA programm	Programme adherence	non - adherence due to injury/illness	Anova, chi square,

				= 170), Mean age 66.5 (8.7).	telephone monitored walking programme of 150 minutes	(self-reported PA, Pedometer), Stage of PA intention ,Self efficacy, Illness and injury	e adherence	(for the walking group) was 84.9 % Mean weekly adherence was 72.8%	(64%).: Weekly adherence decreased significantly over time Men had significantly higher adherence than women self-efficacy at baseline predicted 1.37 % increase in adherence (p = < 0.05), Injury predicted a reduction in adherence by 43.08%	Longitudinal mixed effects regression , Random effects regression
Di Loreto et al.	2020	Preventive Medicine Reports	Systematic review and meta - analysis	34 studies with dementia participants (n = 2149) and 7 studies with MCI participants (n = 970)	Adherence rates, reporting adherence, characteristics associated with adherence.	Mean adherence rate was 70% where MCI and dementia studies are combined, ranging from 16 - 100%. Mean adherence for MCI only was 70.5%.			There was no difference in adherence between MCI and dementia sub - groups. Adherence was significantly associated with endurance/resistance training and interventions that did not include walking (all studies; MCI and AD). Format of delivery was not significantly related to adherence, but adherence was	

									higher in group - based formats compared to individual programmes (	
Umemura et al.	2013	Clinical Interventions in Aging	RCT	44 individuals with MCI, mean age 74.8 (7.3).	Demographics: Age, gender, number of medications and education. Cognitive function), depression, muscle strength, and adherence rate	Change in physical performance (trainability) after PA intervention	Physical performance		Physical performance was negatively correlated with adherence. Cognitive function was correlated with physical performance Adherence was associated with improved physical function after controlling for age and gender.	T test, Correlations, stepwise multivariate linear regression.
Lam et al.	2015	PLOS one	RCT	555 individuals with MCI, 72% were female. Mean age 75.4 and mean education was low 3.9 years.	12-month intervention supervised + home - based	Adherence, Global cog function, depression, IADLs	Cognitive function	Adherence for all conditions was 73.3%. Adherence broken down by condition was (PA, 75%; Cognitive, 75%; Cognitive and	No difference in mean age or education in those who adhered versus dropouts. Age and education were not significantly related to adherence. Women had greater adherence than men Better	

							physical, 65%; Social, 71%	baseline MMSE and delayed recall showed a weak positive correlation with adherence. Greater adherence was associated with improvement in ADAS-Cog scores. Greater adherence was associated with better delayed recall at end of intervention
van Uffelen et al.	2008	British Journal of Sports Medicine	RCT	152 individuals with MCI	Cognitive function		Median adherence (PA) was 63% (2 - 81)	There was a non - significant correlation between general cognition and adherence. In women in the walking group, attention (Stroop combination task) improved by 0.3 seconds (p=0.04) and memory (auditory verbal learning test) by 0.04 words (p=0.06) with each percent increase in session attendance. In

								men attending at least 75 percent of the sessions, the WP improved memory (beta [95%CI]= 1.5 [0.1; 3.0] words). Living with a partner and being less physically active at baseline was related to greater adherence. Health related problems were the most frequent reason for drop out.	
van Uffelen et al.	2009	Journal of Aging and Physical Activity	RCT	179 Dutch individuals with MCI. Mean age 75 (2.8).	Adherence, Cognitive function memory, executive function, Attention, information processing speed	Feasibility and effectiveness of a 12-month walking programme for individuals with MCI		Sub - group analysis showed that baseline AVLT (memory) was significantly related to adherence in the walking group , and general cognitive function was related to adherence in the low intensity activity group but when analysed together these	Mann Whitney U, Chi Square, Independent Samples t test Spearman's correlation

									were not significant.
de Oliviera Silva	2019	Maturitas	RCT	90 Brazilian individuals with MCI (n = 19) and AD (n = 27)	Supervised centre - based intervention, 60 minutes twice weekly, for 12 weeks.	programme sub - groups (MCI or AD)	mobility and cognitive function	adherence was 87% and 90% attendance for AD and MCI respectively	
Chong et al.	2020	Journal of Science and Medicine in Sport	Narrative review	41 studies included	N/A		Development of PA guidelines for Australian individuals with MCI and SCI		Targeted educational material and incorporating social interactions into intervention designs facilitates adherence to PA programmes for adults with SCI and MCI. The relationship between baseline cognitive function and PA programme adherence is inconsistent. Health complaints (including injury) and practical barriers (time and location) were the most significant

							barriers to PA programme adherence. PA should be individually tailored to account for health problems, physical capacity, individual goals, and environment.
van der Wardt	2017	preventive Medicine Reports	Narrative review	12 studies were included for review. Studies included individuals with MCI and dementia.	Evidence regarding the effectiveness of PA adherence support strategies is limited.	Mean adherence was 90% for PA interventions for individuals with MCI and dementia and ranged from 25% to 90% with studies using multiple strategies (a tailored approach to the intervention, information for the	No studies have examined the effectiveness of adherence strategies employed using an RCT design.. Three strategies were assessed more than once: phone calls, information regarding the study and group setting. One study identified the barrier of time intensive programmes Group-based settings were preferred format. PA interventions for MCI and dementia should be individually

							participants and telephone support) achieving higher adherence (77 - 90%)	tailored, include a learning/ adaptation period, and ensure the provision of sufficient information to participants and use phone calls, , exercise logs and/or reminders, and pedometers as well as supervision and planning to support PA programme adherence. Music was the only adherence support strategy that was investigated in an RCT design but was only effective for individuals who were already motivated to participate.	
Gagliardi et al.	2016	International Journal of Environmental Research and Public Health	Cross sectional	305 Italian individuals with MCI, AD and cognitivel	Cognitive function, depression, social support, Smoking,	Physical activity engagement		Healthy adults were significantly more active than individuals with MCI and AD	Chi square, ANOVA

				y healthy. Mean age 75.3 (SD = 6.1).	alcohol, ADLs, IADLs, chronic disease		24.8 % achieved less than 51 mins PA per week (mpw), 28.7% achieved between 52 and 85 mpw, 26.7% achieved between 86 and 118 mpw, and 19.8% of participants achieved over 119 minutes per week Age and education was significantly negatively related to PA in the MCI group. IADLS (but not ADLs) were significantly negatively related in the MCI group.	
Kobayashi et al.	2016	Dementia and Cognitive Disorders Extra	Cross – sectional	590 adults =/> 75 years with MCI, dementia, or no impairment	Global cognitive function, executive function, depression	PA (self – reported)	PA is related to executive function in patients with MCI. In patients with dementia, PA is related to both the executive function and motor intensity	ANOVA

Rovner et al.	2016	Alzheimer's Disease and Associated Disorders	Cross - sectional	221 individuals with MCI, mean age 75	education, depression, literacy, mobility, instrumental activities of daily living (IADL), verbal learning, and subcomponents of executive function	PA engagement	PA was positively associated with gender, depression, IADLs, and subcomponents of executive function. .IADLs, education, depression, and verbal learning as independently predicted PA.	Correlation, linear regression
Van Campfort et al.	2018	Public Health	Cross - sectional	4854 participants with MCI, mean age 64.4 years	Depression, age, unemployment, being underweight, obesity, asthma, chronic lung disease, hearing problems, visual impairment, gait speed, weak grip strength, self-rated health, levels of social cohesion.	PA engagement	The prevalence of low PA was 27.4%. Older age and unemployment correlated with low PA. depression, being underweight, obesity, asthma, chronic lung disease, hearing problems, visual impairment, slow gait, weak grip strength, poor self-rated health, and lower levels of social cohesion were correlated.	Multivariate analysis

O Connell et al.	2015	Journal of Ageing and Physical Activity	Cross - sectional	51 individuals with MCI, dementia, AD and no impairment and 43 caregivers (N = 94).	Opinions and attitudes to PA	PA engagement	Caregivers and patients differed in attitudes to PA. Patients were less likely to believe in the importance of PA for health promotion. Belief in the importance of high intensity exercise for health maintenance significantly predicted PA. Moreover, caregivers' attitudes to high intensity PA predicted memory patients PA engagement	
Wettstein et al.	2015	Journal of Applied Gerontology	Cohort	257 individuals with MCI, AD, or no impairment, mean age 73	Cognitive function	Out of home behaviour	cognitively demanding activities were significantly different between MCI and no impairment and between AD and no impairment	Multinomial logistic regression
Stuckenschneider et al.	2018	Journal of Alzheimer`s Disease	Cross – sectional	121 individuals with MCI or SCI	Cognitive function (stage of MCI),	PA engagement	Participants with late MCI had the lowest PA levels	ANCOVA

	cardiorespiratory fitness

Appendix D: Data extraction for qualitative findings

Table A2.

Data Extraction Table for Qualitative Findings

Author	Year	Journal	Methodology	Method	phenomena of interest	Geographical/Cultural	Participants	Data Analysis	Themes
Chong 2014	2014	Asia Pacific Psychiatry	Qualitative (thematic analysis)	Semi - structured focus groups and individual interviews.	Attitudes, beliefs, and barriers to PA engagement in Adults with MCI, SCI and AD	Australian adults	50 adults over 60 years (mean age 76 (6.4).	Inductive thematic analysis. Themes for SCI and HC participants were compared as people without cognitive impairment against themes from adults with MCI and AD (people with cognitive impairment).	1. Attitudes toward doing PA/ exercise: Good, Important for health, Social, Enjoyable ,Careful/potential danger, Part of identity. 2. Impact of physical activity/exercise on cognitive (thinking) function and dementia: PWCI more often reported a belief that PA was helpful for cognitive function. 3. Barriers towards physical activity/exercise: PWCI listed the barriers of Health problems/disability,

								Motivation/personality, Environment, Lack of companion, memory problems. Regarding preferences for PA programmes or PA engagement, adults with cognitive impairment (MCI/ AD) reported : accessibility (pwci), in a group setting (pwci and HC and SCI together), PWCI said PA must be simple, light, and safe. All participants reported preferring PA that was "tailored" i.e., to their abilities and preferred exercise.
Van der Wardt	2019	Aging & Mental Health	Qualitative (thematic analysis)	MCI or early dementia and their carers who had not previously participated in a research exercise intervention (focus group 1 and 2), one group included people with MCI or dementia and their carers who had participated in	motivators for PA engagement in adults with MCI and dementia and their carers	Dutch adults	13 participants with MCI and AD and clinicians. This broke down was 6 participants with MCI or dementia, 3 family carers and one focus group with 4 clinicians which will not be reported as	1. ‘memory problems’: i.e., reminders such as calendars. Needing support from others to account for memory loss such as needing a partner to ensure they return safely. 2. ‘self-motivation’: was organised into organisation (Goal-setting; reminders; planning; habit/routine; control) and benefits (Enjoyment; remaining independent; keeping fit and healthy) , 3. ‘external motivation’:

				an exercise proof-of-concept intervention study. 3 semi - structured focus groups representing participants with MCI and family carers, and one representing clinicians. Data was thematically analysed.			part of this review.		(Family support, being a Dog owner, Socialising with others, Feedback from clinicians, Information) , 4. 'design of activities': Tailoring (t preferences and abilities) and setting (preference for outdoor setting, or gym setting with adequate support for ability) and 5. 'barriers": Environmental barriers, Health issues, Conflict with other activities, Believing being unable to complete the exercises or physical activities.
Hancox et al.	2019	Plos one	Qualitative	Adherence was categorised based on reported number of times a week they completed prescribed exercises over a 4 month period (<3 times a week = low adherence, 3–4 = meeting adherence	Barriers and facilitators of adherence to a 12 - month home - based strength and balance programme	United Kingdom	20 adults with MCI and early dementia and their carers	Inductive and deductive thematic analysis was used to analyse data. Themes categorised using the Theoretical Domains Framework.	five participants were categorised as exceeding adherence expectations (> 5 times per week), 7 as meeting adherence expectations (3 -4 times per week), and 8 as low adherers (< 3 times per week). Six themes were identified: routine, practical and emotional support, memory support, purpose, past experiences of sport and exercise, and

	expectations, >5 = exceeding adherence expectations). Semistructured interviews were conducted in month 4 of the programme to explore barriers and facilitators to adherence.		belief in and experience of benefits.

Appendix E: NeuroExercise study protocol

The Effects of an Extensive Exercise Program on the Progression of Mild Cognitive Impairment (MCI)

Chief Investigator: Prof Brian Lawlor

Version Number: II Draft IV

Date: 14.12.2015

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CRF	Case Report Form
GCP	Good Clinical Practice
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
AD	Alzheimer's Disease
ND	Neurodegenerative Diseases
MCI	Mild Cognitive Impairment

QOL	Quality of Life
CDR	Clinical Dementia Rating
MoCA	Montreal Cognitive Assessment
WMS	Wechsler Memory Scale
ECG	Electrocardiogram
TIA	Transient Ischaemic Attack
MRI	Magnetic Resonance Imaging
DemQoL	Health Related Quality of Life for People with Dementia
DAD	Disability Assessment for Dementia
CES-D	Centre for Epidemiologic Studies Depression
TMT	Trail Making Test
WHO	World Health Organisation
VO2max	Maximal Oxygen Uptake
EDTA	Ethylenediaminetetraacetic acid
LAPAQ	LASA Physical Activity Questionnaire
TUG	Timed Up and Go
CPET	Cardiopulmonary Exercise Test
NEO-FFI	NEO-Five Factor Inventory
NIRS	Near-Infrared Spectroscopy

Background

Good health is the basis of long, productive and enjoyable lives. Yet, as the population ages and grows (both in number and weight) and the resource intensity of treatments increases, our current healthcare system is becoming unsustainable. To help ensure an aging society live enjoyable and productive lives research into treating or preventing conditions such as Alzheimer's disease (AD) and other forms of age-related neurodegenerative diseases is an urgent public health priority. Today, longevity-related prevalence of neurodegenerative diseases (ND) and especially dementia and the current absence of a cure are among the top prominent societal health-related challenges recently acknowledged by the first G8 Summit on dementia held in London on December 11th, 2013.

Ageing may affect cognitive performances in terms of reduced speed of processing, which in turn may compromise overall memory and, more specifically, working memory. Age-related cognitive decline usually spreads to involve also attention, language, and components of executive functioning (Glisky, 2007; Salthouse et al., 1991). Following just published diagnostic criteria for AD in Lancet Neurology, mild cognitive impairment (MCI) is the preclinical or prodromal stage of AD (Dubois et al., 2014). In MCI, several of the clinical and neuropsychologic pathologic features are present prior to the onset of overt AD, for which no cure exists to date.

Although the incidence of AD is related to longevity, its genesis is based on a number of genetic and environmental risk factors. Nevertheless, recent research suggests that a genetic predisposition combined with longevity is not the only cause for an increasing incidence of AD. The lack of success of the attempts in curing AD is due to the fact that any therapeutic approach with synthetic or semi-synthetic compounds including vitamins, nutraceuticals, acetylcholinesterase inhibitors, NMDA receptor antagonists, neurotropins or anti-amyloid/anti-tau/anti-mitochondrial dysfunction drugs, when applied during the course of the clinically overt disease will not be curative. Not only, in fact,

sporadic AD is a complex age-related syndrome with multiple mechanisms, but its neuropathologic onset occurs decades prior to symptom manifestation. Therefore, any intervention with multidimensional effect established with primary prevention scope as early as possible during the course of life is likely to exert the most beneficial effects against AD (Richard et al., 2012; Solomon et al., 2014). AD risk studies of the past decades have identified protective marks against dementia, including high level of education and a healthy lifestyle. In addition, a role of vascular risk factors and comorbidities has been associated with AD development and clinical research pathways are strongly oriented towards AD prevention by means of vascular risk control (Polidori & Pientka, 2012; Polidori et al., 2012). Especially regular physical activity during midlife seems to play a major role in delaying the onset of AD.

Within a sedentary society a lack of physical exercise is well known to provoke cardiovascular metabolic and metastatic diseases (Allison et al., 1999; Powell & Blair, 1994). Regular physical exercise and an active lifestyle have been successfully proven to counteract this deconditioning (Paffenbarger et al., 1986). Besides this, there is converging evidence from animal and human studies that regular physical exercise acts also as a promoter of "brain health" mediating neural homeostasis and, via neuroprotective and neurorestorative mechanisms, counteracts brain ageing. At the behavioural level, physical exercise has been found to upregulate affective states (Boecker et al., 2008; Vogt et al., 2012) and to improve cognition throughout different age phases (Chaddock et al., 2012; Gomez-Pinilla & Hillman, 2013; Stein et al., 2007; Vaynman & Gomez-Pinilla, 2006) and different dimensions, including spatial / associative learning (Erickson et al., 2011; Holzschneider et al., 2012), attentional processing (Budde et al., 2012), and executive control (Voss et al., 2011). While animal research has allowed unravelling underlying neurobiological mechanisms of exercise at the behavioural (e.g. water maze-type tests), cellular (e.g. neurogenesis, synaptogenesis, neuroangiogenesis), and humoral (e.g. neurotrophic factors, inflammatory cytokines) levels (Gómez-Pinilla & Feng, 2012; Wang & van Praag, 2012), so far the neurobiological and epigenetic effects of

exercise remains poorly understood in humans. MCI patients as envisioned in the present project might represent a patient cohort consistently able to participate in an exercise program.

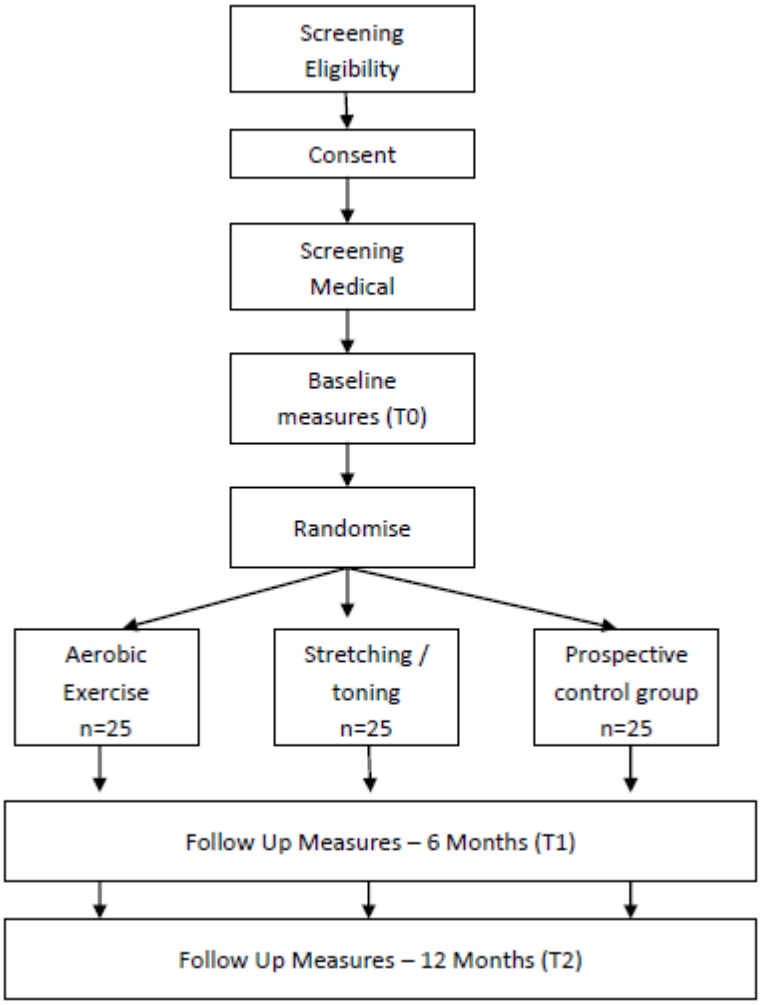
There is a broad amount of literature targeting a relationship between vascular diseases and AD (Polidori et al., 2012). In 2006 Aguero-Torres et al (Aguero-Torres et al., 2006), reported that 49% of a 75+ cohort of clinically diagnosed AD patients showed a vascular component. Although cause-effect relationship might be discussed, further studies showed that vascular diseases increase the relative risk (RR) of AD by 1.5 to 4.3 (hypertension (Patterson et al., 2008; Tzourio et al., 1999)), up to 4.4 (diabetes (Ott et al., 1996)) and up to 3.1 (hypercholesterolemia (Notkola et al., 1998)). In contrast, higher cardiovascular fitness seems associated with less brain atrophy in AD patients (Vidoni et al., 2012).

From exercise science studies dating back to the 1960ies it is known that regular physical exercise prevents vascular diseases as hypertension, insulin resistance and hypercholesterolemia (Paffenbarger et al., 1986). Exercise and regular physical activity is also amongst the top treatment prescriptions medications when it comes to the treatment of cerebrovascular and cardiovascular diseases.

Whereas it has been shown previously that leisure-time physical activity at midlife is associated with a decreased risk of dementia and AD later in life (Adlard et al., 2005; Rovio et al., 2005; Scarmeas et al., 2009; Wang et al., 2006), and although preliminary results indicate that exercise inhibits the progression of AD-like neuropathology in an animal model (Adlard et al., 2005; Ke et al., 2011) and a link between progression of dementia severity and cardiorespiratory health is suggested (Vidoni et al., 2012), currently there is no information about the effects of regular physical activity on the progression of both functional and structural markers at the pre-dementia and early dementia stages in humans.

Study Design

There is evidence of a link between lifetime participation in physical activity and decreased risk of dementia and Alzheimer's disease in later life. This intervention will test the hypothesis that a 12-month structured aerobic exercise programme versus a stretching/toning protocol will prevent progression of cognitive decline in patients with mild cognitive impairment (MCI). This trial will take the form of a randomized controlled trial to be completed across three centres in Europe: the German Sports University Cologne Germany, University of Nijmegen, The Netherlands and Trinity College Dublin. A total of 225 participants will be randomised (n=75 at each site) to either a yearlong supervised and home-based aerobic exercise programme, an equivalent non-aerobic stretching/toning protocol or to the control group . The control group will be measured longitudinal to assess the natural course of the disease. The primary outcome will be change in cognitive performance as measured by a neuropsychological battery (CogState). Secondary outcomes will include changes in gene activity, measures of blood pressure and measures of frailty. Change in all outcomes will be measured at baseline (T0), six months (T1) and 12 months (T2).



Objectives

Primary Objective

To determine if an extensive aerobic exercise program delays progression of cognitive decline in patients diagnosed with MCI

Secondary Objectives

To evaluate the effect of an aerobic exercise programme on aerobic fitness in patients in MCI

To determine the effective of an aerobic exercise programme on quality of life (QOL)

To evaluate the effect of an extensive aerobic exercise programme on cognitive and psychomotor performance (assessed by a battery neuropsychological tests)

To evaluate the effect of an extensive aerobic exercise programme on epigenetics

To evaluate the effect of an extensive aerobic exercise programme on measures of frailty

To evaluate the effect of an extensive aerobic exercise programme on blood pressure variability

Participants

Inclusion criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Diagnosis of MCI due to Alzheimer's disease (AD) following Albert et al (Albert et al., 2011). All enrolled MCI participants will be classified as having memory decline but not dementia (CDR global score = 0.5), consistent with MCI classification (Albert et al., 2011; Petersen, 2004)

Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) score between >18<26

Stable medical condition for more than 6 months

Stable medications for more than 3 months

Caregiver/informant available to accompany patient for scheduled assessment and early intervention visits

Adequate visual and auditory acuity to allow neuropsychological testing

Screening laboratory tests and ECG without significant abnormalities as per the European Society of Cardiology (Corrado et al., 2010) that might interfere with the study

Physical ability sufficient to allow performance of endurance exercise training

Provide signed and dated informed consent form.

Willing to comply with all study procedures and be available for the duration of the study.

Age ≥50 years

Medical clearance to undergo a symptom-limited cardiopulmonary exercise test and vigorous aerobic exercise training.

Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

Diagnosis of AD or other type of dementia

Participants involved in any drug study

Use of cholinesterase inhibitors or Memantine

History in past 2 years of epileptic seizures or any major psychiatric disorder (Particpants with no epileptic seizures and stable off medication for 2 years may be included)

Past history or MRI evidence of brain damage, including significant trauma, stroke, , hydrocephalus, mental retardation, or serious neurological disorder

Carotid stent or severe stenosis

Significant history of alcoholism or drug abuse within the last 10 years

History of myocardial infarction within previous year

Unstable cardiac, renal, lung, liver, or other severe chronic disease

Uncontrolled hypertension (systolic blood pressure >200 mm Hg and/or diastolic blood pressure >110 mm Hg at rest) (Thompson, 2010)

Type 2 diabetes mellitus with hypoglycemia in the last 3 months

Significant obesity limiting active participation in the exercise programme. History of familial early-onset dementia. Pacemaker or other medical metal device that precludes performing MRI (for subjects where MRI required)

Engagement in moderate-intensity aerobic exercise training for more than 30 minutes, 3 times per week, during past 2 years

History of vitamin B12 deficiency or hypothyroidism (stable treatment for at least 3 months is allowed)

Congestive heart failure (New York Heart Association Class II, III or IV)

Serious or non-healing wound, ulcer, or bone fracture.

Study Schedule

Timepoints 1 cycle = 28 days		Pre-Screening Telephone Call	Screening	Study Visit 1	**First Intervention Visit**	**Physical Activity Check 1**	Study Visit 2	Study Visit 2	**Physical Activity Check 2**	Study Visit 3	Study Visit 3
		≥24 h after receiving PIL	<14 days before Cycle 0, Day 1[a]	<13 days following screening	Cycle 0, Day 1	Cycle 3, Day 1 ± 14 days	Cycle 6, Day 1 ± 14 days	<14 days following T1 Day 1	Cycle 9, Day 1 ± 14 days	Cycle 12, Day 1 ± 14 days	<14 days following T2 Day 2
Initial Study	Explain study	X									
	Screen eligibility criteria	X	X								
	Sign consent form		X								

Procedures	Montreal Cognitive Assessment (MoCA)		X								
			X								
	Blood pressure measurements (Finapress)		X								
	Blood sampling		X								
	Cogstate		X								
	Resting vital signs, ECG and submaximal exercise testb		X								
Neuropsychological Study											
							X			X	
	Montreal Cognitive Assessment (MoCA)						X			X	
	Trail Making Test			X			X			X	

Outcomes	Health Related Quality of Life for People with Dementia (DemQOL)			X			X			X	
	Disability Assessment for Dementia (DAD)			X			X			X	
	Center for Epidemiologic Studies Depression (CES-D)			X			X			X	
Secondary Outcomes	Submaximal Exercise Test							X			X
	Physical Activity Tracker			X			X			X	
	Physical activity Questionnaire			X		X	X		X	X	
	Pittsburgh Sleep Quality Index			X			X			X	
	General Self-efficacy Scale			X			X			X	
	Blood samples			X						X	
	NEO-Five Factor Inventory (NEO-FFI)			X						X	
	Timed Up and Go			X			X			X	

	Hand Grip Strength			X			X			X	
	30 second chair stand			X			X			X	
	Randomise			x							
	Blood pressure measurements (Finapress)						X			X	
Safety	Medical Examination		X				X			X	
	Adverse events		X	Continuous from informed consent until 28 days after Cycle 12							
Study Visits per arm	Aerobic Group		X	X	X	X	X	X	X	X	X
	Stretching/toning Group (		X	X	X	X	X	X	X	X	X
	Control Group		(X)	X[c]			X	X		X	X

Footnotes

The results submaximal exercise test completed as part of medical screening will be used at T0 aerobic fitness data for patients who are eligible to participant and are randomised to the study.

Patients who are randomised to the control group will complete assessment at T0,T1 and T2 timepoints.

Exercise Intervention

The exercise intervention will include 48 weeks of either aerobic exercise or stretching/toning to be completed three times per week. The intervention schedule of visits is outlined in Table 1.

		Aerobic		**Stretching/Toning**	
		Supervised	**Non-Supervised**	**Supervised**	**Non-Supervised**
Assessments: T0					
Cycle 0	Week 1-4	2	1	2	1
Cycle 1	Week 5-8	2	1	2	1
Cycle 2	Week 9-12	1	2	1	2
Cycle 3	Week 13-16	1	2	1	2
Cycle 4	Week 17-20	1	2	1	2
Cycle 5	Week 21-24	1	2	1	2
Assessments: T1					
Cycle 6	Week 25-28	1	2	1	2
Cycle 7	Week 29-32	1	2	1	2
Cycle 8	Week 33-36	1	2	1	2
Cycle 9	Week 37-40	1	2	1	2

Cycle 10	Week 41-44	1	2	1	2
Cycle 11	Week 45-48	1	2	1	2
Assessments: T2					

Table 1 Programme Schedule of Visits: Number of weekly supervised and non-supervised classes for both intervention groups

The goal of the aerobic exercise class will be to accumulate 45 minutes of moderate-to-vigorous intensity aerobic exercise, prescribed by heart rate calculated as 180bpm – age, three times per week. For patients on beta blocker medications, target heart rate will be calculated based on their HR as measured on the incremental exercise test when a lactate measurement of 2-2.5mmol/l lactate is reached. The BORG (RPE) scale will also be used in both intervention groups to monitor exercise intensity. The aerobic group will aim for a BORG score of 13. The stretching and toning group will aim for a BORG score of 10 or less. The programme will consist of both supervised and non-supervised sessions. During the first cycle classes will be supervised twice per week and participants will be asked to exercise at home on one other day. A family member will be encouraged to attend the supervised class with the participant during the first four weeks to become familiar with the exercise intervention and to be able to help with implementing the programme at home. From the second cycle onwards classes will be supervised once per week and participants will be required to exercise at home on two other occasions. If a participant is struggling with exercising at home additional supervised classes will be offered at the discretion of the physiotherapist supervising the programme.

The stretching/toning group will complete the same visit schedule (twice per week during cycle 0 and once per week thereafter) and home exercise regime as the aerobic group. The goal of the

stretching/toning group will be to complete non-aerobically stimulating activities such as yoga and Pilates. A list of activities suitable for the stretching/toning group to complete is provided in Table 2. As per the aerobic group a family member will be encouraged to attend the supervised class with the participant during the first four weeks to become familiar with the exercises prescribed and to be able to help with implementing the programme at home. If a participant is struggling with exercising at home additional supervised classes will be offered at the discretion of the physiotherapist supervising the programme. Participants in the stretching/toning group will not be advised about aerobic activity and will not be instructed to avoid completing routine aerobic activity.

List of Suitable Activities for the Stretching/Toning Group
Yoga
Pilates
Tai Chi
Meditation
Flexibility training
Qi-gong
Games like jeu de boules
Strength training
Small games
Balance and coordination training

Table 2 Suitable Activities for the Stretching/Toning Group

Details of Study Assessment to be Completed

Vital Signs

Heart rate, blood pressure and oxygen saturation will be performed and recorded on the case report form (CRF) after resting for 5 minutes at the screening visit and every scheduled assessment and intervention visit. Vital signs will be measured using standard automated devices.

Weight

Body weight will be measured using a digital scale (recently calibrated). Participants will be measured barefoot wearing one layer of light clothing. Weight will be recorded in kilograms (kg), rounded to 1 decimal place.

Height

Height will be measured at screening using a standard stadiometer height measurement. Participants will stand in front of the stadiometer, in bare feet, heels against the wall, arms relaxed by their sides and head in the Frankfort plane (eyes in line with the upper part of the ears). The assessor will slide the rod downwards until it rests on the participant's head to read height. Height will be recorded in centimeters (rounded to 1 decimal place) on the case report form.

Medical Examination

All participants will undergo a medical examination prior to completing submaximal exercise testing to include medical history, current medications, vital signs and resting electrocardiogram (ECG). A standard 12-lead ECG (with a 10-second rhythm strip) will be collected prior to, during, and for 5-minutes after all exercise tests. The pre-exercise ECGs will be collected after the patient has rested

quietly and is awake in a fully supine (or semi-recumbent, if supine is not tolerated) position for 10 minutes. Subsequent pre-exercise ECG readings should be collected with the patient in the same position (e.g., fully supine or semi-recumbent).

CogState Test Battery

International Shopping list Task

Detection Task

Identification Task

One Card learning

One back Verbal fluency (letters and animals) test

Delayed recall shopping list task

Standardised training for all sites.

Trail Making Test (TMT)

The Trail Making Test (TMT) is a pen and paper based task which assesses visual attention and task switching. Patients will complete both parts A and B which require them to join the dots involving a series of numbers and letters. The time taken to complete the task will be recorded. The test will be completed according to the SOP in Appendix **Error! Reference source not found.**.

Health Related Quality of Life for People with Dementia (DemQOL)

The DemQOL is a interview administered questionnaire designed to measure QOL in patients with dementia. The questionnaire is contains 29 questions relating to different aspect of QOL. The questionnaire will be completed at T0, T1 and T2. See Appendix **Error! Reference source not found.** for a copy of the questionnaire.

Activities of Daily Living Assessment

The Disability Assessment for dementia (DAD) scale will be used to measure functional abilities in activities of daily living. The questionnaire is completed by interview with a caregiver. The questionnaire will be completed at T0, T1 and T2. See Appendix **Error! Reference source not found.** for a copy of the questionnaire.

Center for Epidemiologic Studies Depression CES-D

The Center for Epidemiologic Studies Depression (CES-D) Scale is a short self-report questionnaire that measures symptomatic depression. Change in the presence of depressive symptoms will be captured using the CES-D at T0, T1 and T2. See Appendix **Error! Reference source not found.** for a copy of the questionnaire. The general self efficacy scale will be admisistered at T0,T1 and T2The General Self-Efficacy Scale is a 10-item psychometric scale that is designed to assess optimistic self-beliefs to cope with a variety of difficult demands in life.

Blood Pressure Variability

The Heart Rate and BP response to Active Stand will be recorded using a Finometer and NIRs. Participants will be asked to stand up as quickly as possible and remain standing for 5 minutes.

Submaximal Exercise Test

Cardiopulmonary fitness will be assessed during a submaximal exercise test to be completed at screening, T1 and T2. The test will be completed on a standard cycle ergometer and will progress according to the WHO protocol. Gas exchange during the test will be measured by indirect calorimetry. Blood pressure, heart rate, oxygen saturation and ECG will be measured throughout the test. Participants will be familarised with the protocol and the BORG Rate of Perceived Exertion (Appendix **Error! Reference source not found.**) before the test starts. The test will commence with 3 minutes rest, followed by the incremental phase of exercise during which the load will increase by 25 W every 2 minutes until the test is terminated. Heart rate and blood pressure will be recorded after 1.30 minutes of each stage. Blood samples will be collected from finger prick / ear lobe to measure lactate levels and patients will be asked to rate themselves on the BORG Rate of Perceived Exertion scale. The test will terminate when three out of 4 of the following criteria are to be met:

Clinical signs of exhaustion,

Respiratory quotient >= 1.10,

Test finishing within 10 beats of the predicted heart rate (=220-age)

Flattening of the VO2 uptake curve (<= 110 ml increase during the last minute)

Participants should cool down by cycling unloaded for 3 minutes

When the test is complete blood pressure, heart rate, blood lactate levels and BORG Rate of Perceived Exertion will be measured at 1 minute, 3 minutes and 10 minutes post test completion.

Physical Activity Assessment

Physical activity will be assessed at T0, T1 and T2 using the LASA Physical Activity Questionnaire (LAPAQ) physical activity questionnaire (Appendix **Error! Reference source not found.**) and the ActiGraph physical activity accelerometer. The LAPAQ questionnaire is a self-administered physical activity recall questionnaire capturing physical activity completed during the preceding 7 days. The LAPAQ questionnaire will be administered at T0 and at 3-month intervals for

the duration of the study. The physical activity monitor will be set up at the end of the assessment for each participant using required details including weight, height and date of birth. Participants will be required to wear the monitors for one week during both waking hours and while sleeping. The activity monitors will be provided to all participants within the study to wear for one week at T0,T1 and T2 as outlined above. Participants will return the activity monitor to the research group at their next scheduled intervention class. The control group will wear for a week, complete the LAPAQ questionnaire and return to the research group in a stamp addressed envelope that will be provided by the research team. The Pittsburgh Sleep Quality Index (Appendix **Error! Reference source not found.**) will be administered at T0, T1 and T2 to subjectively assess quality and patterns of sleep. The General Self-Efficacy Scale (Appendix H) will be assessed at T0,T1 and T2 to assess patients self efficacy in relation to compliance with Physical Activity.

Blood Sampling

Venous blood samples will be collected at T0 and T2

Two 4ml EDTA tube to be collected at each timepoint

Samples should be placed directly into the fridge and transferred to -80° as soon as possible

Tube labelling instructions:

IRE_4_1a and IRE_4_1b are the two samples from participant number 4 collected at T0 (before intervention) in Ireland.

IRE_4_2a and IRE_4_2b are the two samples from participant number 4 collected at T2 (after intervention) in Ireland.

NEO-Five Factor Inventory

NEO-Five Factor Inventory (NEO-FFI) is a psychological personality inventory consisting of 60 items to measure five personality traits. The questionnaire will be completed following each blood draw to form part of the epigenetics analysis. See Appendix I for a copy of the questionnaire.

Timed Up and Go

The Timed Up and Go (TUG) test will be performed at T0, T1 and T2 to assess the participant's mobility and balance. Before the test starts a chair (height 46cm) with arm rests should be in position with a 3m course clearly marked in a straight line in front of the chair. To start the test the participant will sit in the chair. On the assessor's command the participant will stand up unassisted, and without using armrests, walk a 3m distance, turn and take a seat again. Using a stopwatch the assessor should time the activity from the command to start the test until the participant sits (moment the buttock touches the seat). Mobility aids such as walking sticks or frames are permitted. The use of a mobility aid during each assessment should be recorded. Participants may use a mobility aid or different aid for repeat assessment even if different to preceding assessments. All participants should complete a practice test before completing the final test.

The following instructions should be delivered to the participant:

"When I say "Go" I want you to:

Stand up from the chair

Walk to the line on the floor at your normal pace

Turn

Walk back to the chair at your normal pace

Sit down again

The absolute time taken to complete the TUG in seconds will be recorded. The results of the TUG will be interpreted from the time taken to complete the test as per Table X below:

Time Taken to Complete the Test	**Interpretation**
<10 seconds	Independent daily life mobility
11-19 seconds	Minor mobility restrictions normally without relevance for daily living
20-29 seconds	Functionally relevant restriction of mobility, need for further assessments
>30 seconds	Distinct mobility restrictions

Hand Grip Strength

Hand grip strength will be measured at T0, T1 and T2 using a Jamer Digital Dynamometer as a measure of upper limb strength.

The participant will sit upright in a chair with:

Hips and knees at 90°

Shoulder adducted and neutrally rotated

Elbow flexed at 90°

Forearm in neutral position

Wrist in slight extension (0°-30°)

Adjust the grip size to a position that is comfortable for the participant. The individual squeezes the dynamometer as hard as possible using one brief maximal contraction and no extraneous body movement. Administer three trials for each hand, allowing a 1 minute rest between trials. Use the **best score** as the client's static strength

30 Second Chair Stand

The 30 second chair stand will be completed at T0, T1 and T2 to measure leg strength and endurance. The test is completed using a chair with a straight back (height 43-45cm) **without arm rests**. The chair should be positioned against the wall during the test to stop it moving. The number of times the participant can achieve a full standing position in 30 seconds is recorded. The participant should complete two practice stands before the assessor starts the timed test. The following instructions are given to the participant:

Sit in the middle of the chair

Place your hands on the opposite shoulder crossed at the wrists

Keep you feel flat on the floor

Keep your back straight and keep your arms against your chest

On the instruction "Go" rise to a full standing position and then sit back down again

Repeat this for 30 seconds

The assessor should start timing the activity on the command "Go". Stop the test and record as 0 if the participant requires the use of their arms to help them to stand. If the participant is over halfway to the standing position when 30 seconds have elapsed, count it as a stand.

Missed Sessions, Adverse Events and Protocol Violations

Missed sessions

Missed sessions should be rescheduled within the same week if possible to ensure a total of three 45 minute exercise sessions (either supervised or non-supervised) in any one week. Attendance will be defined as the number of exercise sessions completed divided by the total number of planned sessions. The number of exercise sessions completed weekly will be captured by the exercise physiologist/physiotherapist leading the supervised exercise class by asking the following questions:

Did you exercise during the past week?

How many exercise sessions did you complete?

How long was the exercise session(s)?

What kind of exercise did you complete?

What intensity was the exercise that you completed?

The number of missed sessions per participant and the reasons for missing sessions will be recorded and reported. If a participant misses an exercise sessions they will be contacted by the research team to determine the reason and to reschedule the class. If a participant misses more than 75% of total exercise sessions (supervised and non-supervised) during either T0 and T1 or T1 and T2 in the absence of a defined reason (acute illness or scheduled holiday), it will be recorded as a protocol violation.

Adverse Events and Reporting Requirements

Adverse events will be assessed at every clinic visit and the following details recorded: type, incidence, severity, timing, seriousness, and relatedness to a) disease and b) the intervention.

Clinical Adverse Events (AE)

A clinical adverse event is any unfavorable or unintended sign, symptom, or disease temporally associated with the study intervention and occurring in a patient assigned to the intervention. In this intervention all potential participants will be screened via their medical charts as well as through in-person assessments to assess cardiovascular contraindications to exercise.

However, rare but serious AEs are possible. Those that may occur during either cardiopulmonary exercise testing (CPET) or exercise training include myocardial infarction (heart attack), stroke, unconsciousness or other serious injury.

Events during a CPET are rare (<1/100,000 in well individuals and 1/10,000 in sick individuals). A trained health professional (e.g. medical staff and exercise physiologist) will monitor the exercise test in a location staffed by physicians, in the rare event that such an event occurs.

Similar to a CPET, exercise training may cause temporary risks of an adverse cardiovascular event, such as a heart attack. The CPET with ECG-monitoring that must be completed prior to randomization will ensure that all randomized participants are healthy enough to engage in exercise training.

Absolute and relative indications for stopping exercise (both testing and training) are provided in Table 3. In the event of a participant presenting with any of the below symptoms exercise should be stopped.

Indicators for Stopping Exercise
Absolute indications for Stopping Exercise: Suspicion of a myocardial infarction or acute myocardial infarction (heart attack)

Onset of moderate-to-severe angina (chest pain) Drop in systolic blood pressure (SBP) below standing resting pressure or drop in SBP with increasing workload accompanied by signs or symptoms Hypotensive response resulting in SBP <60mmHg Signs of poor perfusion (circulation or blood flow) including pallor (pale appearance to the skin), cyanosis (bluish discoloration) or cold and clammy skin Severe or unusual shortness of breath CNS (central nervous system symptoms Ataxia (failure of muscular coordination) Vertigo (an illusion of dizzying movement) Visual or gait (pattern of walking or running) problems Confusion Patient's request to stop Irregular pulse Extreme fatigue
Relative Indications: Increasing chest pain Physical or verbal manifestations of shortness of breath or severe fatigue Wheezing Leg cramps or intermittent claudication (grade 3 on a 4-point scale) Hypertensive response

Table 3 Indications for Stopping Exercise

Other examples of AEs include but are not limited to:

Abnormal test findings

Clinically significant signs and symptoms

Changes in physical examination findings

Worsening of signs and symptoms of the disease under study.

Signs or symptoms resulting from exercise overload

Drug interactions

Serious Adverse Events (SAE)

A serious adverse event (SAE) is any adverse event occurring at any level of intervention that has serious consequences such as death, is life-threatening or requires hospitalization.

In the case of an emergency during an exercise assessment or class the hospital emergency response crash team will be contacted. All internal reporting procedures will be adhered to in accordance with the Clinical Research Facility and St James's Hospital policies.

Non-Serious Adverse Events

This includes all other adverse events. In the event of a participant becoming unwell during an exercise assessment or class they will be evaluated by a doctor and treated appropriately.

Return to Exercise Following an Adverse Event

Return to exercise following reporting of an adverse event which requires updated medical clearance will be discussed on a case by case basis with the study coordinator. Where physician clearance to return to exercise is deemed necessary, the participant will only be allowed to return to exercise

training when medical clearance is provided in writing. The exercise physiologist/therapist supervising the exercise program will modify the program accordingly at re-introduction. If no physician clearance is deemed necessary the participant can return to training upon clearance from the exercise physiologist/therapist.

Protocol violation

A protocol violation occurs when a patient or Investigator fails to adhere to specific protocol requirements affecting the inclusion, exclusion, patient safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to:

Failure to meet the inclusion/exclusion criteria

Failure to complete the exercise intervention as stated within the protocol (≤75% adherence to the prescribed protocol between either T0 and T1 or T1 and T2).

Any other deviation that presents significant risk or safety concerns to the patient

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The local Principle Investigator, will determine if a protocol violation should result in withdrawal of a patient.

Withdrawal of participants

Participants are free to withdraw from the trial at any stage without providing a reason and without consequence. This information will be stated in the participant information leaflet. Participants can inform the research team at their local site of their decision to withdraw. If a participant withdraws from the study, any data collected on them up to that point in the study will go forward for study analysis. This information will be stated in the participant information leaflet. If a participant

withdraws from the intervention, but provides consent to complete subsequent follow-up measurements they will continue to attend study assessments and data will be used for intention-to-treat analysis. If a patient experiences the event or chooses to withdraw prior to T1 or T2, the research team will request to complete an exit study assessment. Reasons for stopping the intervention will be recorded and reported.

Appendix F: Application for ethical approval

Discipline of Physiotherapy,

Trinity Centre for Health Sciences,

St James's Hospital

Dublin 8

26/04/17

AMNCH/SJH Research Ethics Committee,

AMNCH Hospital,

Tallaght,

Dublin 24

REC Reference: 2015/09/04

Dear Dr Lavin and members of the Research and Ethics Committee,

The above study protocol was reviewed by the Chairman on behalf of the Research Ethics Committee in September 2015 and approval was granted and subsequent amendments have been approved. We now write to the committee to seek approval for further changes to the protocol prior to recruitment to the study closing on 31/6/17.

Participants will have a 5ml serum collected at T2 (12 month) timepoint. Ethical approval has already been obtained to collect 2 x 4 ml EDTA but we wish to add an additional serum at the same time the EDTA collection is taking place. An additional measure of the Cantab Paired Associate Learning Task will also occur at T2 as longitudinal follow up of episodic memory.

As part of a PHD study exploring the factors associated with adherence to an exercise intervention in individuals with MCI and the feasibility of an exercise intervention aimed at individuals with MCI, it is proposed that 10 participant interviews will be conducted at two time points (on entry into the study and again on exit from the study) with 10 NeuroExercise study participants. These participants will be sampled using convenience sampling, meaning that they will be recruited consecutively based on the timing of their entry into the study until 10 participants have been recruited. Participants will be provided with an updated version of the NeuroExercise PIL (see Appendix A) detailing what will be involved.

The research team proposes 5 further interviews with people who previously registered interest in taking part in the NeuroExercise study but ultimately declined participation. The purpose of these interviews will be to explore factors related to participation and non- participation in this type of exercise intervention designed for people with cognitive impairment and to answer the research question of why people with cognitive impairment may or may not be inclined to part take in this type of programme. This will help to inform a feasibility study of the intervention itself. Participants will be identified from the study database of potential participants based on i) their initial interest in participation and ii) their decision not to participate. Potential participants will be contacted by phone

via a gatekeeper (to be identified) and asked if they would be interested in receiving a Participant Information Letter and consent form (see Appendices B & C) detailing what would be involved if they were to consent to participate in these interviews conducted at one time point. If they wish to participate in these interviews they will then be required to contact the research team who will then arrange an interview time, date and location to be agreed with the participant. The interviews may take place in the Clinical Research Facility in St. James` Hospital or at a location of the interviewees choosing.

It is also proposed that to get a greater understanding of factors related to exercise behaviour in individuals with MCI that quantitative analysis will be carried out on NeuroExercise study data with a focus on the outcome measures of exercise participation and exercise adherence. This study proposes to analyse NeuroExercise data to test for relationships between those outcome variables and the independent variables of age, gender, frailty, self- efficacy, health related quality of life, baseline fitness, depression and cognitive function.

As part of this amendment to the study it is also proposed that 3 key experts and 10 health care professionals will be interviewed to gather qualitative data concerning attitudes and opinions regarding the referral of exercise to MCI patients. The researcher proposes to conduct 3 expert interviews with the purpose of identifying health care professionals most relevant to this topic, and to inform HCP interview structure. Key expert interviewees will be identified using purposive sampling i.e. researchers or practitioners that have published work in the areas of exercise and dementia and referral of exercise by HCP``s. The purpose of this set of interviews is to further expand on the factors related to the feasibility of an exercise intervention aimed at people with MCI. Both Key experts and health care professionals will be contacted by the researcher via a gatekeeper who will send an invitation email to ask if they would wish to receive a Participant Information Leaflet and consent form (Appendices D & E). Once they have received a PIL they will be asked to contact the research team to indicate that they agree to participate in this study. A member of the research team will then contact them directly to arrange a time and date to be interviewed. Interview locations will be set according to the interviewee’s preference.

Please find all supplementary materials attached below. Should you have any queries re the above please do not hesitate to contact me.

Kind Regards,

_____

Prof Brian Lawlor

Principle Investigator

Email: blawlor@tcd.ie

Cc: Leona Connolly, Researcher connoll7@tcd.ie

Appendix A

Amended NeuroExercise PIL (version 2.1):

Patient Information Leaflet

Study Title:

(1) The effects of an extensive exercise program on the progression of Mild Cognitive Impairment (MCI)

(2) The effects of acute exercise on cognitive function in individuals with Mild Cognitive Impairment (MCI)

Sponsor: Health Research Board

Principal Investigators:	Professor Brian Lawlor
	Dr Emer Guinan
Research Physiotherapist:	Kate Devenney
Study Doctor:	Professor Brian Lawlor
Site Address:	St James's Hospital, Dublin

This is a clinical study, a type of research study. The Research Team will explain the clinical study to you. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

Why is this study being done?

Mild cognitive impairment is characterised by deficits in memory and thinking skills that does not significantly impact day-to-day function. To help ensure an aging society live enjoyable and productive life, research into treating conditions such as Alzheimer's disease, and other forms of age-related diseases, is an urgent public health priority. The purpose of this study is to investigate the effect of a 12 month exercise programme in patients who have mild cognitive impairment. The exercise programme is testing the theory that exercise may prevent the progression of cognitive decline (decline in the mental processes of perception, memory, judgement and reasoning) in patients with mild cognitive impairment.

Why am I being asked to take part?

People who have attended the memory clinic at St. James's Hospital with a diagnosis of Mild Cognitive Impairment are being asked to participate.

Do I have to take part?

No, it is up to you to decide whether or not you take part.

If you decide to take part, you will be asked to sign the consent form. You will be given a copy of this information sheet and a signed consent form for you to keep.

You will still be free to leave the study at any time, with or without giving a reason. If you decide to leave the study, this will not affect your future treatment and care.

How many people will take part in the study?

Approximately 75 people will take part in this study, in St James's Hospital, Dublin. An additional 150 people will take part in the study which is also being conducted in two other European centres.

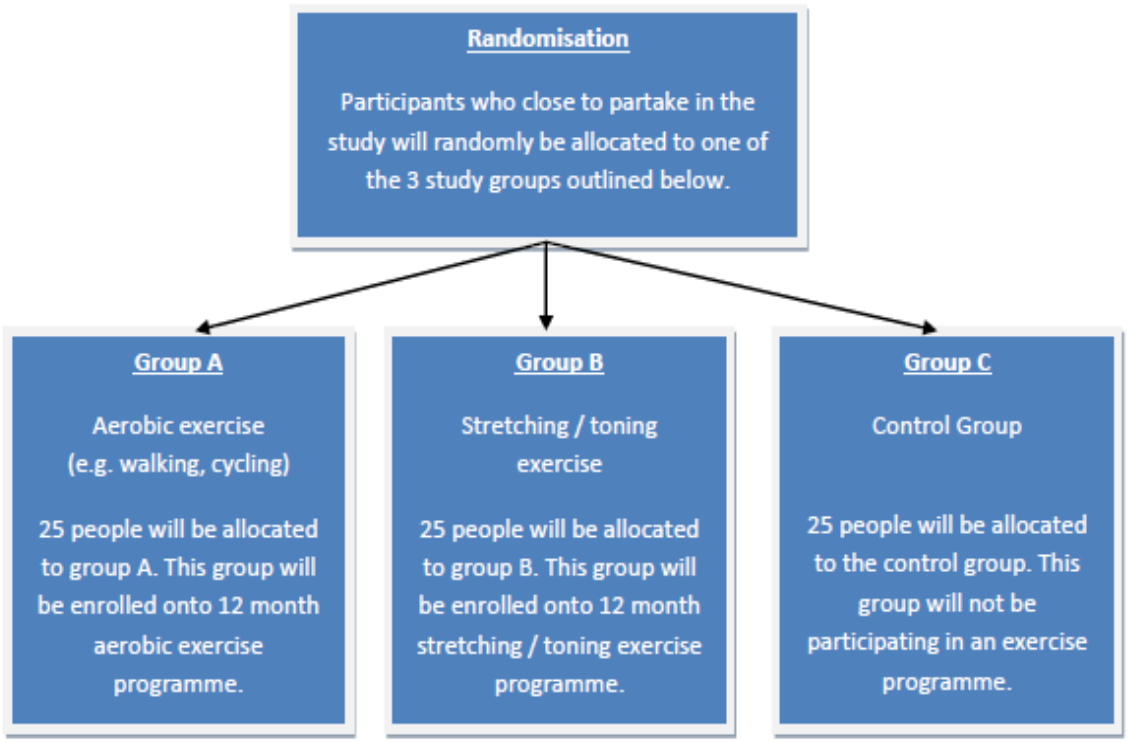
The study will last approximately two years and your participation will last for 12 months.

What will happen to me if I take part?

You will be invited to participate in this programme when your doctor has indicated to the research team that you are medically well and able for the interventions involved and you clear the screening criteria.

There will be 3 different groups involved in the study. If you choose to take part in the study, you will be "randomised" into one of the study groups. Randomisation means that you are put into a group by chance. A computer program will place you in one of the 3 study groups. Neither you nor your doctor can choose the group you will be in. One group will act as the "control group" and will not participate in the exercise programme. If you are selected to be in the "control" group, you will be required to attend for assessments at the Clinical Research Facility at St. James's Hospital as detailed below.

The exercise groups will both undertake a 12 month supervised and home based exercise programme. One group will complete a stretching and toning programme. The other group will complete an aerobic exercise programme (examples of aerobic exercise include cycling and walking). These interventions will be provided in addition to your usual medical care provided at St. James's Hospital.



The aim of this study is to deliver a 12 month exercise programme (3 exercise sessions per week. This equals 56 supervised and 88 unsupervised/home based exercise sessions in total) for patients with mild cognitive impairment. The supervised exercise sessions will take place at the Clinical Research Facility in St. James's Hospital. The unsupervised exercise sessions will be completed at home and you will wear a monitor to record your activity. Each exercise session will last approximately 1 hour.

If you decide to participate in the study, you will be assessed by the research team at three time points:

prior to commencing the exercise programme (0 months)

six months into the exercise programme (at 6 months)

upon completion of the exercise programme (at 12 months)

The second study will examine the effects of single bouts of exercise on cognitive function in individuals with Mild Cognitive Impairment (MCI). Prior to exercise testing, participants will be randomised to group A or B. You will have the similar testing done, in differing order. Blood samples and tests of your cognitive function will be obtained around the exercise testing.

Participants who are randomly selected to one of the exercise groups will have blood tests and tests of their cognitive function during week 1, 6 and 12 of their exercise programme. Blood samples and cognitive tests will be performed on each of these time points prior to the supervised exercise class in the CRF in St. James's Hospital. The bloods and cognitive tests will then be repeated after the exercise session.

We also aim to assess the factors that are related to exercise participation and adherence, specifically in people who are experiencing mild cognitive decline. The purpose of this is to assess the feasibility of the exercise programme. This sub- study consists of two phases. Phase one is concerned with gathering information on the factors related to exercise participation in people with mild cognitive impairment, and phase two is concerned with gathering information on the factors related to their adherence to the study intervention. In both phases, information will be collected via face- to- face interviews with the participant and one researcher. Therefore you will be asked to participate in two interview sessions, one on entry into the study to take place during your initial assessment and one on exit from the study at 12 months. Each interview will last approximately one hour.

Details of the initial assessments are detailed below.

Vital signs: Heart rate, blood pressure and oxygen saturation will be recorded at the screening visit and prior to commencing all supervised exercise sessions

Body composition: Weight and height will be recorded at initial assessment

Medical examination: all participants will undergo a medical examination by a doctor prior to completing exercise testing

The following assessments will be completed at 0, 6 and 12 months during the study period.

These assessments will take place over a 2 day period. It will take approximately **3 hours on each day** to complete assessment.

Cognitive performance will be measured by a number of tests that test attention, memory and ability to perform certain tasks

One-to- one participant interview to assess exercise habits and behaviours will take place on entry into the study at 0 months and again on exit from the study at 12 months

You will be required to complete 7 separate **Questionnaires** pertaining to:

quality of life

physical activity

ability to carry out activities of daily living

depression

Sleep quality

personality traits

behavioural traits

We will record your **Blood pressure** when you move from a lying position into sitting and then standing

An **exercise test** will be carried out to assess your physical fitness**.** During the exercise test, you may experience general fatigue and shortness of breath

You will be given a **physical activity monitor** to wear at home for a week at the three assessment time points

A **blood sample** will be obtained for analysis – about 3 teaspoons of blood every time blood is taken.

You will be required to complete 3 **physical assessments** to ascertain your general strength, endurance, mobility and balance

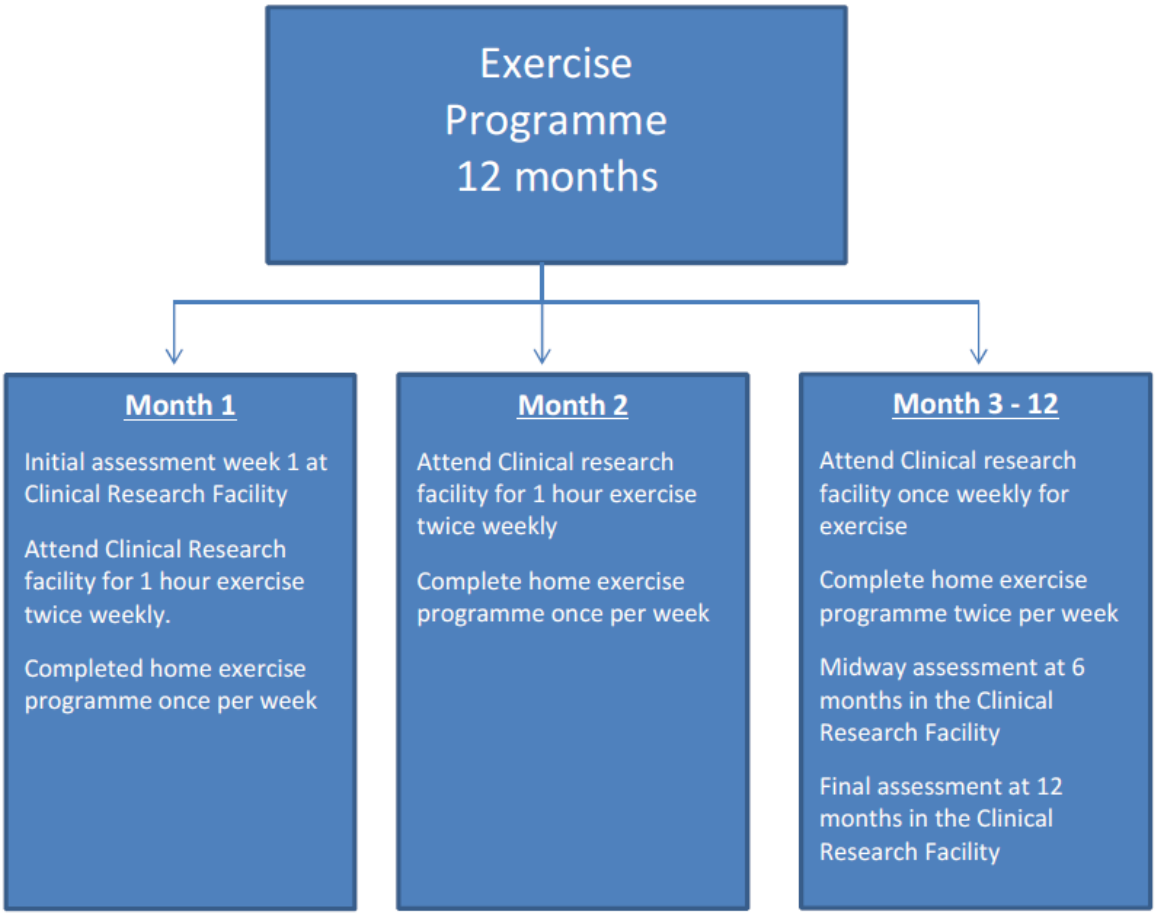
If you exit the study prior to completing the 12 months of exercise, you will be invited to complete an exit assessment with the research team. The exit assessment will be optional; you may choose to decline completing the exit assessment.

What will I have to do?

If you are in the control group, you will attend the Clinical Research Facility at 0, 6 and 12 month time points to undergo assessments. You will not be involved in the exercise programme detailed below. You will receive a newsletter in the post every 3 months to keep you updated on how the trial is progressing. You will be contacted by phone every 2 months by a member of the research team to check how you are doing.

If you are enrolled in the exercise programme, you will need to attend the Clinical Research Facility at St James's Hospital for supervised exercise sessions over a 12 month period. Each exercise session will last approximately 1 hour. You will also have to complete exercise sessions at home. Please see diagram below for further details. Where possible, study appointments will be scheduled for a time that is convenient for you to attend.

You will also be asked to take part in a one- to -one interview with a member of the research team on entry into the study, and again on exit from the study at 12 months. These interviews will assess your opinions and behaviour regarding exercise in general and with regard to the study exercise programme. They will last approximately one hour and will be recorded so that they can later be transcribed and analysed.



What are the benefits of taking part?

There may or may not be direct benefits to people taking part in the study. The study aims to examine the effect of different exercise interventions in people with mild cognitive impairment. The results will help us establish if exercise interventions may be of benefit for people with mild cognitive impairment in the future.

What are the risks of taking part?

We do not anticipate adverse effects during the assessments or participating in the prescribed exercise intervention. The proposed exercise intervention has been designed in line with established protocols, thereby posing minimal risk.

Participation in the exercise intervention will be with the consent of your doctor and will be supervised closely by your physiotherapist. Your risk of adverse events will be minimised through thorough medical screening prior to exercise testing and monitoring during exercise intervention.

While rare, adverse events are possible. Serious adverse events may include: heart attack, stroke, unconsciousness or other serious injury.

You may feel a little tired after the exercise test and during the initial stages of the exercise intervention but we expect that you will recover quickly.

There is a risk of bruising or fainting when taking blood samples. If any results with potentially harmful consequences are discovered your team will be informed immediately.

Will I receive payment for being part of this study?

You will not be paid for taking part of this study. However, you will receive remuneration for car parking costs incurred while attending study assessments and exercise sessions at the Clinical Research Facility.

What happens if I get hurt taking part in this study?

All participants and professionals working on the study are covered by clinical indemnity insurance. This insurance covers any damage resulting from the research. For further details please contact Kate Devenney. Contact details are listed at the end of this document.

Will my information be kept private?

If you decide to take part in the study, you give the researchers permission to collect information about you and share it with the Health Research Board. Any information that identifies you (such as your name and address) will not be shared with the Health Research Board.

Your study data will be identified with a code number which will not include your name or other information that directly identifies you.

As this research project is taking place at 2 other research sites in Europe (Nijmegen, Netherlands and Cologne, Germany), information collected related to the study and some of the blood samples collected will be transferred to these sites to be pooled together centrally for analysis. The additional blood samples will be kept on site in St. James's Hospital.

Personal and medical information, and interview recordings and transcripts identifying you will be kept. We will keep it in a secured file. At any time, you may ask to see your personal information.

Your study information will be used to determine the effect of a long term exercise programme on patients with mild cognitive impairment. The information gained will help inform the planning of future exercise programmes for people with mild cognitive impairment.

Your information will be kept on file for up to 15 years and will be destroyed securely after that time.

The results of the study may be used in presentations or be published in scientific reports. You will not be identified in any presentation or publication.

To make sure the data collected during the study is correct and accurate, it may be checked by researchers, representatives of Trinity College Dublin or the Health Research Board, external auditors or inspectors or members of the Ethics Committee. They will keep your information confidential. By signing consent, you are agreeing to allow such access.

Who should I contact if I have any questions?

For more information or answers to your questions about the study please contact any member of our research team, Monday – Friday from 9.00 am to 5.00pm.

Research Team Contact Details

Kate Devenney, Research Physiotherapist	01-8963613
Dr. Emer Guinan, Principal Investigator	01-8964809

Has this study been approved?

Yes, this study has been reviewed and approved by the AMNCH/SJH Research Ethics Committee (Approval reference number 2015/09/04).

Consent Form

Study Title:

1. The effects of an extensive exercise programme on the progression of Mild Cognitive Impairment

2. The effects of acute exercise on cognitive function in individuals with Mild Cognitive Impairment

Sponsor: Health Research Board

Principal Investigator Professor Brian Lawlor

Dr Emer Guinan

Research Physiotherapist: Kate Devenney

Study Doctor: Professor Brian Lawlor

Site Address: St James's Hospital, Dublin

Please tick each box to confirm you have read, understood and agreed to each of the points in this form.

I have read and understood the Patient Information Leaflet, Version 2.2, dated _____. I have had time to consider it and the opportunity to ask questions. ☐

I understand that my taking part is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. If I withdraw, I understand that my data can still be used up to when I withdrew, unless I state otherwise. ☐

I understand that my medical records may be looked at by authorised personnel from Health Research Board, the ethics committee, the regulatory authority, where it is relevant to my taking part in this study. I give my permission for such personnel to have access to my records. I understand that if I withdraw from the study, my records may need to be accessed in order to verify data collected while I was still in the study. ☐

I understand what will happen to my blood/tissue samples and I consent to the retention of my biological samples for research purposes. ☐

I consent to the collection and use of personal and sensitive information about me, including medical information, which will not include my name. ☐

I agree to the use of data collected in this study to be used in future studies without the need for giving consent again. ☐

I agree to take part in this study ☐

Name of Patient (CAPITALS)	*Signature*	*Date (Day Month Year)*
Investigator Name (CAPITALS)	*Signature*	*Date (Day Month Year)*
Name of Person taking Consent (if different to Investigator)(CAPITALS)	*Signature*	*Date (Day Month Year)*

Appendix B

Amended NeuroExercise PIL2 (Version 1.1 Community recruitment):

Patient Information Leaflet

Study Title:

(1) The effects of an extensive exercise program on the progression of mild cognitive impairment (MCI)

(2) The effects of acute exercise on cognitive function in individuals with Mild Cognitive Impairment (MCI)

This study comprises of two parts. You will be requested to take part in both parts.

Sponsor: Health Research Board

Principal Investigators: Professor Brian Lawlor

Dr Emer Guinan

Research Physiotherapist:	Kate Devenney
Study Doctor:	Professor Brian Lawlor
Site Address:	St James's Hospital, Dublin

This is a clinical study, a type of research study. The Research Team will explain the clinical study to you. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

Why is this study being done?

Mild cognitive impairment is characterised by deficits in memory and thinking skills that do not significantly impact day-to-day function. The purpose of this study is to investigate the effect of a 12 month exercise programme in patients who have mild cognitive impairment. The exercise programme is testing the theory that exercise may prevent the progression of cognitive decline (decline in the mental processes of perception, memory, judgement and reasoning) in patients with mild cognitive impairment.

Why am I being asked to take part?

People who are interested in taking part and have Mild Cognitive Impairment are invited to participate.

Do I have to take part?

No, it is up to you to decide whether or not you take part.

If you decide to take part, you will be asked to sign the consent form. You will be given a copy of this information sheet and a signed consent form for you to keep.

You will still be free to leave the study at any time, with or without giving a reason. If you decide to leave the study, this will not affect your future treatment and care.

How many people will take part in the study?

Approximately 75 people will take part in this study, in St James's Hospital, Dublin. An additional 150 people will take part in the study which is also being conducted in two other European centres.

The study will last approximately two years and your participation will last for 12 months.

What will happen to me if I take part?

You will be invited to participate in this study if the research team ascertain that you meet the study screening criteria.

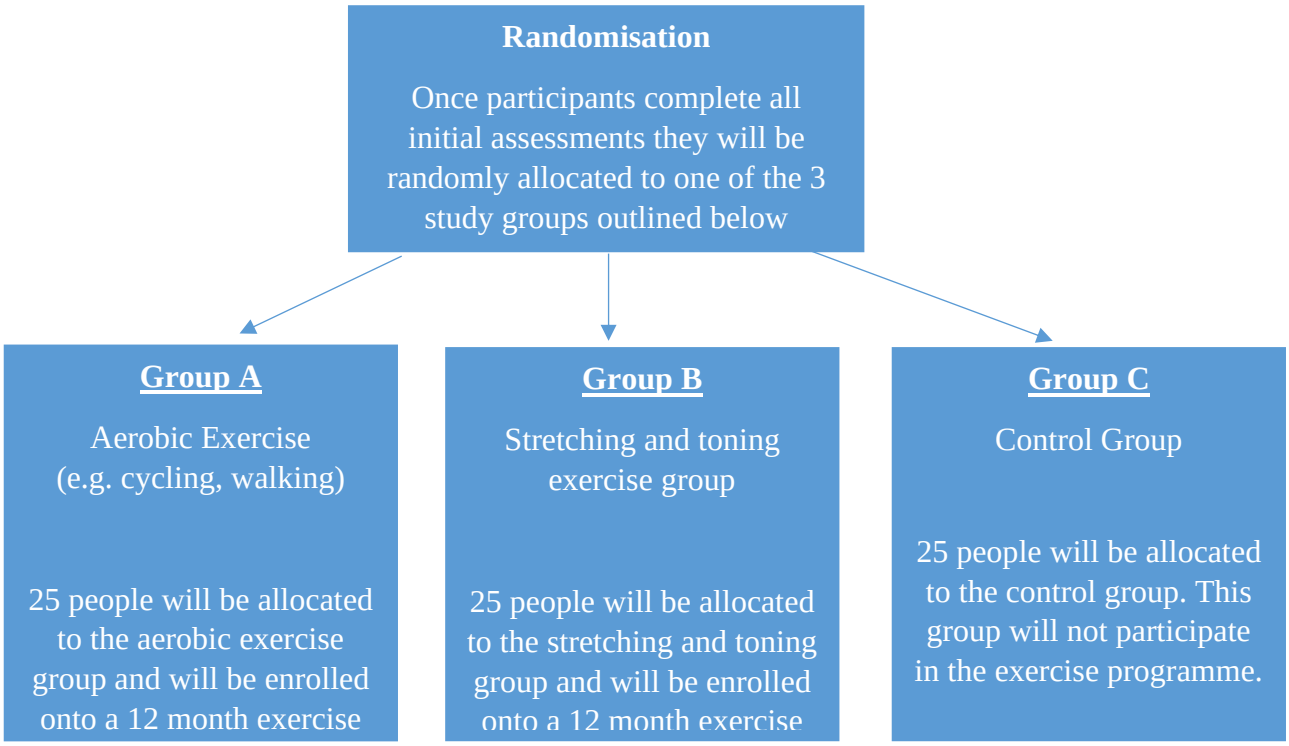
After making contact with the research team, you will be sent the study information leaflet and consent form in the post. You will also be sent a letter that has to be completed and signed by your GP and brought along to your first screening visit. The research team will arrange a screening visit on a time and day that suits you. All visits will take place at the Clinical Research Facility in St. James's Hospital.

Visit 1	The research team will complete a number of cognitive tests and review your medical history to assess your suitability to participate in the study	This visit will take approximately 45 minutes.
Visit 2	The research team will complete an exercise test on a stationary bike to assess your cardiovascular fitness. A doctor will supervise the exercise test and you heart rate and blood pressure will be monitored. Bloods will be taken before and after the exercise test and a number of cognitive tests performed. About 3 teaspoons of blood will be drawn each time a sample is taken.	This visit will take approximately 2 hours
Visit 3	The research team will complete a number of additional cognitive tests, questionnaires and measurements of your physical function. You will also be asked to wear a physical activity monitor for a week.	This visit will take approximately 1.5 hours
Visit 4	A member of the research team will conduct a face- to- face interview with you to discuss issues related to your current exercise patterns. This interview process will be repeated on exit from the study at 12 months.	This visit will take approximately 1 hour

After completing the 3 visits, you will be "randomised" into one of the study groups. Randomisation means that you are put into a group by chance. A computer program will place you in one of the 3 study groups. Neither you nor your doctor can choose the group you will be in.

One group will act as the "control group" and will not participate in the exercise programme. If you are selected to be in the "control" group, you will be required to attend for assessments at the Clinical Research Facility at St. James's Hospital.

Study One: This study is examining the effect of a 12 month exercise programme in Mild Cognitive Impairment. In this study, you may be selected to one of three exercise groups



If you are selected to an exercise group, it will involve completing three exercise sessions weekly. For the first 8 weeks of the exercise programme, two supervised exercise classes will take place at the Clinical Research Facility in St. James's Hospital and one exercise session will take place at home unsupervised.

After completing 8 weeks of the exercise programme, you will attend the Clinical Research Facility in St. James's Hospital once weekly for a supervised exercise class and complete two unsupervised exercise sessions at home for the duration of the 12 month programme. Each supervised exercise class in the Clinical Research Facility will last approx. 1 hour.

If you are selected to be in the "control" group, you will not participate in the exercise programme. You will be required to attend for assessments at the Clinical Research Facility at St. James's Hospital at 6 and 12 months.

Study Two: In this study, we aim to examine what effect a single bout of exercise has on certain blood markers and also cognitive function. In order to examine this, a blood sample will be obtained before and after you complete your exercise test at your initial visit.

About 3 teaspoons of blood will be taken on each blood draw. In addition to this, cognitive testing will be performed before and after the exercise test.

This blood sampling and cognitive testing will then be repeated before and after your supervised exercise class at week 1, week 6 and week 12 during your exercise programme. Obtaining the blood sample and completing the cognitive testing will take 60 minutes (30 minutes before class and 30 minutes after class).

In this study, we aim to assess the factors that are related to exercise participation and adherence, specifically in people who are experiencing mild cognitive decline. The purpose of this study is to assess the feasibility of the exercise programme. This study consists of two phases. Phase one is concerned with gathering information on the factors related to exercise participation in people with mild cognitive impairment, and phase two is concerned with gathering information on the factors related to their adherence to the study intervention. In both phases, information will be collected via

face- to- face interviews with the participant and one researcher. Therefore you will be asked to participate in two interview sessions, one on entry into the study (visit 4) and one on exit from the study at 12 months. Each interview will last approximately one hour.

If you exit the study prior to completing the 12 months of exercise intervention, you will be invited to complete an exit assessment with the research team. The exit assessment will be optional; you may choose to decline completing the exit assessment.

What are the benefits of taking part?

There may or may not be direct benefits to people taking part in the study. The study aims to examine the effect of different exercise interventions in people with mild cognitive impairment. The results will help us establish if exercise interventions may be of benefit for people with mild cognitive impairment in the future.

What are the risks of taking part?

We do not anticipate adverse effects during the assessments or participating in the prescribed exercise intervention. The proposed exercise intervention has been designed in line with established protocols, thereby posing minimal risk.

Participation in the exercise intervention will be with the consent of your doctor and will be supervised closely by your physiotherapist. Your risk of adverse events will be minimised through thorough medical screening prior to exercise testing and monitoring during exercise intervention.

While rare, adverse events are possible. Serious adverse events may include: heart attack, stroke, unconsciousness or other serious injury.

You may feel a little tired after the exercise test and during the initial stages of the exercise intervention but we expect that you will recover quickly.

There is a risk of bruising or fainting when taking blood samples. If any results with potentially harmful consequences are discovered your team will be informed immediately.

Will I receive payment for being part of this study?

You will not be paid for taking part of this study. However, you will receive remuneration for car parking costs incurred while attending study assessments and exercise sessions at the Clinical Research Facility.

What happens if I get hurt taking part in this study?

All participants and professionals working on the study are covered by clinical indemnity insurance. This insurance covers any damage resulting from the research. For further details please contact Kate Devenney. Contact details are listed at the end of this document.

Will my information be kept private?

If you decide to take part in the study, you give the researchers permission to collect information about you and share it with the Health Research Board. Any information that identifies you (such as your name and address) will not be shared with the Health Research Board.

Your study data will be identified with a code number which will not include your name or other information that directly identifies you.

As this research project is taking place at 2 other research sites in Europe (Nijmegen, Netherlands and Cologne, Germany), information collected related to the study and some of the blood samples collected will be transferred to these sites to be pooled together centrally for analysis. The additional blood samples will be kept on site in St. James's Hospital.

Personal and medical information identifying you will be kept confidential. We will keep it in a secured file. At any time, you may ask to see your personal information.

Your study information will be used to determine the effect of a long-term exercise programme on patients with mild cognitive impairment. The information gained will help inform the planning of future exercise programmes for people with mild cognitive impairment.

Your information will be kept on file for up to 15 years and will be destroyed securely after that time.

The results of the study may be used in presentations or be published in scientific reports. You will not be identified in any presentation or publication.

To make sure the data collected during the study is correct and accurate, it may be checked by researchers, representatives of Trinity College Dublin or the Health Research Board, external auditors or inspectors or members of the Ethics Committee. They will keep your information confidential. By signing consent, you are agreeing to allow such access.

Who should I contact if I have any questions?

For more information or answers to your questions about the study please contact any member of our research team, Monday – Friday from 9.00 am to 5.00pm.

Research Team Contact Details

Kate Devenney, Research Physiotherapist 01-8963613

Dr. Emer Guinan, Principal Investigator 01-8962128

Has this study been approved?

Yes, this study has been reviewed and approved by the AMNCH/SJH Research Ethics Committee (Approval reference number 2015/09/04)

Consent Form

Study Title:

1. The effects of an extensive exercise programme on the progression of mild cognitive impairment

2. The effects of acute exercise on cognitive function in individuals with Mild Cognitive Impairment (MCI)

Sponsor: Health Research Board

Principal Investigator	Professor Brian Lawlor
	Dr Emer Guinan
Research Physiotherapist:	Kate Devenney
Study Doctor:	Professor Brian Lawlor
Site Address:	St James's Hospital, Dublin

Please tick each box to confirm you have read, understood and agreed to each of the points in this form.

I have read and understood the Patient Information Leaflet, Version 1.1__, dated _____. I have had time to consider it and the opportunity to ask questions. ☐

I understand that my taking part is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. If I withdraw, I understand that my data can still be used up to when I withdrew, unless I state otherwise. ☐

I understand that my medical records may be looked at by authorised personnel from Health Research Board, the ethics committee, the regulatory authority, where it is relevant to my taking part in this study. I give my permission for such personnel to have access to my records. I understand that if I withdraw from the study, my records may need to be accessed in order to verify data collected while I was still in the study. ☐

I understand what will happen to my blood/tissue samples and I consent to the retention of my biological samples for research purposes. ☐

I consent to the collection and use of personal and sensitive information about me, including medical information, which will not include my name. ☐

I agree to the use of data collected in this study to be used in future studies without the need for giving consent again. ☐

I agree to take part in this study ☐

Name of Patient (CAPITALS)	*Signature*	*Date (Day Month Year)*
Investigator Name (CAPITALS)	*Signature*	*Date (Day Month Year)*

Name of Person taking Consent (if different to Investigator)(CAPITALS)	*Signature*	*Date (Day Month Year)*

Appendix C

Letter to accompany PIL for decliners study:

_____

Dear _____,

Thank you for your interest in this research study assessing the feasibility of an exercise intervention for people with Mild Cognitive Impairment (MCI).

Please find enclosed a Patient Information Leaflet that will give you greater detail about what participating in the study would entail. If you have any questions, please do not hesitate to contact me.

Please contact me on the study mobile 01 8962762 and we will arrange an interview time and date that best suits you.

Kind Regards,

_____

Leona Connolly

NeuroExercise Researcher

Tel: 01- 8962762

Email: connoll7@tcd.ie

Appendix D

PIL for Decliners study

Patient Information Leaflet

Study Title:

A feasibility study of a semi- structured exercise intervention in adults with Mild Cognitive Impairment: a mixed methods approach.

Sponsor: Health Research Board

Principal Investigators:	Professor Brian Lawlor
	Dr Emer Guinan
Researcher	Leona Connolly
Study Doctor:	Professor Brian Lawlor

Site Address: St James's Hospital, Dublin

This is a qualitative study, a type of research study which uses interviews with participants to answer the research question. The Research Team will explain the clinical study to you. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

1.Why is this study being done?

Mild cognitive impairment is characterised by deficits in memory and thinking skills that do not significantly impact day-to-day function. You have previously been asked to participate in an exercise programme testing the theory that exercise may prevent the progression of cognitive decline (decline in the mental processes of perception, memory, judgement and reasoning) in patients with mild cognitive impairment. We are now interested in interviewing people who declined to participate in this exercise programme to help to determine why people may or may not participate in this type of exercise intervention. Therefore, the purpose of this study is to investigate the feasibility of a 12-month exercise programme in patients who have mild cognitive impairment.

2.Why am I being asked to take part?

We are interested in interviewing people who have previously declined to participate in the exercise programme mentioned above to explore the reasons why people who are at risk of mild cognitive impairment may or may not take part in an exercise program designed to prevent the progression of cognitive decline.

3.Do I have to take part?

No, it is up to you to decide whether or not you take part.

If you decide to take part, you will be asked to sign the consent form. You will be given a copy of this information sheet and a signed consent form for you to keep.

You will still be free to leave the study at any time, with or without giving a reason. If you decide to leave the study, this will not affect your future treatment and care.

4. How many people will take part in the study?

Approximately 5 people who declined to take part in the NeuroExercise study will be asked to take part in this study. An additional 10 people who consented to take part in the NeuroExercise study will take part in similar interviews. Your participation will be limited to one face- to- face interview with a study researcher. Interviews will take place at either the Clinical Research Facility, St. James`Hospital or at a location of your choosing.

5.What will happen to me if I take part?

You will be invited to participate in this study if the research team ascertain that you meet the study screening criteria.

After making contact with the research team, you will be sent the study information leaflet and consent form in the post. The research team will arrange an interview time and day that suits you.

Visit 1	One researcher will conduct a semi- structured face- to- face interview to assess your feelings and opinions relating to exercise in general and also relating to your participation/ non- participation in the NeuroExercise study. The purpose of these interviews is to allow the research team to gain a greater understanding of patient needs to	This visit will take approximately 1 hour

	inform how we can design more patient- centred exercise interventions in the future.	

6. What are the benefits of taking part?

There may or may not be direct benefits to people taking part in the study. The study aims to examine the factors which relate to participation in exercise interventions in people with mild cognitive impairment. The results will help us establish the feasibility of an exercise intervention designed for people with mild cognitive impairment in the future.

7.What are the risks of taking part?

We do not anticipate adverse effects during participation in this study.

8.Will I receive payment for being part of this study?

You will not be paid for taking part of this study. However, you will receive remuneration for car parking costs incurred while attending study interviews, if the interview is set at the Clinical Research Facility, St. James`Hospital.

9.What happens if I get hurt taking part in this study?

All participants and professionals working on the study are covered by clinical indemnity insurance. This insurance covers any damage resulting from the research. For further details please contact Leona Connolly. Contact details are listed at the end of this document.

10. Will my information be kept private?

If you decide to take part in the study, you give the researchers permission to collect information about you and share it with the Health Research Board. Interviews will be recorded for transcription and analysis purposes. Any information that identifies you (such as your name and address) will not be shared with the Health Research Board.

Your study data will be identified with a code number which will not include your name or other information that directly identifies you.

Personal and medical information identifying you will be kept confidential. We will keep it in a secured file. At any time, you may ask to see your personal information.

Your study information will be used to determine the feasibility of a long- term exercise programme on persons with mild cognitive impairment. The information gained will help inform the planning of future exercise programmes for people with mild cognitive impairment.

Your information will be kept on file for up to 15 years and will be destroyed securely after that time.

The results of the study may be used in presentations or be published in scientific reports. You will not be identified in any presentation or publication.

To make sure the data collected during the study is correct and accurate, it may be checked by researchers, representatives of Trinity College Dublin or the Health Research Board, external auditors or inspectors or members of the Ethics Committee. They will keep your information confidential. By signing consent, you are agreeing to allow such access.

11. **Who should I contact if I have any questions?**

For more information or answers to your questions about the study please contact any member of our research team, Monday – Friday from 9.00 am to 5.00pm.

Research Team Contact Details

Leona Connolly, Researcher 01- 8962762

Prof Brian Lawlor, Principal Investigator 01-8968576

12. Has this study been approved?

Yes, this study has been reviewed and approved by the AMNCH/SJH Research Ethics Committee (Approval reference number 2015/09/04).

Consent Form

Study Title:

A feasibility study of a semi- structured exercise intervention in adults with Mild Cognitive Impairment: a mixed methods approach.

Sponsor: Health Research Board

Principal Investigator Professor Brian Lawlor

Researcher: Leona Connolly

Study Doctor: Professor Brian Lawlor

Site Address: St James's Hospital, Dublin

Please tick each box to confirm you have read, understood and agreed to each of the points in this form.

I have read and understood the Patient Information Leaflet, Version __, dated _____. I have had time to consider it and the opportunity to ask questions. ☐

I understand that my taking part is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. If I withdraw, I understand that my data can still be used up to when I withdrew, unless I state otherwise. ☐

I understand that my medical records may be looked at by authorised personnel from Health Research Board, the ethics committee, the regulatory authority, where it is relevant to my taking part in this study. I give my permission for such personnel to have access to my records. I understand that if I withdraw from the study, my records may need to be accessed in order to verify data collected while I was still in the study. ☐

I consent to the collection and use of personal and sensitive information about me, including medical information, which will not include my name. ☐

I agree to the use of data collected in this study to be used in future studies without the need for giving consent again. ☐

I agree to take part in this study ☐

Name of Patient (CAPITALS)	*Signature*	*Date (Day Month Year)*
Investigator Name (CAPITALS)	*Signature*	*Date (Day Month Year)*
Name of Person taking Consent (if different to Investigator)(CAPITALS)	*Signature*	*Date (Day Month Year)*

Appendix E

PIL for HCP study

Patient Information Leaflet

Study Title:

A feasibility study of a semi- structured exercise intervention in adults with Mild Cognitive Impairment: a mixed methods approach.

Sponsor: Health Research Board

Principal Investigators:	Professor Brian Lawlor
	Dr Emer Guinan
Researcher	Leona Connolly
Study Doctor:	Professor Brian Lawlor

Site Address: St James's Hospital, Dublin

This is a sequential explanatory mixed methods study, a type of research study. The Research Team will explain the clinical study to you. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

Why is this study being done?

Studies have demonstrated that physical activity may be correlated with a reduction in cognitive decline. This study in concerned with assessing the feasibility of a semi- structured exercise intervention designed to reduce cognitive impairment. As part of this study, we will be exploring the factors related to exercise referral by health care professionals to adults with cognitive impairment. We are interested in interviewing health care professionals to determine at one time point to gain a greater understanding of the issue of exercise referral for patients with cognitive impairment.

Why am I being asked to take part?

We are interested in interviewing health care professionals to explore the barriers and facilitators to exercise referral to patients presenting with cognitive impairment to assess the feasibility an exercise program designed to prevent the progression of cognitive decline.

Do I have to take part?

No, it is up to you to decide whether or not you take part.

If you decide to take part, you will be asked to sign the consent form. You will be given a copy of this information sheet and a signed consent form for you to keep.

You will still be free to leave the study at any time, with or without giving a reason. If you decide to leave the study, this will not affect your future treatment and care.

How many people will take part in the study?

Approximately 10 health care professionals will be asked to take part in this study, in St James's Hospital, Dublin. Interviews will take place at this location or at a location of your choosing. An additional 10 people who consented to take part in the NeuroExercise study will take part in similar interviews. Your participation will be limited to one face- to- face interview with a study researcher.

What will happen to me if I take part?

After making contact with the research team, you will be sent the study information leaflet and consent form. The research team will arrange an interview time and day that suits you.

Visit 1	One researcher will conduct a semi- structured face- to- face interview to assess your feelings and opinions relating to exercise in general and also to assess your opinions on the barriers or facilitators you may encounter regarding the referral of exercise to patients with cognitive impairment.	This visit will take approximately 1 hour

What are the risks of taking part?

We do not anticipate adverse effects during participation in this study.

Will I receive payment for being part of this study?

You will not be paid for taking part of this study.

What happens if I get hurt taking part in this study?

All participants and professionals working on the study are covered by clinical indemnity insurance. This insurance covers any damage resulting from the research. For further details please contact Leona Connolly. Contact details are listed at the end of this document.

Will my information be kept private?

If you decide to take part in the study, you give the researchers permission to collect information about you and share it with the Health Research Board. Any information that identifies you (such as your name and address) will not be shared with the Health Research Board.

Your study data will be identified with a code number which will not include your name or other information that directly identifies you.

Personal and medical information identifying you will be kept confidential. We will keep it in a secured file. At any time, you may ask to see your personal information.

Your study information will be used to determine the feasibility of a long- term exercise programme on persons with mild cognitive impairment. The information gained will help inform the planning of future exercise programmes for people with mild cognitive impairment.

Your information will be kept on file for up to 15 years and will be destroyed securely after that time.

The results of the study may be used in presentations or be published in scientific reports. You will not be identified in any presentation or publication.

To make sure the data collected during the study is correct and accurate, it may be checked by researchers, representatives of Trinity College Dublin or the Health Research Board, external auditors

or inspectors or members of the Ethics Committee. They will keep your information confidential. By signing consent, you are agreeing to allow such access.

Who should I contact if I have any questions?

For more information or answers to your questions about the study please contact any member of our research team, Monday – Friday from 9.00 am to 5.00pm.

Research Team Contact Details

Leona Connolly, Researcher	01- 8962762
Prof Brian Lawlor, Principal Investigator	01-8968576

Has this study been approved?

Yes, this study has been reviewed and approved by the AMNCH/SJH Research Ethics Committee (Approval reference number 2015/ 09/04)

Consent Form

Study Title:

A feasibility study of a semi- structured exercise intervention in adults with Mild Cognitive Impairment: a mixed methods approach.

Sponsor: Health Research Board

Principal Investigator	Professor Brian Lawlor
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I understand that my medical records may be looked at by authorised personnel from Health Research Board, the ethics committee, the regulatory authority, where it is relevant to my taking part in this study. I give my permission for such personnel to have access to my records. I understand that if I withdraw from the study, my records may need to be accessed in order to verify data collected while I was still in the study. ☐

I consent to the collection and use of personal and sensitive information about me, including medical information, which will not include my name. ☐

I agree to the use of data collected in this study to be used in future studies without the need for giving consent again. ☐

I agree to take part in this study ☐

Name of Patient (CAPITALS)	*Signature*	*Date (Day Month Year)*
Investigator Name (CAPITALS)	*Signature*	*Date (Day Month Year)*
Name of Person taking Consent (if different to Investigator)(CAPITALS)	*Signature*	*Date (Day Month Year)*

Appendix F

Letter to accompany PIL for HCP study:

_____

Dear _____,

Thank you for your interest in this research study.

Please find enclosed a Patient Information Leaflet that will give you greater detail about what participating in the study would entail. If you have any questions, please do not hesitate to contact me.

Please contact me on the study mobile 01- 8962762 and we will arrange an interview time and date that best suits you.

Kind Regards,

_____

Leona Connolly

NeuroExercise Researcher

Tel: 01- 8962762

Email: connoll7@tcd.ie

Appendix G: Research ethics committee letter of approval

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

JH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Prof. Brian Lawlor
Consultant
St. James's Hospital
James Street
Dublin 8

18th September 2017

Re: The Effects of an Extensive Exercise Programme on the Progression of Mild Cognitive Impairment (MCI)

REC Reference: 2017-09 List 33 (9)
(Please quote reference on all correspondence)

Dear Prof. Lawlor,

Thank you for your recent correspondence to SJH/AMNCH Research Ethics Committee in which you submitted an amendment in relation to the above referenced study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed this request and grants permission for this amendment.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix H: LASA Physical Activity Questionnaire

LASA Physical Activity Questionnaire (LAPAQ)

1. Do you walk outside?
Explanation: with walking outside we mean walking to go shopping or doing other daily activities, like visiting someone. We do not mean: a walking tour.
   1. no (go to question 5)
   2. yes

2. Did you walk during the past two weeks?
   1. no (go to question 5)
   2. yes

3. How many times did you walk during the past two weeks?
   …….. times

4. How long did you usually walk each time?
   …….. hours
   …….. minutes

5. Do you cycle?
Explanation: with cycling we mean cycling to go shopping or doing other daily activities, like visiting someone. With cycling we do not mean: a cycling tour.
   1. no (go to question 9)
   2. yes

6. Did you cycle during the past two weeks?
   1. no (go to question 9)
   2. yes

7. How many times did you cycle the past two weeks?
   …….. times

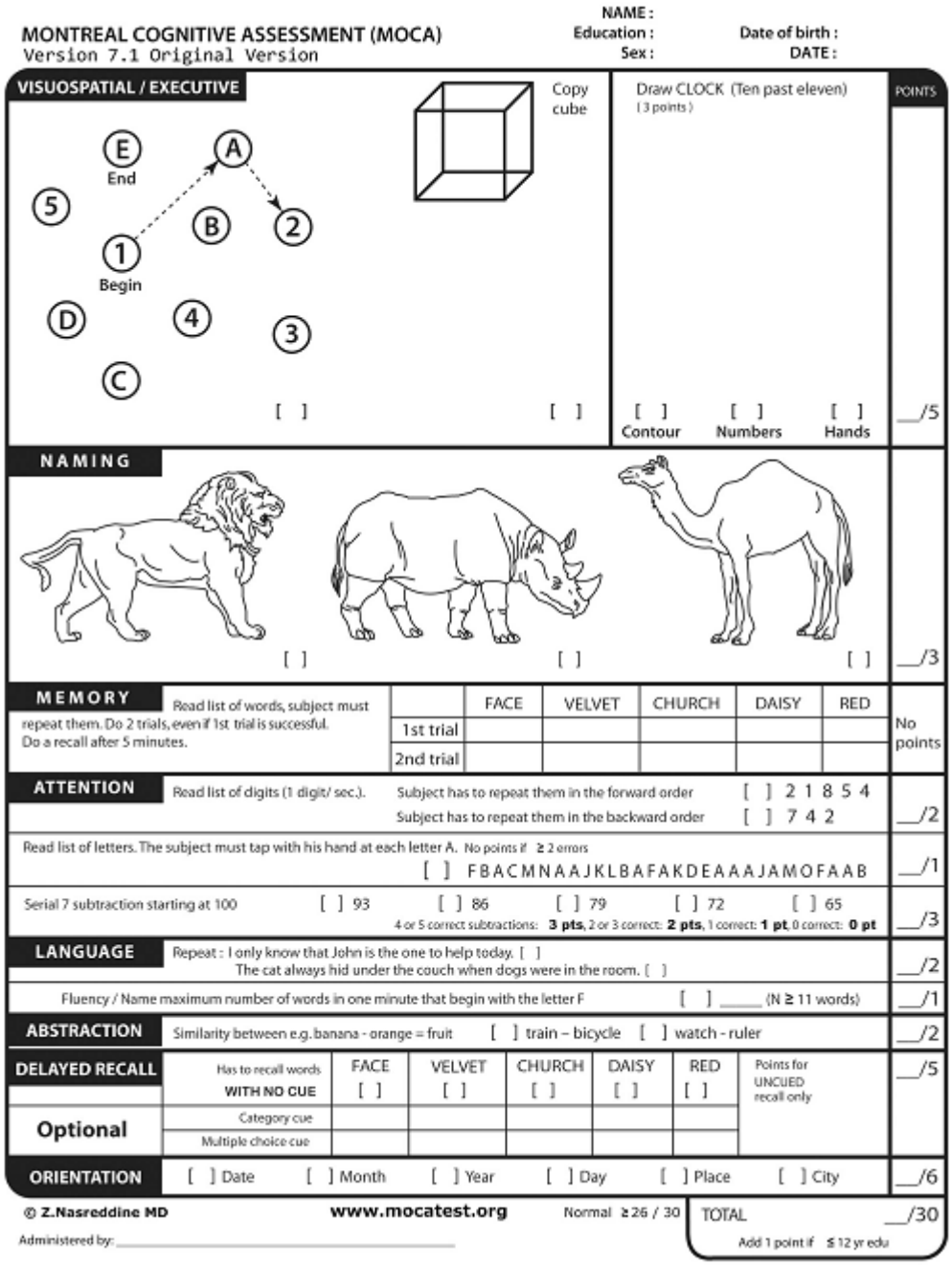
8. How long did you usually cycle each time?
   …….. hours
   …….. minutes

9. Do you have a garden (including allotment)?
   1. no (go to question 15)
   2. yes

10. During how many months per year do you work regularly in your garden?
Explanation: by regularly we mean at least once a week.
   …….. months

11. Did you work in the garden during the past two weeks?
   1. no (go to question 15)
   2. yes

Appendix I: Montreal Cognitive Assessment questionnaire (MoCA)



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube [ ]

Draw CLOCK (Ten past eleven) (3 points) [ ] Contour [ ] Numbers [ ] Hands __/5

NAMING [ ] [ ] [ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Appendix J: Quality of Life for Dementia Questionnaire (DemQoL)

Study ID □□□□□

DEMQOL (version 4)

Instructions: Read each of the following questions (in bold) verbatim and show the respondent the response card.

I would like to ask you about your life. There are no right or wrong answers. Just give the answer that best describes how you have felt in the last week. Don't worry if some questions appear not to apply to you. We have to ask the same questions of everybody.

Before we start we'll do a practise question; that's one that doesn't count. *(Show the response card and ask respondent to say or point to the answer)* **In the last week, how much have you enjoyed watching television?**

a lot **quite a bit** **a little** **not at all**

Follow up with a prompt question: **Why is that?** *or* **Tell me a bit more about that.**

For all of the questions I'm going to ask you, I want you to think about the last week.

First I'm going to ask about <u>your feelings</u>. In the last week, have you felt.....

1. **cheerful? ****	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
2. **worried or anxious?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
3. **that you are enjoying life? ****	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
4. **frustrated?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
5. **confident? ****	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
6. **full of energy? ****	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
7. **sad?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
8. **lonely?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
9. **distressed?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
10. **lively? ****	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
11. **irritable?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
12. **fed-up?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
13. **that there are things that you wanted to do but couldn't?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all

Next, I'm going to ask you about <u>your memory</u>. In the last week, how worried have you been about.....

14. **forgetting things that happened recently?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
15. **forgetting who people are?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
16. **forgetting what day it is?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all

17. **your thoughts being muddled?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
18. **difficulty making decisions?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
19. **poor concentration?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all

Now, I'm going to ask you about <u>your everyday life</u>. In the last week, how worried have you been about.....

20. **not having enough company?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
21. **how you get on with people close to you?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
22. **getting the affection that you want?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
23. **people not listening to you?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
24. **making yourself understood?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
25. **getting help when you need it?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
26. **getting to the toilet in time?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
27. **how you feel in yourself?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all
28. **your health overall?**	☐ a lot	☐ quite a bit	☐ a little	☐ not at all

We've already talked about lots of things: your feelings, memory and everyday life. Thinking about all of these things in the last week, how would you rate.....

29. **your quality of life overall? ****	☐ very good	☐ good	☐ fair	☐ poor

** items that need to be reversed before scoring

Appendix K: Centre for Studies Depression Scale (CES – D)

Center for Epidemiologic Studies Depression Scale (CES-D)

Date: _____

Below is a list of some of the ways you may have felt or behaved. Please indicate how often you've felt this way during the **past week**. Respond to all items.

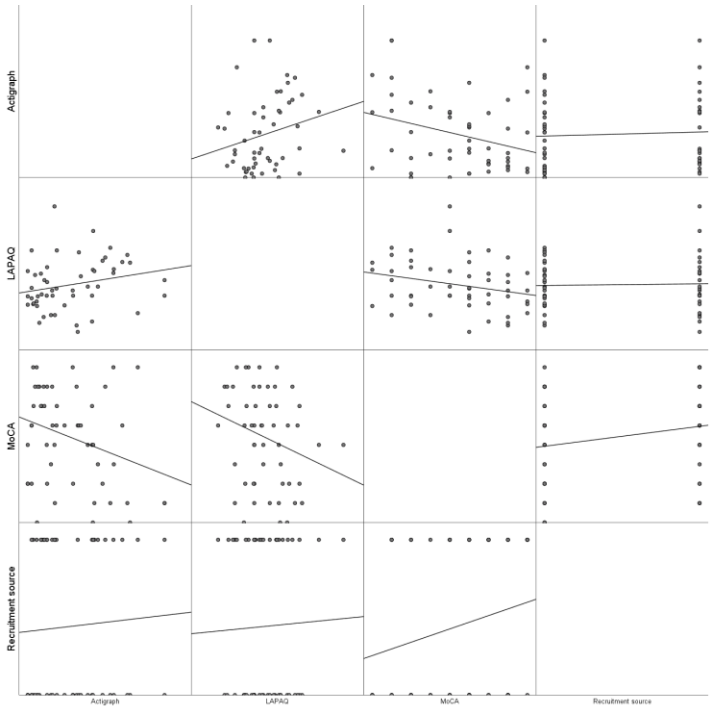
Place a check mark (✓) in the appropriate column. **During the past week...**	**Rarely or none of the time (less than 1 day)**	**Some or a little of the time (1-2 days)**	**Occasionally or a moderate amount of time (3-4 days)**	**All of the time (5-7 days)**
1. I was bothered by things that usually don't bother me.				
2. I did not feel like eating; my appetite was poor.				
3. I felt that I could not shake off the blues even with help from my family.				
4. I felt that I was just as good as other people.				
5. I had trouble keeping my mind on what I was doing.				
6. I felt depressed.				
7. I felt that everything I did was an effort.				
8. I felt hopeful about the future.				
9. I thought my life had been a failure.				
10. I felt fearful.				
11. My sleep was restless.				
12. I was happy.				
13. I talked less than usual.				
14. I felt lonely.				
15. People were unfriendly.				
16. I enjoyed life.				
17. I had crying spells.				
18. I felt sad.				
19. I felt that people disliked me.				
20. I could not "get going."				

Source: Radloff, L.S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*: 385-401.

Appendix L: Scatterplot for recruitment source, cognitive function, and PA outcome measures

Figure A1.

Scatterplot Matrix of Recruitment Source by LAPAQ, Actigraph and MoCA Values



Appendix M: Assessment of normality

Table A3.

Summary of Skewness and Kolmogorov- Smirnov Values for All Variables

Variable	Skewness values	Kolmogorov – Smirnov values
Age screening	0.112	.053
Years of education	0.095	.200
Number of meds	0.161	.001*
MoCA	0.146	.002*
Handgrip left	0.113	.051
Handgrip right	0.086	.200
DemQol	0.103	.099
CES – D	0.064	.200
Actigraph	.169	.001*
LAPAQ	0.112	.053

*$p < .05$ indicates violation of the assumption of normality

Appendix N: Study 1 inspection of outliers

Figure A2.

Boxplot for Years of Education

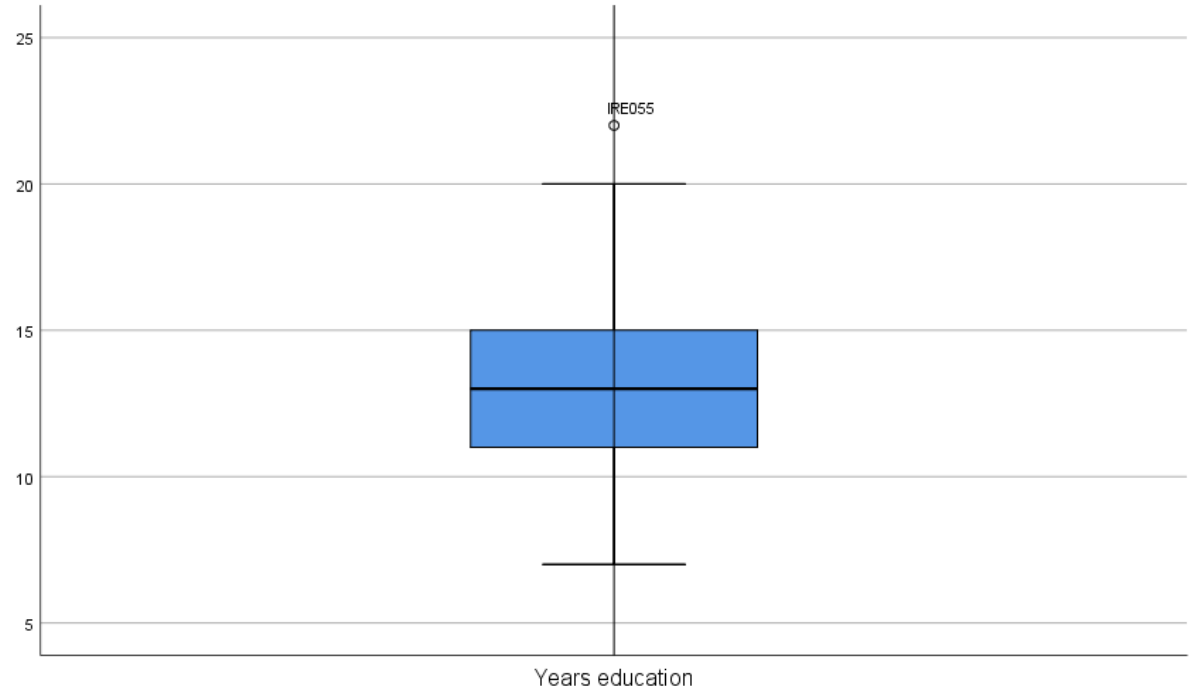


Figure A3.

Boxplot for Number of Medications

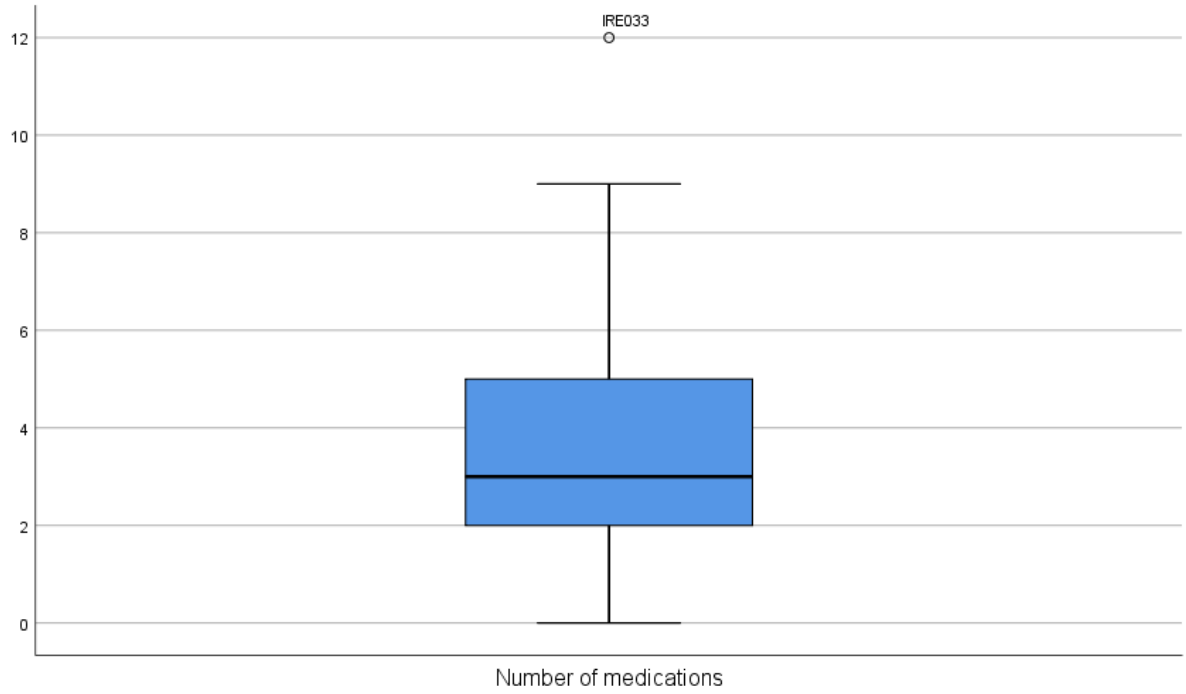


Figure A4.

Boxplot for the LAPAQ Physical Activity Questionnaire

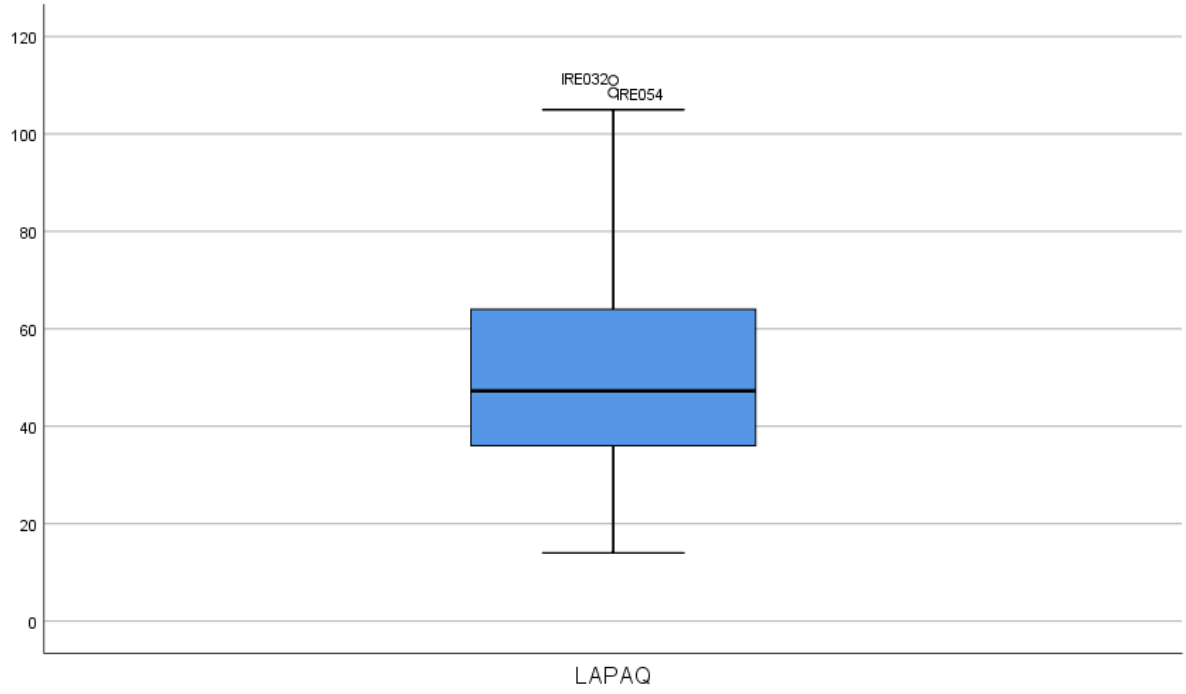
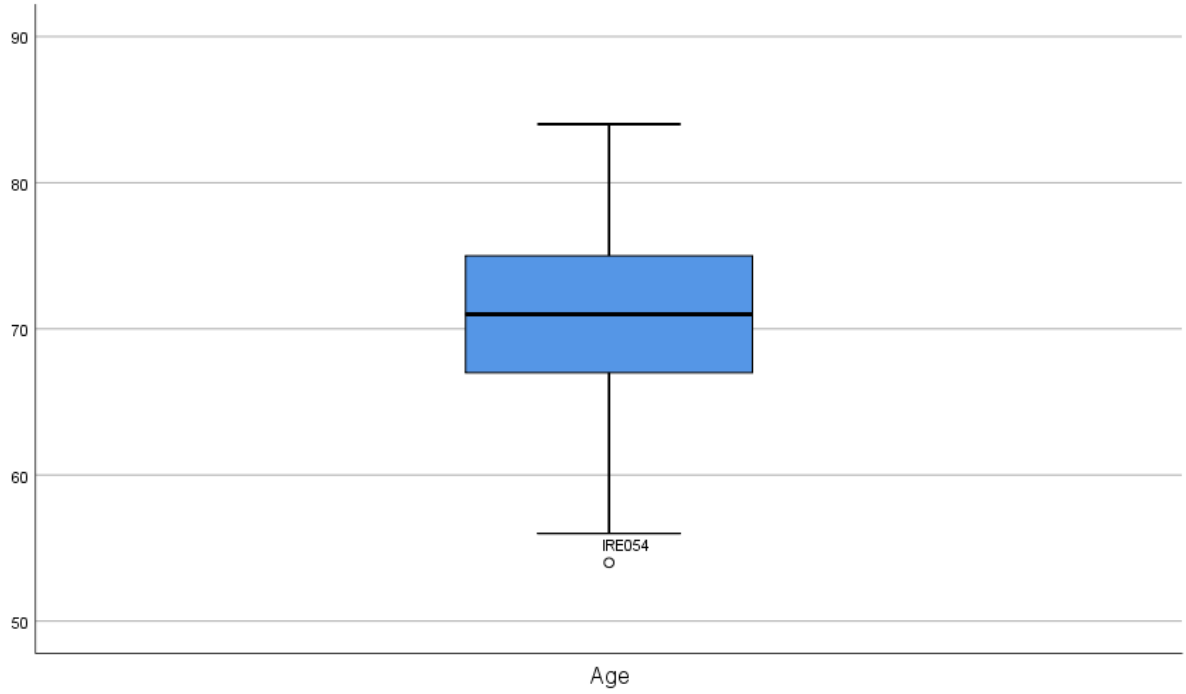


Figure A5.

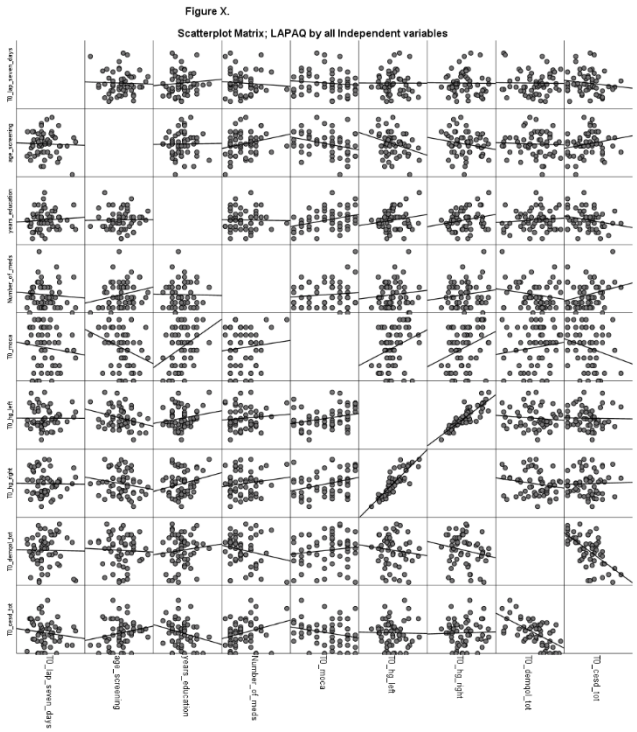
Boxplot for Age



Appendix O: Study 1 scatterplots for all independent variables by LAPAQ

Figure A6.

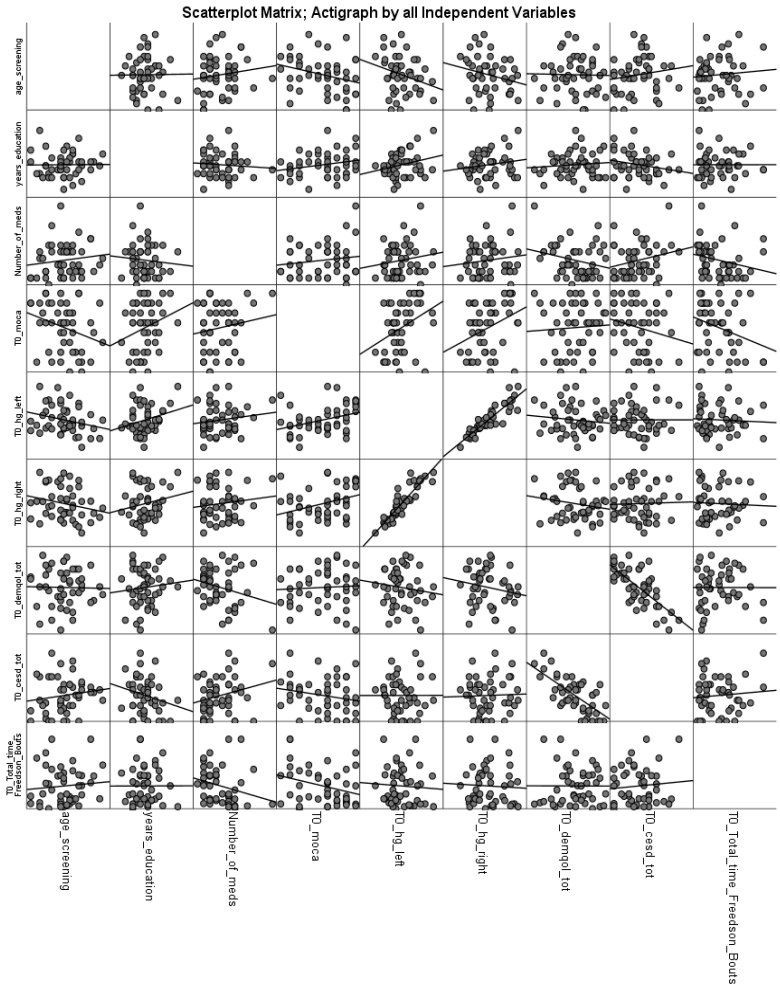
Scatterplot of Independent Variables



Appendix P: Study 1 scatterplots for all independent variables by Actigraph

Figure A7.

Scatterplot of Independent Variables by Actigraph Data



Appendix Q: Study 1 frequency tables for all variables

Table A4.

Frequencies for Age

Age	N	%
54	1	1.6
56	1	1.6
60	3	4.8
61	1	1.6
62	1	1.6
63	2	3.2
64	1	1.6
65	3	4.8
66	2	3.2
67	5	8.1
68	1	1.6
69	1	1.6
70	7	11.3
71	5	8.1
72	4	6.5
73	3	4.8
74	5	8.1
75	2	3.2
76	3	4.8
77	5	8.1
78	1	1.6
80	2	3.2
81	1	1.6
83	1	1.6

84	1	1.6
Total	62	100

Table A5.

Frequencies for Years of Education

Years of Education	N	%
7	2	3.2
8	1	1.6
9	3	4.8
10	7	11.3
11	5	8.1
12	7	11.3
13	9	14.5
14	8	12.9
15	5	8.1
16	4	6.5
17	3	4.8
18	6	9.7
20	1	1.6
22	1	1.6
Total	62	100.0

Table A6.

Frequencies for MoCA Scores

MoCA	N	%
18	6	9.7
19	6	9.7
20	6	9.7
21	4	6.5
22	7	11.3
23	11	17.7
24	7	11.3
25	10	16.1
26	5	8.1
Total	62	100.0

Table A7.

Frequencies for Dementia Related Quality of Life (DemQol)

DemQol scores	N	%
65	1	1.6
72	1	1.6
73	2	3.2
74	1	1.6
75	1	1.6
77	2	3.2
79	1	1.6
81	1	1.6
82	1	1.6
83	1	1.6
84	2	3.2
86	2	3.2
87	2	3.2
88	1	1.6
89	2	3.2
90	3	4.8
91	2	3.2
92	1	1.6
93	2	3.2
94	3	4.8
95	1	1.6
96	2	3.2
97	4	6.5
98	4	6.5
99	3	4.8
100	1	1.6
101	3	4.8

103	5	8.1
105	2	3.2
106	1	1.6
107	2	3.2
109	1	1.6
110	1	1.6
Total	62	100.0

Table A8.

Frequencies for Depression Scores (CES- D)

CES - D Score	N	%
0	6	9.7
1	1	1.6
3	2	3.2
4	4	6.5
5	1	1.6
6	4	6.5
7	2	3.2
8	3	4.8
9	3	4.8
10	3	4.8
11	5	8.1
12	5	8.1
13	3	4.8
14	4	6.5
15	2	3.2
16	1	1.6
17	4	6.5
18	2	3.2
20	1	1.6
22	1	1.6
23	1	1.6
26	1	1.6
Total	59	95.2
Missing	3	4.8
	62	100.0

Table A9.

Frequencies for Number of Medications

Number of Medications	N	%
0	2	3.2
1	12	19.4
2	11	17.7
3	8	12.9
4	4	6.5
5	10	16.1
6	6	9.7
7	4	6.5
8	1	1.6
9	1	1.6
12	1	1.6
Total	60	96.8
Missing	2	3.2

Table A10.

Frequencies for Handgrip Scores for Males in kg

Handgrip males (kg)	N	%
20	1	3.4
21	1	3.4
25	1	3.4
26	1	3.4
27	1	3.4
29	1	3.4
29	1	3.4
30	1	3.4
31	1	3.4
31	1	3.4
32	1	3.4
32	1	3.4
32	1	3.4
33	1	3.4
37	1	3.4
38	1	3.4
38	1	3.4
40	1	3.4
41	1	3.4
41	1	3.4
42	1	3.4
42	1	3.4
42	1	3.4
43	1	3.4
45	1	3.4
47	1	3.4
47	1	3.4

48	1	3.4
Total	28	96.6
Missing	1	3.4
	29	100.0

Table A11.

Frequencies for Handgrip Scores for Females in kg

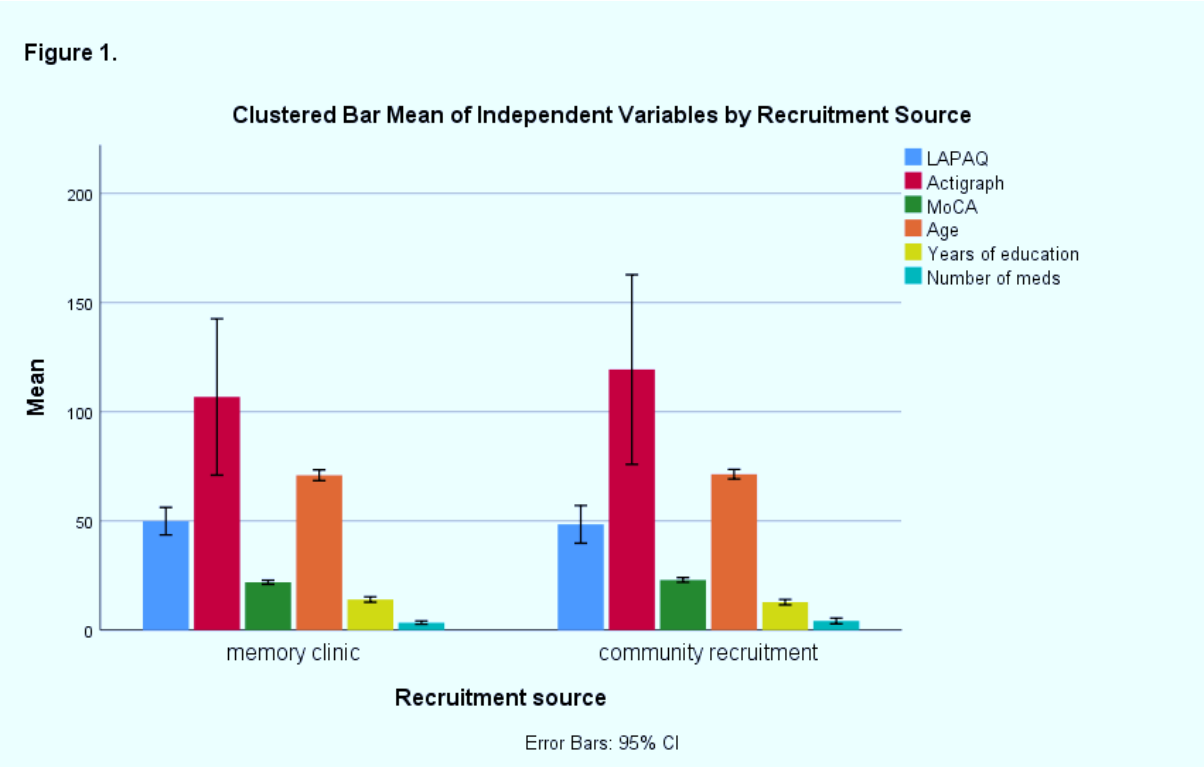
Handgrip females (kg)	N	%
9	1	3.0
13	1	3.0
14	1	3.0
15	1	3.0
15	1	3.0
15	1	3.0
17	1	3.0
17	1	3.0
17	1	3.0
17	1	3.0
17	1	3.0
18	1	3.0
19	1	3.0
19	1	3.0
20	1	3.0
21	1	3.0
21	1	3.0
21	1	3.0
22	1	3.0
22	1	3.0
23	1	3.0
23	1	3.0
24	1	3.0
25	1	3.0
25	1	3.0
26	1	3.0
28	1	3.0

29	2	6.1
29	1	3.0
30	1	3.0
32	1	3.0
Total	32	97.0
Missing	1	3.0
	33	100.0

Appendix R: Study 1 barchart of independent variables by recruitment source

Figure A8.

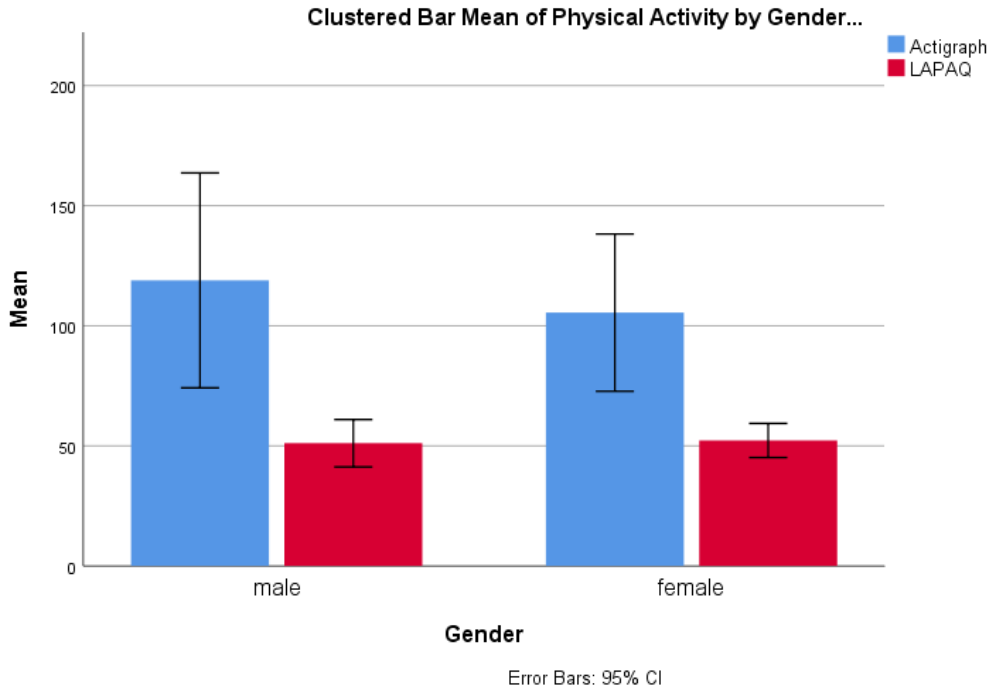
Clustered Bar Chart for Mean of Independent Variables by Recruitment Source



Appendix S: Study1 means of physical activity engagement by gender

Figure A9.

Clustered Bar Chart of Physical Activity by Gender



Appendix T: Study 1 linearity and homoscedasticity of Actigraph and LAPAQ data

Figure A10.

Scatterplot of Homoscedasticity for the LAPAQ by Actigraph

Appendix U: Participant Information Leaflet and Consent Form

Patient Information Leaflet

Study Title:

A feasibility study of a semi- structured exercise intervention in adults with Mild Cognitive Impairment: a mixed methods approach.

Sponsor: Health Research Board

Principal Investigators:	Professor Brian Lawlor
	Dr Emer Guinan
Researcher	Leona Connolly
Study Doctor:	Professor Brian Lawlor
Site Address:	St James's Hospital, Dublin(qualitative + quantitative)

This is a mixed methods (qualitative + quantitative) study, a type of research study. The Research Team will explain the clinical study to you. Please take your time to make your decision about taking part.

Why is this study being done?

Studies have demonstrated that physical activity may be correlated with a reduction in cognitive decline. This study in concerned with assessing the feasibility of a semi- structured exercise intervention designed to reduce cognitive impairment. As part of this study, we will be exploring the factors related to exercise engagement in adults with cognitive impairment. We are interested in interviewing participants at one time point to gain a greater understanding of the barriers and facilitators to exercise in adults with cognitive impairment.

Why am I being asked to take part?

We are interested in interviewing you to explore the barriers and facilitators to exercise in participants with cognitive impairment to assess the feasibility an exercise program designed to prevent the progression of cognitive decline.

Do I have to take part?

No, it is up to you to decide whether or not you take part.

If you decide to take part, you will be asked to sign the consent form. You will be given a copy of this information sheet and a signed consent form for you to keep.

You will still be free to leave the study at any time, with or without giving a reason. If you decide to leave the study, this will not affect your future treatment and care.

How many people will take part in the study?

Approximately 10 participants will be asked to take part in this study, in St James's Hospital, Dublin. Interviews will take place at this location or at a location of your choosing. Your participation will be limited to one face- to- face interview with a study researcher.

What will happen to me if I take part?

After making contact with the research team, you will be given the study information leaflet and consent form. The research team will arrange an interview time and day that suits you.

Visit 1	One researcher will conduct a semi- structured face- to- face interview to assess your feelings and opinions relating to exercise in general and also to assess your opinions on the barriers or facilitators you may encounter regarding exercise engagement.	This visit will take approximately 1 hour

What are the risks of taking part?

We do not anticipate adverse effects during participation in this study.

Will I receive payment for being part of this study?

You will not be paid for taking part of this study.

What happens if I get hurt taking part in this study?

All participants and professionals working on the study are covered by clinical indemnity insurance. This insurance covers any damage resulting from the research. For further details please contact Leona Connolly. Contact details are listed at the end of this document.

Will my information be kept private?

If you decide to take part in the study, you give the researchers permission to collect information about you and share it with the Health Research Board. Any information that identifies you (such as your name and address) will not be shared with the Health Research Board.

Your study data will be identified with a code number which will not include your name or other information that directly identifies you.

Personal and medical information identifying you will be kept confidential. We will keep it in a secured file. At any time, you may ask to see your personal information.

Your study information will be used to determine the feasibility of a long- term exercise programme on persons with mild cognitive impairment. The information gained will help inform the planning of future exercise programmes for people with mild cognitive impairment.

Your information will be kept on file for up to 15 years and will be destroyed securely after that time.

The results of the study may be used in presentations or be published in scientific reports. You will not be identified in any presentation or publication.

To make sure the data collected during the study is correct and accurate, it may be checked by researchers, representatives of Trinity College Dublin or the Health Research Board, external auditors or inspectors or members of the Ethics Committee. They will keep your information confidential. By signing consent, you are agreeing to allow such access.

Who should I contact if I have any questions?

For more information or answers to your questions about the study please contact any member of our research team, Monday – Friday from 9.00 am to 5.00pm.

Research Team Contact Details

Leona Connolly, Researcher 01- 8962762

Prof Brian Lawlor, Principal Investigator 01-8968576

Has this study been approved?

Yes, this study has been reviewed and approved by the AMNCH/SJH Research Ethics Committee (Approval reference number 2015/ 09/04)

Consent Form

Study Title:

A feasibility study of a semi- structured exercise intervention in adults with Mild Cognitive Impairment: a mixed methods approach.

Sponsor: Health Research Board

Principal Investigator Professor Brian Lawlor

Researcher: Leona Connolly

Study Doctor: Professor Brian Lawlor

Site Address: St James's Hospital, Dublin

Please tick each box to confirm you have read, understood and agreed to each of the points in this form.

I have read and understood the Patient Information Leaflet, Version __, dated _____. I have had time to consider it and the opportunity to ask questions. ☐

I understand that my taking part is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. If I withdraw, I understand that my data can still be used up to when I withdrew, unless I state otherwise. ☐

I understand that my medical records may be looked at by authorised personnel from Health Research Board, the ethics committee, the regulatory authority, where it is relevant to my taking part in this study. I give my permission for such personnel to have access to my records. I understand that if I withdraw from the study, my records may need to be accessed in order to verify data collected while I was still in the study. ☐

I consent to the collection and use of personal and sensitive information about me, including medical information, which will not include my name. ☐

I agree to the use of data collected in this study to be used in future studies without the need for giving consent again. ☐

I agree to take part in this study ☐

Name of Participant (CAPITALS)	*Signature*	*Date (Day Month Year)*
Investigator Name (CAPITALS)	*Signature*	*Date (Day Month Year)*
Name of Person taking Consent (if different to Investigator)(CAPITALS)	*Signature*	*Date (Day Month Year)*

Appendix V: Study 1 interview topic guide

Interview Guide: Exercise and MCI

Hi _____, thank you for coming in to meet with me today. My name is Leona and I am a PhD student researching the factors that are related to exercising or not exercising in adults with Mild Cognitive Impairment.

The purpose of this interview is to try to get a greater understanding of what influences exercise behaviour in people who have mild cognitive impairment. My aim is to build up a complete picture of the different personal, social and illness related factors that either help you or hinder you when it comes to exercising. This information will be useful in designing future exercise interventions that are built around the actual needs of the people they are designed for.

I expect that this interview will last for approx. 1 hour. It may be longer or shorter depending on how we get on, but you can stop the interview at any time if you feel that you need to.

I am recording this interview so that I can later transcribe it, it`s really to make sure that I capture everything that you are telling me and so that I don't forget or misinterpret anything that you say. Is this ok with you? Are you still happy to proceed with the interview? Do you have any questions before we get started?

1. Please tell me about yourself:

What is important in your life;

The kind of person you are;

Likes and dislikes;

People in your life;

Interests and how you spend your time;

Diagnosis;

2. Please tell me about your experience of living with MCI? What is it like for you?

Have you received a diagnosis? When?

How did you feel when you received a diagnosis?

How does MCI affect your daily activities? Differences before and after?

Knowledge of exercise/ dementia link?

3. So now that we`ve touched on the issue of exercise, please tell me a little bit about how you feel about exercise:

Do you exercise?

How do you exercise? (frequency/ intensity/ duration/ outdoors/ alone)

How important is exercise to you in your day to day life?

What is your exercise history?

What do you like/ dislike about exercising?

How do you think MCI impacts on your exercise habits?

What helps/ hinders you to exercise now?

6. Recap…..Is there anything you would like to ask me?

Thank you so much for participating in this study. I hope it has been a positive experience for you.

Appendix W: Study 1 example of initial line by line codes

Table A12.

Example of line-by-line coding

Data Extract	Units of Data (Interview Transcripts)	Early Descriptive Codes/ Line by Line Coding
Example 1	"Well, either of them. There's an emphasis on the exercise and the… em the… and the understanding of not doing exercise, one doesn't outweigh the other. I just want to have a balanced view of it and… survive… to tell you the truth. No, the better you feel in yourself it's easier to accept life and get on with doing the things you have to do. Once you've a programme laid out that you must get through… like looking after (carer to daughter)… it can slow you up a lot…". *057.*	*Knowledge* *Attitudes to PA* *Lack of time* *Being a carer* *Barriers to PA* *Motivation for PA* *Moderation/ Acceptable level of PA*
Example 2	"So, I do… it's about half an hour. You can make it (online brain training programme) as long as you want, they… you can get a programme each day to do em… different things, but then it leaves it up to yourself, do you want to continue doing another half an hour of bits and pieces, and I might do that as well. And I do find it's an awareness. That's what I find. It's just…yeah, I try to… exactly. Exactly, because when you`re not out working anymore that's another thing. My husband`s got Parkinson`s, so he`s not a chatterbox at home by any stretch of the imagination… I`m out and I golf and do all sorts of other sports, and swimming and I associate with all those people, but at home I sort of feel sometimes I just need to have… and this programme I find is very good. It covers a lot of things, and it's different every day. Always different. And so that's what I kind of do for the old brain, keep it… let it know I`m still here sort of thing, you know (laughs), you know. That's about it, yeah, and that's about it". *014.*	*Memory issues* *Dealing with MCI* *Knowledge* *Conceptions of how to maintain brain health.* *Exercising the brain* *Being retired* *Being a carer* *Needing stimulation*

Appendix X: Study 1 early category development

Table A13.

Example of Semantic Category Development

Category	Sub – Category	Code	Sub - Code
Practical Issues	Barriers	Lack of time for PA	Being a carer/ home and family commitments
		Weather	
		Overcoming barriers	
	Ability	Physical ability	Injury or illness
		Cognitive ability	Memory issues/ symptoms
			Coping with MCI
Reasons for Exercising/ Motivations	Health	Physical health	
		Psychological health	
		Cognitive health	
	Enjoyment	PA being purposeful	
		Boredom	
		Moderation	
		Being told to vs wanting to	
		Being outdoors/ Fresh air	
		Social aspect	

Appendix Y: 15-point checklist of criteria for good thematic analysis process

Table A14.

Braun & Clarkes Checklist of Criteria for Good Thematic Analysis

Transcription	1.	The data have been transcribed to an appropriate level of detail, and the transcripts have been checked against the tapes for 'accuracy'.
Coding	2.	Each data item has been given equal attention in the coding process.
	3.	Themes have not been generated from a few vivid examples (an anecdotal approach) but, instead, the coding process has been thorough, inclusive and comprehensive.
	4.	All relevant extracts for all each theme have been collated.
	5.	Themes have been checked against each other and back to the original data set.
	6.	Themes are internally coherent, consistent, and distinctive.
Analysis	7.	Data have been analysed rather than just paraphrased or described.
	8.	Analysis and data match each other – the extracts illustrate the analytic claims.
	9.	Analysis tells a convincing and well-organised story about the data and topic.
	10.	A good balance between analytic narrative and illustrative extracts is provided.
Overall	11.	Enough time has been allocated to complete all phases of the analysis adequately, without rushing a phase or giving it a once-over-lightly.
Written report	12.	The assumptions about Themes are clearly explicated.
	13.	There is a good fit between what you claim you do, and what you show you have done – ie, described method and reported analysis are consistent.
	14.	The language and concepts used in the report are consistent with the epistemological position of the analysis.
	15.	The researcher is positioned as *active* in the research process; themes do not just 'emerge'.

Note. A 15 – point checklist for good thematic analysis. Reprinted from "Using Thematic Analysis in Psychology" by Braun & Clarke, 2006, *Qualitative Research in Psychology, 3* (2). available online at: http://www.tandfonline.com/. doi.org/10.1191/1478088706qp063oa.

Appendix Z: Study 2 linearity of variables

Figure A11.

Scatterplot Matrix for all Independent Variables and Total PA Programme Adherence

Appendix AA: Study 2 boxplots for variables containing outliers

Figure A12.

Boxplot of Outliers for the CES - D

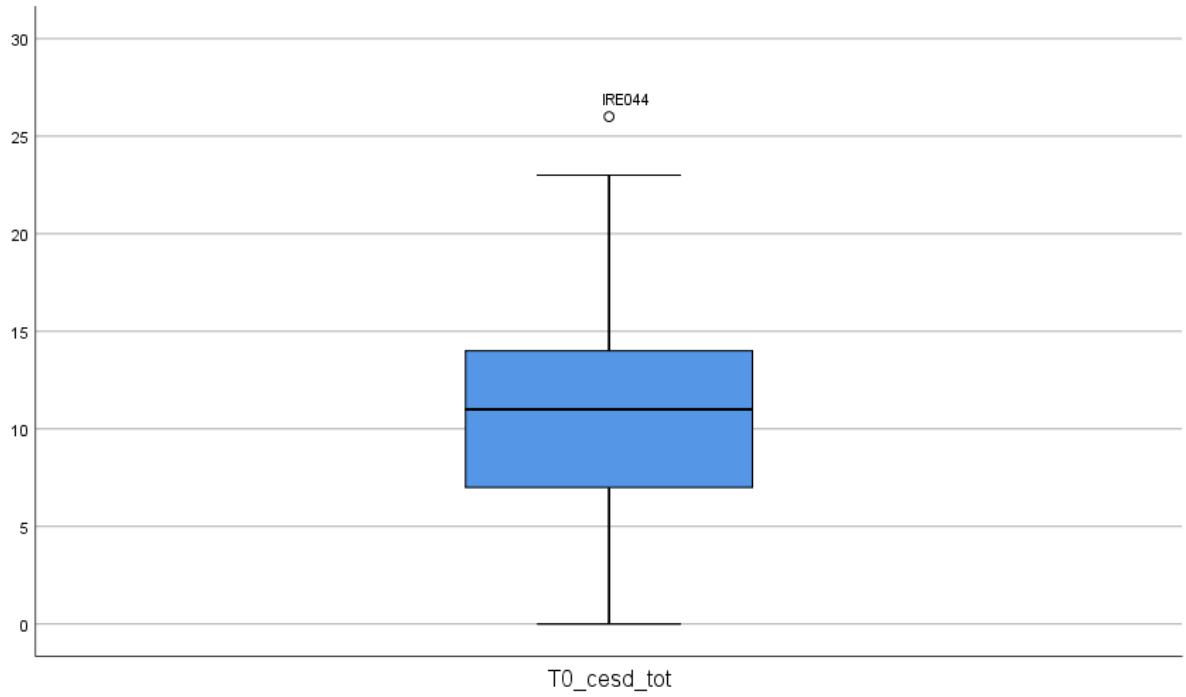
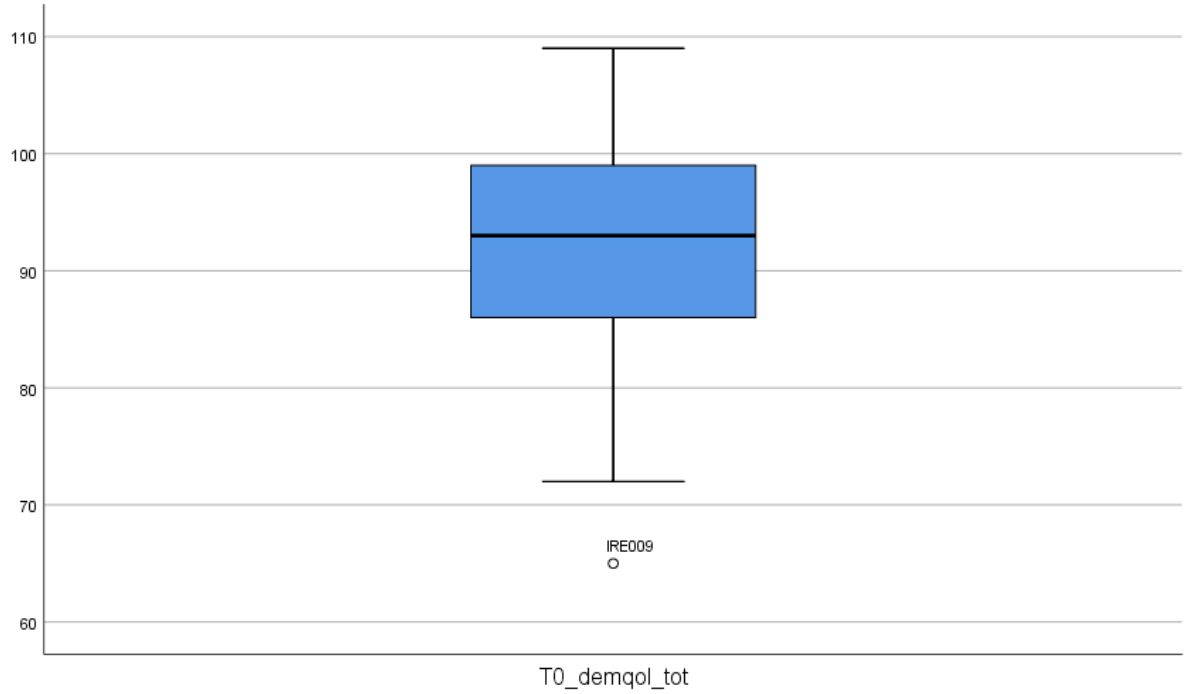


Figure A13.

Boxplot of Outliers for the DemQol



Appendix BB: Study 2 multicollinearity and homoscedasticity for independent variables and total PA programme adherence

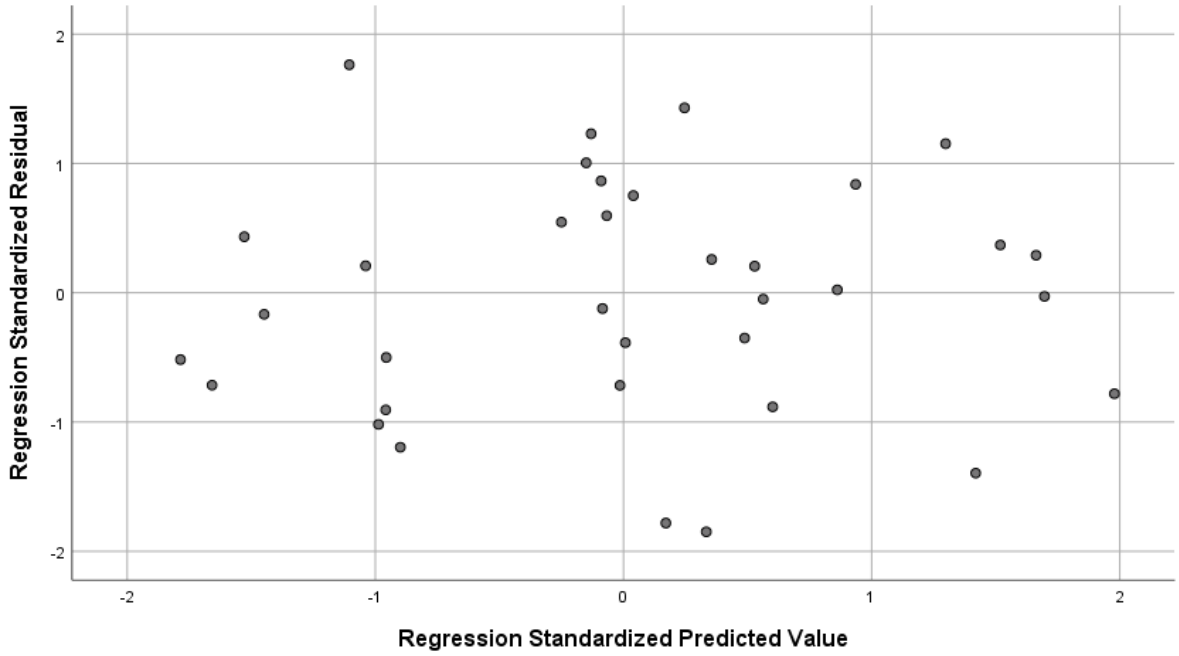
Table A15.

Analysis of Multicollinearity for all Independent Variables and the Outcome of Total PA Programme Adherence

Variable	Collinearity Statistic Tolerance	VIF
MoCA	.72	1.40
Age	.93	1.08
Years of education	.96	1.04
Baseline PA	.77	1.30
Number of medications	.70	1.42
Handgrip strength	.58	1.74
CES – D	.57	1.75
DemQoL	.72	1.40

Figure A14.

Homoscedasticity for all Study Variables for the Outcome of Total PA Programme Adherence



Appendix CC: Study 2 multicollinearity and homoscedasticity for independent variables and class adherence

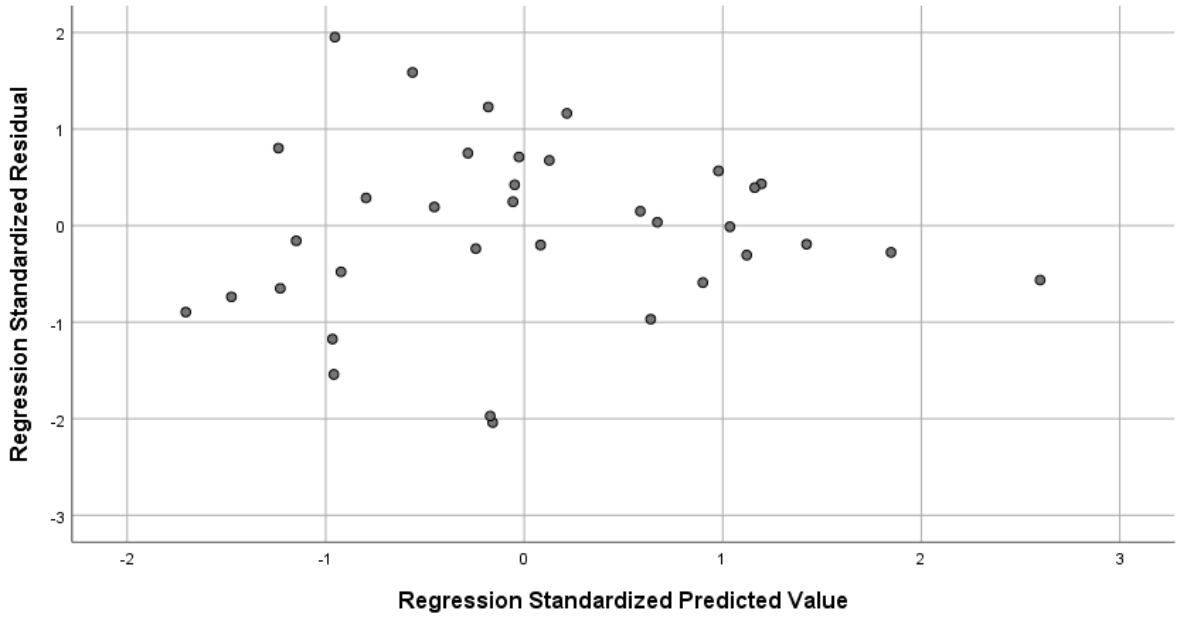
Table A16.

Analysis of Multicollinearity for all Independent Variables and the Outcome of Class Adherence

Variable	Collinearity Statistic Tolerance	VIF
MoCA	.72	1.40
Age	.93	1.08
Years of education	.70	1.42
Baseline PA	.96	1.04
Number of medications	.77	1.30
Handgrip strength	.70	1.42
CES – D	.58	1.74
DemQoL	.57	1.75

Figure A15.

Homoscedasticity for all Study Variables for the Outcome of Class Adherence



Appendix DD: Study 2 multicollinearity and homoscedasticity for independent variables and home - based adherence

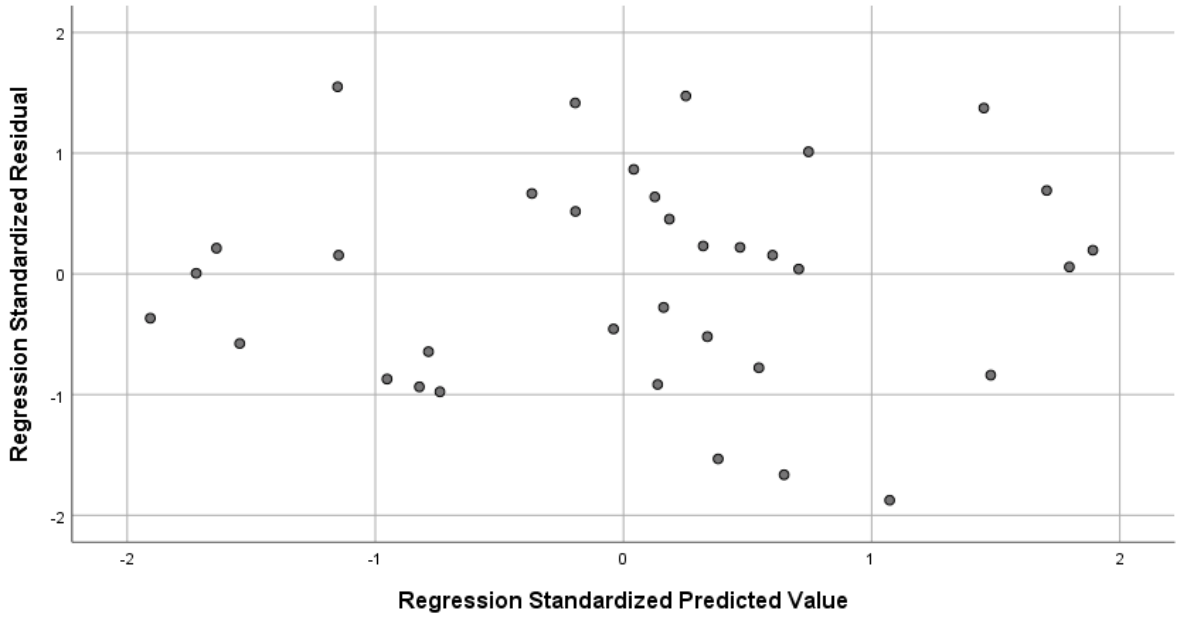
Table A17.

Analysis of Multicollinearity for all Independent Variables and the Outcome of Home - Based Adherence

Variable	Collinearity Statistic Tolerance	VIF
MoCA	.72	1.40
Age	.93	1.08
Years of education	.70	1.42
Baseline PA	.96	1.04
Number of medications	.77	1.30
Handgrip strength	.70	1.42
CES – D	.58	1.74
DemQoL	.570	1.754

Figure A16.

Homoscedasticity for all Study Variables for the Outcome of Class Adherence



Appendix EE: Study 2 interview topic guide

Interview Guide: Adherence to NeuroExercise

Hi _____, thank you for coming in to meet with me today. My name is Leona and I am a PhD student researching the factors that are related to exercising or not exercising in adults with Mild Cognitive Impairment.

The purpose of this interview is to get feedback on the exercise programme that you have just completed. We want to understand how you felt about all aspects of the programme, and how, or if, you were able to incorporate it into your everyday life. This information will be useful in designing future exercise programmes that are built around the specific needs of the people that they are designed for.

I expect that this interview will last for 166pprox.. 1 hour. It may be longer or shorter depending on how we get on, but you can stop the interview at any time if you feel that you want to.

I am recording this interview so that I can later transcribe it, it`s really to make sure that I capture everything that you are telling me and so that I don't forget or misinterpret anything that you say. Is this ok with you? Are you still happy to proceed with the interview? Do you have any questions before we get started?

1. Please tell me about yourself and how you came to be involved in this study: *(for those who were not interviewed at T0)*

2. I`d like to learn a little more about your feelings/ opinions about exercise: *(only for those who were not interviewed at T0)* . So now I`d like for us to talk a little about exercise:

How much exercise where you doing before this study?

Do you think exercise is good for you? In what way/ what are the benefits?

Do you think that there are benefits to you?

Do you exercise? How? (mode/frequency/ duration/ outdoors/ alone)

Do you know what the recommended guidelines are? If so, where did you hear about them?

Do you think intensity matters? How?

How do you think MCI impacts on your exercise habits?

What helps/ hinders you to exercise now?

3. Lead into MCI…. Please tell me about your experience of living with MCI? What is it like for you?: *(for those who were not interviewed at T0)*

Have you received a diagnosis? When?

How did you feel when you received a diagnosis?

How does MCI affect your daily activities? Differences before and after?

4. Now I just want to ask you about this study (i.e. the exercise programme you are part of) and your experience of participating in it?

What did you think about the programme?

What did you like/ dislike about the exercise programme?

Were you able to complete most of the sessions

How did you feel about how the intervention was administered? (time commitment/ location/ group setting Vs exercising at home)

Were there any barriers to completing/ attending sessions?

What helped you?

What were the main differences between attending class and homme sessions? Which did you prefer and why?

Will you continue to exercise to the same level after the intervention?

6. Recap…..Is there anything you would like to ask me?

Thank you very much for participating in this study. I hope it has been a positive experience.

Appendix FF: Study 2 example of early line by line coding

Table A17.

Example of line-by-line coding

Data extract units of data (interview transcripts)	Early descriptive codes/ line by line coding
Example 1: "I stopped playing when I was about 45, I played until I was 45 but at that time we were running seven or eight teams in the club. I am 22 years retired, I retired in 1995, the best thing I ever did in one way, and thinking back the thing that struck me was the fact that I... Sorry, there was a great group of fellows retired with me and we played golf together and then I had trouble with my leg and couldn't play the golf. I was saying to myself with the dementia aspect, or the memory, did I stop using or functioning as much, although I don't think I did too much, I am just thinking was it the right thing to do…..More than anything I think, and Pat died, and I became the only guy in the house and the only person I had to talk to was myself and I was taking that as an aspect of it as well. Although actually, I absolutely feel the year I have done here, I think it has stood me really well. I think I am a little more positive about it and a little less fearful, obviously I don't want to end up with dementia and not know my own name, but I think as long as I can keep myself fit, the fitness aspect of it was frightening, I felt absolutely horrific…. That had a big time, a big effect on me because I had stopped doing that type of thing".	*Being injured* *Being concerned about health* *Fitness* *Being anxious about memory* *Being alone* *Decline* *Fearing decline/ fearing dementia* *Positive experience of intervention* *Fighting decline* *Being inactive/ unfit*
Example 2: "Well I`m feeling it more now, and I suppose that's to be expected. But I went up on the bank holiday week- end to the daughter of a friend of mine, she lives up in X, and her mother and father were with me, and we had a lovely time, but… I got my medication all mixed up and I had been unsure, I had to go to the chemist, I`m terrible for putting things off, but I will have to go to get them sorted out again. And I don't know whether I was very anxious because I was afraid… I had changed chemists because the one that the one nearest to me would be better as this gets progressive anyway (referring to MCI) and em… they packed it all up completely different to what I was used to so that was my fault, but it went on, kid of… I was up and down during the days trying to get it sorted and eventually I just went off on the trip without really sorting it, and I didn't take all of my medication and I`m beginning to worry about it now. Well, I got a shock initially when it… when they actually said it (MCI diagnosis). But in actual fact I was very anxious before I even got to that session, and I kind of em… closed my eyes for a minute and I said… I didn't feel so anxious anymore. I kind of knew really that I wasn't getting any better and I`m not getting any better here still because I got mixed up now this morning and… I did get up early, walked the dog, came home, got involved with a man looking for the graveyard, and em… everything just seemed to… I mean I was up at… ten past seven".	*Getting older/ ageing* *MCI & Confusion* *Polypharmacy* *MCI, fear & anxiety* *Illness related anxiety* *Not getting better/ accepting decline* *No benefit of intervention on MCI*

Appendix GG: Study 2 example of early theme development

Table A18.

Example of Early Theme Development

Theme	Sub – theme	Code
Home sessions	Confusion/ misunderstanding	*Being confused regarding home session commitments*
	Personal motivation	*"Boring"*
		Not good at doing home sessions
		Needing exercise/ habitual exerciser
		Being accountable to staff motivated adherence/ needing incentive
		Organising/ scheduling increased adherence/ setting aside time
		Found partner for home sessions
		Home adherence tapered off
	Needing support/ structure	*"Not keen to do it on my own"*
		Scheduled class sessions easier to adhere to
		Difficulty adhering alone/ needing supervision
		setting own structure (reminders)
		Tracking exercise helped focus home adherence
		Class sessions motivated home sessions (through increased fitness)
	Practical barriers	*Bad weather a barrier*
		No difference "living normally" (already walk dog every day/ had exercise routine)
		Illness
		Demands on time as barrier "things are hectic"

Getting distracted at home

Appendix HH: Study 2 example of early theme of "needing support"

Table A19.

An example of an early latent theme, "Needing support".

Latent theme	Theme	sub – theme	Exemplar quote
Needing or having support	Practical support	Needing structure/ routine	*"I think routine is terribly important and to set up a routine and to incorporate exercise, a walking exercise or some exercise in that routine. I would have a routine". 027*
		Needing guidance/ supervision	*"But the whole stream of that… I`d tried gyms twice and I couldn't ever get anybody to help me once I`d joined, and I`d leave it, do you know what I mean? And I was always more afraid of like that… tears and torn ankles, I do different things, and I wanted supervision so the idea of a supervised" 035*
		MCI related confusion	*" I didn't have that (home sessions). I don't remember it." 030*
	Social/group support	Group support	*"I think the team were very focused, and very encouraging. Also, the people who were also on the programme, there was a great camaraderie among us, and we were kind of saying what we were doing or not doing. So, whether it was walking the dog or walking up the hills or jogging, that motivated you to see how you do the next week. So, it was a combination of things." 027*
		Enjoyment	*" I found it very good, I enjoyed it, it encouraged me to do more exercise." 027*
		making friends	*" I made some very good friends among the people there and among the staff. They were terrific staff." 030*