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PROTOCOL

Piloting a complex intervention involving physical exercise, cognitive training and socialising to delay the onset of dementia in mild cognitive impairment.

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Introduction

Dementia

Dementia is a common debilitating illness which has devastating effects on sufferers and carers alike. The cost to individuals and society is likely to rise as the population of older adults increases [Ferri *et al.* 2005]. Globally more than 25 million people are affected by dementia which is set to rise to 40 million by 2020 and to continue doubling in prevalence every 20 years. Dementia is characterised by acquired cognitive deficits sufficient to impair activities of daily living. Early diagnosis and effective treatment offers hope for reducing the negative impact of dementia. There is currently no cure for the leading causes of dementia which include Alzheimer's disease and vascular disease. Care needs for those affected by dementia are primarily determined by physical impairment, cognitive deficits, social isolation and psychological symptoms (depression). Forty percent of residents in residential care suffer significant cognitive impairment and this rises to 80% in nursing care. Arresting the progression of cognitive decline and delaying the onset of dementia will improve quality of life for patients and reduce the cost of care. Currently the average cost of residential care is approximately £800 a week and therefore one year's delay to institutionalisation could save £42 000 per person per year (Heywood and Turner).

Mild Cognitive Impairment

Mild cognitive impairment is the most prevalent high risk state for the development of dementia. It is characterised by impairment in one or more cognitive domains, such as memory or attention, while performance of everyday activities is preserved. Four subtypes of MCI have been described. Amnestic MCI-single domain (AMCI) is characterised by isolated episodic memory impairment in the absence of other obvious cognitive or behavioural deficits and not related to pre-existing physical or emotional disorders. The current diagnostic criteria for AMCI include (1) memory complaint corroborated by an informant, (2) objective memory impairment for age (3) essentially preserved general cognitive function, (4) largely intact functional activities, and (5) not demented [Petersen 2004]. AMCI appears to represent a high-risk and prodromal state for AD with a 10 to 15% annual conversion rate to dementia compared to 1-2% in healthy elderly; longitudinal studies reveal a 80% dementia conversion rate after 6 years

[Petersen *et al.* 1999;Petersen *et al.* 2001;Fischer *et al.* 2007;Petersen 2004]. The other subtypes of MCI include amnestic MCI-multiple domains, non-amnestic MCI-single domain and non-amnestic MCI-multiple domains; each subtype respectively considered prodromal for AD or vascular dementia; dementia with Lewy bodies or frontotemporal dementia; dementia with Lewy body or vascular dementia [Petersen 2004]. Not all AMCI convert to AD but it appears to be a strong and prevalent risk indicator [Fischer, Jungwirth, Zehetmayer, Weissgram, Hoenigschnabl, Gelpi, Krampla, and Tragl 2007].

Physical exercise

Regular participation in exercise reduces the risk of dementia, keeping older adults independent. Lower incidences for both the most prevalent cause of dementia, Alzheimer's disease, as well as all other causes are associated with physical activity [Rovio *et al.* 2005;Lytle *et al.* 2004;Abbott *et al.* 2004]. The majority of older adults do not exercise however, regular exercise can significantly benefit older people with improvements in heart and lung function, balance, coordination, mood and quality of life (Grove and Spier 1999; Dishman 1994). The barriers to exercise in older adults include limited access to programs and facilities, lack of support and low awareness of benefits. Evidence suggests that regular exercise for at least 30 minutes at a predetermined moderate intensity (65-77% of maximum heart rate) may be more beneficial than unsupervised exercise in improving general cardiovascular fitness. The most effective exercise intensity (70 to 85% of maximum heart rate) may be more beneficial but is associated with increased risk of injury and high drop out rates due to discomfort [Juneau *et al.* 1987]. Heart rate monitors which provide real time feedback via sound or vibratory alerts can be used to supervise and pace physical exercise as far as intensity and duration is concerned. Exercise intensity can also be adjusted as fitness levels increase. Systematic analysis of available evidence on physical exercise programs have identified certain design aspects which are associated with larger treatment effects and better long term adherence. Home based programs have better long term adherence and centre based programs have better short term effects, whilst high intensity exercise on 3 days a week had better adherence than low intensity on 5 days a week [Ashworth *et al.* 2005;King *et al.* 1995]. Adherence and outcomes are further

improved by regular telephone contact, goal setting and relapse prevention training.

Cognitive exercise

Participation in cognitively stimulating activities and occupations is associated with reduced risk of cognitive decline in later life [Wilson *et al.* 2007;Wilson *et al.* 2002;Schooler *et al.* 1999]. Participation in cognitively stimulating leisure activities decreases the risk of vascular or AD related cognitive impairment and dementia [Schooler and Mulatu 2001;Verghese *et al.* 2009;Verghese *et al.* 2006;Verghese *et al.* 2003]. Cognitive training benefits healthy individuals and also appears beneficial in those with cognitive impairment and dementia. In healthy elderly, improvements in processing speed, episodic memory, mental flexibility and overall cognitive function appear related to the average intensity of exercise activities as well as to the diversity of exercises [Angevaren *et al.* 2007]. Reasoning training appears to benefit everyday activity ability [Willis *et al.* 2006;Ball *et al.* 2002].

Cognitive training can be achieved via tasks and exercises designed to train a specific area such as attention or to simultaneously train a number of areas. Examples of tasks include letter cancelation tasks (searching and crossing out certain letter), pattern recognition (finding a pattern in word sequences) and choice reaction tasks (pressing a button when a target appears on a computer screen). Recent evidence suggests that training related cognitive improvement depends on the amount of time spent in training [Jaeggi *et al.* 2008]. Cognitive training can be presented and monitored by using computers. Training on complex computer games has shown to benefit executive functioning and working memory [Basak *et al.* 2008]. Computer based training allows data capture and feedback of performance. Meta-analysis of memory training studies in the elderly revealed that better results are associated with training in small groups, sessions of less than 90 minutes, and when pre-training on certain aspects of memory, such as visual imagery training, is included [Verhaeghen *et al.* 1992]. Older adults appear to show a more rapid loss of training related improvements post training and may require regular booster practice sessions to maintain benefits long-term [Li *et al.* 2008;Cherry *et al.* 2009]. This could potentially be achieved by engaging in cognitively stimulating leisure pursuits.

Social exercise

Socialising exercises a number of cognitive skills including memory (facial recognition, naming, episodic encoding and recall), attention (divided attention for simultaneous monitoring of non-verbal and verbal communication) and executive control of these functions. Supervised socialising in groups provides opportunity to involve participants in cognitively stimulating activities that also promote emotional well-being. Groups based strength and coordination training improves physical parameters but also improves quality of life and provides cognitive stimulation (McLaughlin 1995; Hickey 1992). Health promoting information, such as the benefits of exercise and dietary advice, can be provided in group settings. The social cohesion that develops in groups increases compliance and provides support for participants. Group settings can also be used to introduce activities that diversify the everyday activities of participants and thereby provide cognitive stimulation.

Mutimodal intervention programs

Multimodal intervention programmes which include physical exercise, cognitive training and socialising are thought to be the most likely to delay the need for care in those at risk (Oswald et al. 2007). Studies have reported improvement in physical status, functional abilities, mood and engagement in physical activity following multimodal multi-sensory interventions (Heyn 2003; Oswald et al. 2007). A combination of physical and cognitive exercise appears most beneficial, leading to improved independence and mood.

Implementing and monitoring interventions with information technology

Information technology (IT), including personal computers and the internet, has the potential to play a pivotal role in delivering a multimodal intervention program to those at increased risk of developing dementia. With recent advances in technology, interventions can be delivered to isolated people with no pre-existing computing skills, and at affordable cost. Supervision of participation can be achieved by connecting participants in real time with facilitators via the internet and video teleconferencing (VTC). With VTC communication takes place over the internet with a screen and camera on both ends allowing both verbal

and non-verbal communication. Initial findings indicate that VTC is acceptable, effective and feasible in assessing cognition and delivering cognitive interventions to older people with cognitive deficits [Poon *et al.* 2005;Cullum *et al.* 2006]. Online cognitive training can be facilitated via remote desktop applications, whereby the facilitator remotely controls the computer used by the participant. VTC also provides the opportunity for participants to socialise with other participants. Electronic heart rate monitors can provide real time feedback of performance which can be used to pace exercise at desired intensity levels whilst guarding against over exertion.

Motivation and adherence to exercise regimes

Motivation appears the best indicator of adherence to exercise programs. Exercise facilitation by a health professional exercise instructor, sensitive to the life changes experienced by older adults and knowledgeable about exercise, can improve adherence by motivating participants (Gillett 1993). Building up an exercise related social group and peer support also increases compliance (Pfister-Minogue 1993). Other motivational factors include simplicity, repetition, cognitive motivational techniques, individually tailored regimes and taped or written instructions (Terpstra 1992).

Behaviour interventions can be used to increase behavioural flexibility and personal mastery which then in turn increases the likelihood of behavioural change such as engaging in health promoting novel pursuits. The Do-Something-Different (DSD) program has been developed to increase behavioural flexibility and has been used successfully to alter eating and occupational behaviour (ref B Fletcher). With the DSD program participants are issued with a list of DSD activities presented on cards contained in a pack. A card is drawn at random at a set time or in a specified situation and the participant then engages in the suggested activity. The activities are not specifically related to the desired behaviour.

Measuring changes in brain function with near infrared spectroscopy heamoenephalography (NIRS-HEG)

Increased cardiovascular fitness following a 6 month physical training program has been shown to improve attention and increase brain activation as measured by functional magnetic resonance imaging (fMRI) in healthy elderly people

[Colcombe *et al.* 2004]. The areas of increased activation (prefrontal and parietal cortex) are closely related to attentional function. The effects of cardiovascular fitness training on brain activation in MCI have not been studied and it is therefore not known if similar changes occur as in healthy elderly. This can be studied by NIRS-HEG which is a relatively inexpensive bedside technique measuring changes in brain perfusion/activation.

Based on the available findings, indicating beneficial effects of physical exercise, cognitive training and socialising, we plan a feasibility study to develop and implement a multimodal intervention program in MCI aimed at improving cognition, cardiovascular fitness and quality of life. We plan to design, develop and assess cognitive, physical fitness and social interventions suitable for a group and individual participation and implemented and monitored by IT. We also plan to study the effects of these interventions on brain activation using NIRS-HEG.

Study Aims

- To design and implement a multimodal intervention in MCI subjects aimed at delaying the onset of dementia and therefore the need for care.
- To establish treatment protocols for physical, cognitive and social exercise.
- To study treatment effects and determine the sample size for a future randomized controlled trail.
- To prospectively follow MCI patients to monitor the rate of conversion to dementia and to compare rate of conversion to historic controls.

Methods

Subjects

MCI Subjects

We plan to recruit 128 patients diagnosed with MCI (amnestic and non-amnestic) from the Derwent Memory Clinic at St Margaret's and Princess Alexandra Hospitals, Essex, UK. The general practitioner of all subjects will be informed of their participation in the study.

Inclusion criteria for patients with MCI

1. Patients fulfilling criteria for AMCI [Petersen, Doody, Kurz, Mohs, Morris, Rabins, Ritchie, Rossor, Thal, and Winblad 2001]:
    i. Memory impairment for age and education
    ii. No impairment in other cognitive domains
    iii. Normal social activities
    iv. Patient is not demented
2. Patients diagnosed with other subtypes of MCI (cognitive impairment in one or more non-memory domain)
3. Sedentary lifestyle with no regular participation in physical exercise defined as two or three times a week for at least 20 minutes duration, or participation in active organised sport more than once a week, in the previous six months.
4. Willing and able to give informed consent.
5. Availability and access to safe exercise environments, such as paths or roads with sidewalks for walking or cycling.
6. At low risk from serious adverse effects from increased physical activity as indicated by performance on the revised Physical activity readiness questionnaire (PAR-Q).

Exclusion criteria for patients with MCI

1. Type 1 (insulin dependent) diabetes mellitus.
2. Blood pressure above 160/100 mmHg.
3. Body weight more than 140% of ideal body weight.
4. Musculoskeletal or other medical problems preventing safe participation in regular moderate intensity exercise (65-77% of predicted maximum heart rate). This will include a resting tachycardia (heart rate above 100 bpm) and history of myocardial infarction or unstable angina within the last month.

Participants with modifiable exclusion criteria will be reconsidered after successful management. Patients will be referred for medical /cardiological review and management prior to commencing exercise if indicated by the PAR-Q and the intervention will be guided by the PARmed-X.

Participants taking medications affecting heart rate will need to be on a stable dosing regime for 3 months prior to commencing in order to control for potential spurious results on fitness measures caused by these treatments.

Historic MCI control subjects

Historic MCI control subjects will be identified from the Derwent Memory Clinic data base which contains data on more than 400 MCI patients. These controls will be used in the analyses for comparison of outcomes in treated and untreated patients. Controls will be matched on the following criteria:

- age
- gender
- MMSE score
- education

A placebo social contact control group will not be included as previous studies indicate no difference between social-contact and no-contact control groups on cognitive or functional measures [Willis, Tennstedt, Marsiske, Ball, Elias, Koepke, Morris, Rebok, Unverzagt, Stoddard, and Wright 2006;Willis *et al.* 1983;Clark *et al.* 1997].

Clinical assessment

The standard clinical workup includes a detailed history of cognitive impairment from the patient and an informant, a full psychiatric history, a mental state examination, a physical examination with an emphasis on neurological examination and a neuropsychological test battery. Measures/tests included are:

- National Adult Reading Test (NART) [Nelson 1991]
- The Mini-Mental state examination (MMSE) [Folstein *et al.* 1975]

- Cambridge Cognitive Examination (CAMCOG-R) [Huppert *et al.* 1995]
- Logical Memory Test [Wechsler 1997]
- Halstead Trail Making test (TMT) [Davies 1968]
- The Clinical Dementia Rating (CDR) [Berl 1988]
- Clifton assessment procedure for the elderly, Behavioural rating scale only (CAPE) [Pattie and Gilleard 1979]
- 15 item Geriatric Depression Scale (GDS-15) [Yesavage *et al.* 1982]

Trail design

We plan a longitudinal study where participants will serve as their own controls. Participants will start with **phase one** during which they will engage in 12 weeks DSD program designed to increase behavioural flexibility and therefore adherence with the planned physical, cognitive and social interventions in phase two. This will be followed by **phase two** during which they will take part in a 12 weeks physical, cognitive and social activity program. Outcome measures will therefore be collected at three time-points: baseline (Time 1), midway, week 12 (Time 2) and following phase 2 (Time 3).

Outcome measures

The main outcome is the development and implementation of the multimodal intervention program. Success will be measured as participant compliance during the program (% of participants compliant with intervention program), feedback on the interventions and continued engagement after completion.

Secondary outcomes include measures of cardiovascular fitness, improvements on neurocognitive testing, everyday activities and quality of life.

Cardiovascular fitness, cognitive performance, activities of daily living and brain activation will be measured at baseline, after 12 weeks of phase 1 and at the end of phase 2.

1. Cardiovascular fitness measure

Cardiovascular fitness will be measured with a modified **Siconolfi Step Test** which has been validated in clinical samples [Marcora *et al.* 2007;Siconolfi *et al.* 1985]. The original test has a step height of 10 inches but we have found that this raises heart rate above 77% of predicted maximum heart rate, making it unsuitable for sub-maximal fitness testing. Our participants will step up and down a 6 inch (152mm) bench for three minutes, completing 17 (step up and down) cycles per minute. Heart rate (HR) will be measured during, immediately after completion of step -test and at one minute intervals for three minutes. The step-test will be paced using a metronome to ensure standard application. This sub-maximal stress test has a very low risk when combined with an exercise safety questionnaire such as the revised **Physical activity readiness questionnaire** (PAR-Q). Waist circumference and BMI (weight (kg) / height^2 (m)) will also be recorded.

2. Cognitive measures

Participants will complete the following cognitive measures:

- **Visual and auditory divided attention task** [Dannhauser *et al.* 2005]. This measures speed of processing and attentional set shifting.
- **Verbal episodic encoding and recognition task** [Dannhauser *et al.* 2008]
- **Halstead Trail Making test** (TMT) [Davies 1968]. This measures speed of processing (reaction time) and accuracy (corrected recognition).
- **Verbal fluency** [Lezack, 1995]
- **Working memory tests**: digit span forwards/ backwards [Miller, 1956]
- **Verbal Reasoning and Working Memory** [e.g. Hitch, 1976].

The standard neuropsychological test battery described above will be repeated annually as part of the standard clinical procedure in the memory clinic. This will provide long term follow-up data on all participants until they either make a full recovery or convert to dementia.

3. Measures of quality of life and everyday activities

Quality of life will be measured on the World Health Organization Quality of Life (WHOQOL) – BREF and change in every day activities on the Alzheimers' Disease Cooperative Study MCI Activities of Daily Living Scale (ADCS-MCI-ADL)[Galasko *et al.* 1997].

4. Measure of brain activation /perfusion with near infrared spectroscopy heamoenephalography (NIRS-HEG)

We will collect brain activation data from all participants at the three time points during administration of the divided attention paradigm which runs for 5 minutes.

We will use a CE marked Oxymon Mk (Artinis, Netherlans) to measure changes in light attenuation at four discrete wavelengths (775,825,,850 and 905 nm) using four laser diodes as light sources and photon multiplier tube as detector. Sensors will be placed over the left prefrontal (F3), the superior parietal (P3) and the occipital cortex (O1) and the right frontal pole (Fp2), according to the international 10-10 system developed for EEG. This portable system does not involve any ionising radiation.

Treatment sessions

1. Physical exercise

Participants will be asked to complete 36 training sessions at a frequency of two to three per week. Half of all the groups (Feedback participants, **FP-group**) will be randomly allocated sound and vibration feedback to help them to stay in a predetermined training zone. Heart rate for the moderate training zone (less than 60% of VO2 max; 65-77% of maximum heart rate) will be determined for each participant from their predicted maximum heart rate (HR max = 220 – age). The other groups will not receive feedback but heart rate will still be measured (Monitoring participants, **MP-group**); this group will receive instruction on utilising subjective reports of effort to guide their optimal level of effort. Assignment to FP-group and MP-group will alternate so equal numbers are obtained for statistical comparison. In addition each participant will be issued

with a large poster providing visual instructions of how to use the equipment and do a 10 minute warm-up routine (Appendix B). They will receive home visits and supervision at sessions 1, 3, 8, 14 and 20 (see Appendix C for a timelines). They will also receive regular weekly telephone contact to provide support and monitor progress. Heart rate monitors (Oregon Scientific SE102I) measure electrocardiographic signals via a chest strap. Heart rate zones are programmed into the monitors and auditory signals and vibration of the monitor attached to the arm provides feedback and alerts the patient when heart rate is outside the preset parameters. Heart rate monitors will be programmed by the research team. An electronic data logger (Oregon Scientific WM100) which collects continuous data from the chest strap will be activated during activity so that heart rate data during physical activity is captured for later analysis.

Patients taking beta blocker medication will exercise at a heart rate equivalent to a specific effort (14 on the Borg scale) as these medications lower heart rate and result in sub optimum training when training zones are calculated as described above [Tabet *et al.* 2008;Borg 1970]. The relevant rate will be determined during the initial supervised walking sessions.

2. Cognitive training

In addition to Physical exercise participants will be asked to complete 12 cognitive training sessions at a frequency of 1-2 per week. Training will take place on an individual and group basis, both supervised and unsupervised. The duration of training sessions will vary from 30 to 90 minutes depending on the type of training. A variety of training techniques will be employed with the aim to improve specific cognitive components such as attention, speed of processing, working memory, problem solving and reasoning. For training we will use the program developed by Lumosity (www.lumosity.com). Centre-group participants will have access to online resources either at training centres provided and staffed by the Adult Community Learning (ACL) Service in Essex, or at home. Online-group participants will be provided with access to computers and the internet for the duration of the study. These participants will not require any existing computing skills as all content will be accessed and supervised remotely by the researchers and ACL staff. Participation on the cognitive Lumosity program will be anonymised and data will be collected on the time and duration

of activity as well as performance. The Lumosity program provides feedback on performance and participants can do additional activities if they choose.

3. Socialising

Socialising will take place in groups of 8 for the centre based participants. Participants will attend for 12 weeks, a 2.5 hour long session at facilities provided by ACL Essex. All sessions will broadly follow the same format.

0-15 Minutes: Greeting and light chair based balance and stretching activities. These activities will be lead by a video prompt (video: Active Health 50+ from *Age Concern*) and monitored by research staff.

15-45 Minutes: Reporting on and presentation of completed tasks from previous week and advice on practicalities of tasks.

45 – 60 Minutes: Break

60 to 120 Minutes: Group based creative or physical activity.

120 to 150 Minutes: Feedback and relaxation training (video guided relaxation)

The first two group sessions will be used to introduce participants to each other and familiarise them with computers and using a mouse to facilitate the cognitive training sessions. The sessions will be lead by trained tutors and detailed instructions on the scope and sequencing of activities will be provided in a training manual. Creative and physical activities included are designed to stimulate cognition and emphasis is placed on variety and multi-sensory stimulation. Home activities described in detail in Appendix D. Group based activities described in detail in Appendix E.

Motivating adherence.

Participants will be made aware that specific persuasion techniques will be implemented to improve their long term commitment to physical activity, cognitive stimulation and socialising. These will include the principals of reciprocity, authority, scarcity, liking and social proof.

Each new group of participants will receive an introductory talk from an expert patient who has already undergone the training. The high level of similarity of the expert patient and recruited participants will provide social proof of the

anticipated success of planned activities. Participants will be informed that the 12 week wait before they start the program will be due to the popularity of the study. This will encourage herding which could enhance engagement due to perceived scarcity of opportunity. Participants will be informed of the cash value of the treatment they will receive (reciprocity). Participants will be made aware of the expertise of all the involved researchers (authority) and the researchers will receive specific instruction to makes them more likeable to participants. This will include instructions to encourage desirable or successful behaviour in the group setting whilst dealing with difficulties arising from training on an individual basis. Choices related to any part of the interventions will be kept to the minimum as increased choice is strongly associated with decreased engagement. The "fear message" which is the high risk of developing dementia in this study population will be accompanied by specific information on potential ways of reducing the risk in order to avoid future recruits from "blocking out" the message with problematic behaviour.

Implementation of DSD program during preparatory phase

Participants will be asked to complete DSD activities in order to increase their behavioural flexibility for the second phase of the program. They will complete a different DSD task everyday of the week for four weeks of the last 12-weeks of the control period (7 tasks a week x 4 weeks= 28 tasks). Tasks are not to be repeated and in order to provide some choice we provide a list of 36 tasks, which will enable participants to aviid some activities. They will do each activity once and then record the date, location any comments and assign a mark on a 4 point like-dislike scale (I enjoyed doing this activity: I agree strongly/agree/disagree/disagree strongly). This record will serve as a reminder that the activity has already been completed and will also aid in memorising the episode. The list of activities is listed in Appendix A

2. We would also like to measure the effects of the DSD on behavioural flexibility in the mild cognitive impairment patient group in order to see if the intervention alters

behaviour flexibility and if this correlates with the primary or secondary outcome measures, thereby allowing us to determine the effectivety of the DSD program. We plan to measure behavioural flexibility with an informant completed rating scale (FIT-720) consisting of 15 items which should take no longer than 5 minutes to complete. The FIT-720 is a standardised tool for assessing the gap between how a person sees their behaviours and how they are perceived by others. The questionnaire is completed by someone close to the participant who would be able to observe changes in behaviour. Please see version 1: dated 22nd January 2010.

Information technology resources

Online-group participants will be issued with personal computers (iMac 24 inch, Apple Computer) and a broadband internet connection (Business Broadband NET connection) activated over existing British Telecoms lines. The computers will be password protected and secured with a safety cable. Participants will be contacted by telephone prior to video teleconferencing sessions and will then agree to receive the call, thereby protecting privacy. Computers will be set up so that only named research staff will be able to connect remotely and facilitate use. Participants will not have free access to use the computers outside the programmed activities. Access to all other resources on the internet will be blocked but may be accessed if necessary by research staff during supervised sessions, particularly during the social activities. No personal information will be used or stored on the computers. The computers will be placed and removed by research staff. The internet connection and computer will be provided at no cost to participants for the 12 weeks of their participation in phase 2.

Centre group participants will have supervised access to computers at ACL centres provided under existing safety regulations and data protection policies.

Expected adverse events

The following adverse events are associated with the planned activities:

Physical training related

Overexertion

Headache

Sore / painful muscles

Chest pain
Low abdominal pain
Sprain
Strain
Muscle cramps
Fatigue
Blisters, soft tissue injury
Breathlessness
Exertional dyspnoea
Elevation of BP
Irregular heart beat
Palpitations
Nausea
Dizziness
Falls
Sunburn
Feeling very hot and perspiring profusely
Dehydration
Getting lost
Confusion
Wandering
Lack of coordination
Increased recovery time

Cognitive activity related

Headache
Fatigue
Wrist pain/strain from using mouse
Eye strain

Social activity related

Feelings of frustration
Social anxiety

Ethical approval

Ethical approval will be sought for the study from the local research ethics committee.

Statistical analysis

Subjects will serve as their own controls and data will be captured at baseline, following 12 weeks of DSD and at the end of phase two (study week 26). Continuous variables will be compared using paired t-tests and analyses of variance. All statistics will be analysed using SPSS / PC+ version 10.0 (Statistical Package for Social Sciences).

Sample Size.
The planned sample size (n=128) will enable us to detect a change of 0.25 standard deviations in the performance outcomes (details here) with 80% power at the 5% level of significance. The planned comparison between the community based /centre based groups (n=64) will enable us to detect a 0.5SD difference with 80% power at 5% significance. In this feasibility study, it is unlikely that this scale of change will be observed. More important will be our ability to estimate the potential size of the changes. In this case, with 128 subjects we can estimate the change to within +/- 17.5%SD (i.e. the width of the 95% CI will be 35%SD).

Analysis

The principle analysis will focus on the estimation of the change resulting from the intervention. This will be estimated by mean change and 95% CI. Supplementary analyses will employ Repeated Measures ANOVA

to examine the changes from Baseline, start of therapy to the end of therapy. These analyses will be extended to assess the role of background covariates, such as age, sex health status etc.

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