PROTOCOL

Physical Activity programmes for community dwelling people with mild to moderate dementia

Dementia **A**nd **P**hysical **A**ctivity - DAPA

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
BADL	Bristol Activities of Daily Living
BDNF	Brain derived neurotrophic factor
CRF	Case Report Form
CSSD	Cornell Scale for Depression in Dementia
CTU	Clinical Trials Unit
DeNDRoN	Dementia and Neurodegenerative Disease Research Network
DMEC	Data Monitoring and Ethics Committee
DSM	Diagnostic and Statistical Manual
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
MRC	Medical Research Council
MREC	Multicentre Research Ethics Committee
NICE	National Institute for Health and Clinical Excellence
NPI	Neuropsychiatric Inventory
PWD	Person with Dementia
QOL	Quality of Life
ROS	Reactive Oxygen Species
R&D	Research and Development
SAE	Serious adverse event
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit
ZBI	Zarit Burden Interview

1. Background

1.1 Epidemiology and burden of the condition

Dementia is a syndrome characterized by acquired progressive deterioration in memory, general cognitive function, self-care and personality. About half of cases are caused by Alzheimer's disease, while vascular dementia, mixed Alzheimer/Vascular dementia and Dementia with Lewy bodies are the other common causes. Mild dementia should be distinguished from mild cognitive impairment (MCI), a term used for people who experience more cognitive impairment than would be expected for their age, but unlike dementia, the impairment is not so severe as to interfere with activities of daily living. Although MCI is a risk factor for dementia, many people with MCI do not progress to dementia.

In the UK, it is estimated that more than 800,000 people have dementia, with an annual cost to the UK economy of £23 billion (Luengo-Fernandez et al 2010). In the next 30 years the number of people with dementia will double and costs will treble to more than £50 billion pa. Although the recent national dementia strategy for the UK (NDS 2009) calls for a focus on early diagnosis, treatment options for dementia are relatively limited, with no new drugs available since 2002. NICE (NICE 2011) recommends cholinesterase inhibitors (donepezil, galantamine and rivastigmine), but only for mild to moderate Alzheimer's disease (not for vascular dementia). The only other drug licensed in the UK is memantine, but is supported by NICE only for limited use in moderate to severe dementia, or in patients unable to tolerate cholinesterase inhibitors. In reality, for many people with mild to moderate dementia, a major focus of services after diagnosis is on carer training, family support, and indirect interventions to alleviate risk, such as home carers, day care, respite admissions, sitting services and carer support services.

1.2 Existing knowledge

The protective effects of moderate levels of physical activity on the progression of (subjective memory impairment) and mild cognitive impairment to dementia have been observed consistently in several large scale epidemiological studies (Geda et al 2010; Etgen et al 2010; Erikson et al 2009). Studies of transgenic Alzheimer mice and dogs suggest several potential mechanisms by which exercise may prevent the progression of dementia. Brain derived neurotrophic factor (BDNF) is stimulated by exercise in Alzheimer mice, leading to increased concentrations in many areas of the brain, including the hippocampus which is thought to have a key role in mediating some of the effects of dementia. In animal dementia models, effects on BDNF are observed 3-4 weeks after initiation of exercise, and translate into improvements in spatial memory which last for some period of time, but in the absence of an on-going exercise stimulus, begin to decline thereafter. Other effects of exercise include improved synaptic function, increased blood flow and neurogenesis (potentially of importance for the vascular dementias), stimulation of anabolic metabolism, improved mitochondrial ROS production and reduction of damaging beta amyloid effects. Encouragingly, recent epidemiological studies of autopsied human brain have shown positive associations between physical activity and the volume of the hippocampus and other areas of the central nervous system sensitive to pathological change in dementia, all of which are targets considered

important for treatment (Deslandes et al 2009).

These studies provide encouraging evidence, and some guide to the type, dose and duration of exercise required to benefit people with, or at risk of, dementia. Moderate intensity activity is the prime candidate, defined as exercise 3 times a week. Animal model studies are limited to aerobic type exercise which raises the heart rate and blood flow. Interventional studies in humans are scarce, but a few, predominantly in mild cognitive impairment and memory impairment, provide important data to guide the development of an exercise programme. The most pertinent Cochrane Review (Forbes et al. 2008) included 4 studies, but could draw no conclusion about the effectiveness of interventions. Since the last update (2007/8) Baker et al tested high intensity aerobic training (>75% of heart rate max, 4* times a week, ~ 1hr per session, 6 months) in people with mild cognitive impairment, demonstrating improvements in biomarkers associated with Alzheimer's as well as tests of executive and other aspects of cognitive function. There was some evidence of a differential effect between men and women. No follow up data have been published and the sustainability is unknown.

Supervised walking programmes are possible for people with mild cognitive impairment, but have not been tested in people with more established dementia. In a randomised controlled trial of a year long, twice weekly walking programme, there was no overall benefit in terms of cognitive function, although the effect may vary by gender (Weuve et al 2004; Abbott et al 2004). Lautenschlager et al (2008) studied people with subjective memory impairment (a pre-cursor to Alzheimer's disease) and demonstrated modest improvements in cognition resulting from a 24 week physical activity intervention. Encouragingly, improvements were sustained over an 18 month follow up period. In a pilot for the LIFE study, which is testing twice weekly physical activity over a 12 month period, improving physical activity was related to improvements in cognitive status in people with normal cognition (LIFE Study Team 2006).

Resistance (or strength) training is an important component of many interventions targeted at geriatric syndromes (of which cognitive impairment is one), but has received less attention. Strength training may improve cognition by altering levels of homocysteine and insulin like growth factor 1, but more importantly, will improve physical functioning, reduce fall risk, agitation and possibly some behavioural problems (Liu Ambrose et al 2009). Logsdon et al (2009) have reviewed approaches to making physical activity accessible to older adults with memory loss, using many techniques that we currently use within our OPERA intervention.

Although much of the current evidence informing the choice of type of exercise to improve cognition is derived from animal studies, and studies of healthy humans or people with MCI, it is widely recognised that exercise has the potential to be a very important intervention in the management of people with dementia. Exercise will improve physical fitness and functioning, and selection of the right type of exercise stimulus can reduce fall risk, improve mobility and reduce cardiovascular risk factors, just as in people who are not cognitively impaired.

Systematic reviews

For the DAPA study, we will carry out a systematic review of interventions to improve cognition through exercise. We will investigate issues of dose of exercise by extracting information on duration, intensity and type of exercise provided. As before, we will adhere to best practice in carrying out systematic reviews (Higgins & Green 2009). As depression and cognitive impairment are linked, and share similar biological pathways (and based on our knowledge of the literature), we do not anticipate that the intervention will change substantially as a result of this new review (see below for links to previous trial).

1.3 Research Objectives

Our objectives are to:

1. Refine an existing intervention for delivery to community dwelling populations of people with dementia, including an update/expansion of a systematic review completed as part of the HTA funded Older People's Exercise in Residential Accommodation (OPERA (HTA 06/02/01)) trial and user involvement processes.

2. Pilot critical procedures prior to the trial.

3. Complete a definitive, individually randomised controlled trial to estimate the effectiveness of the DAPA programme in addition to usual care on *cognitive impairment* (primary outcome), *function and quality of life* (secondary outcomes) in people with mild or moderate dementia, and for carers, carer burden (secondary outcome).

1.4 Good Clinical Practice

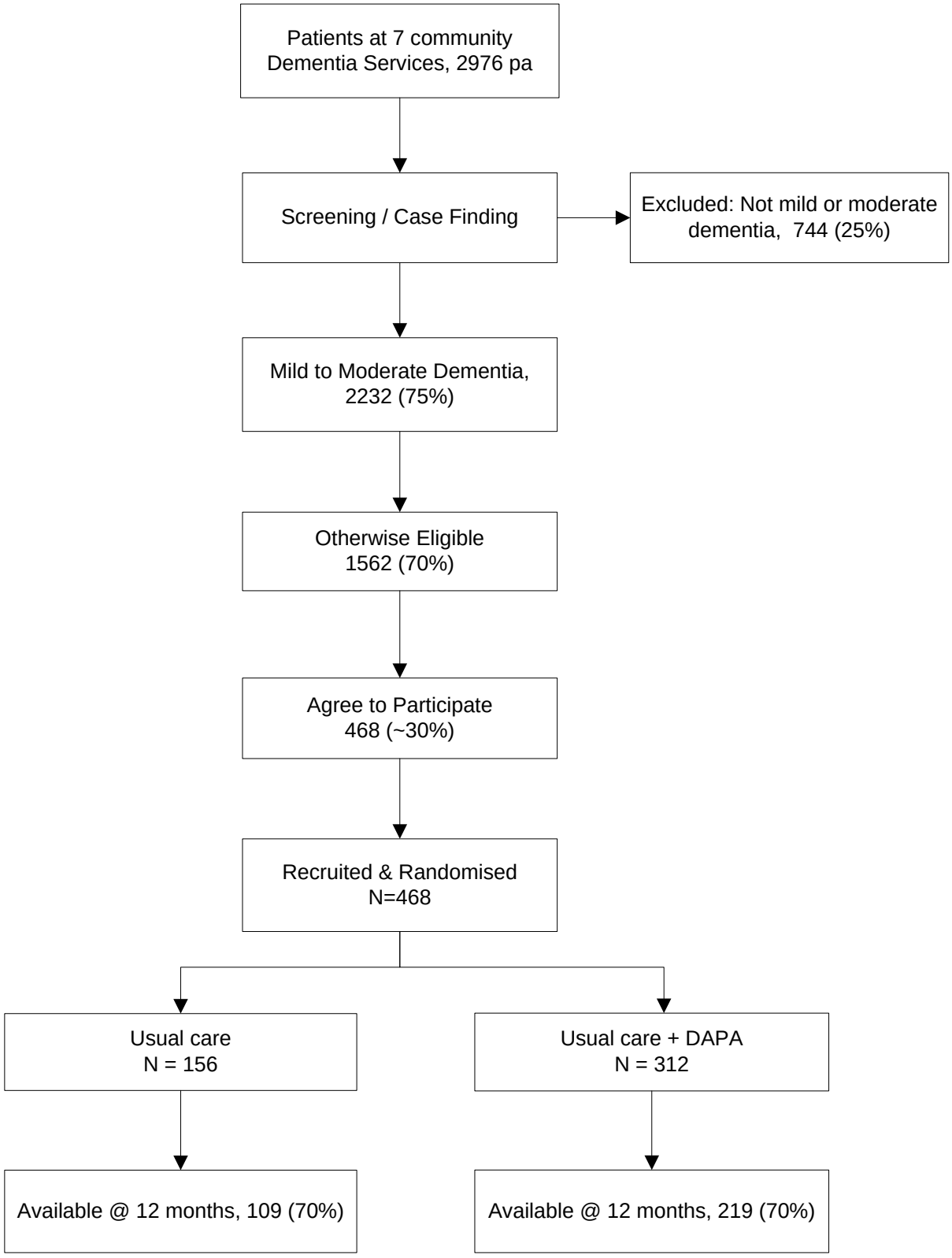
The trial will be carried out in accordance with the Medical Research Council (MRC) Good Clinical Practice Guidelines, and applicable UK legislation.

2. TRIAL DESIGN

2.1 Trial summary

The DAPA trial aims to establish whether exercise is effective in treating against functional and cognitive decline in community dwelling adults with mild to moderate dementia. It is a randomised controlled trial comparing an additional structured exercise regimen to best practice usual care. The trial will include a pilot phase for the refinement of an existing intervention previously used in the OPERA trial (ISRCTN43769277). The structured exercise intervention will be carried out over a 4 month period with a transition to community based sustainable physical activity.

Figure 1 Trial flow diagram



2.2 Objectives

2.2.1 Primary objective

The primary objective of this trial is to undertake a definitive randomised controlled trial to estimate the effects of an exercise/physical activity intervention that is feasible for delivery within the current constraints of National Health Service delivery.

2.2.2 Secondary objective

Secondary objectives of the study are to

- Complete a parallel cost study and conduct an economic analysis from a healthcare and societal perspective.
- Investigate intervention effects in pre-defined sub-groups of gender and dementia severity.

2.3 Outcome Measures

2.3.1 Primary

The primary outcome measures will be cognition and function.

Dementia is a complex multi-faceted condition with deterioration in multiple domains. Cognitive deterioration is recognised as a core feature of the condition, and leads to deterioration in functional ability. Both cognition and functional deterioration have been shown to predict carer stress and increased costs in dementia, and hence function is also an important outcome. Cognitive function will be measured using a validated and widely used measure, the ADAS-Cog (Mohs et al 1997).

Function will be measured using the Bristol Activity of Daily Living scale (BADL Bucks et al 1996). Both scales have established validity and sensitivity to change, and have been used widely in interventional research studies in dementia (Black et al 2009). Existing data allow clear predictions of deterioration over time in both scales, and calculation of clinically important differences between groups (Molner et al 2009).

The outcomes are all among those recommended by a consensus recommendation of outcome scales for non-drug interventional studies in dementia (Moniz-Cook et al 2008). We will test the acceptability of the outcome measure package in the pilot study, including issues concerning the need for, and consistency of, proxy completion.

2.3.2 Others

Other outcomes will include:

- Health-related quality of life (Euro-QoL [EQ-5D] EuroQoL Group 1990)
- Dementia quality of life (Quality of Life in Alzheimer's Disease [QoL-AD] Logsdon et al 1999),
- Behavioural symptoms (Neuropsychiatric Inventory [NPI] Cummings et al 1994),
- Carer burden (Zarit Burden Interview [ZBI] Zarit et al 1980).
- Self-reported falls and fractures.

2.4 Power and Sample Size

Proposed sample size

The sample size will be 468 participants. We have used a between group difference of 2.45 points on the ADAS-COG, baseline standard deviation of 7.8 (equating to a standardised effect size of 0.31), 80% power, $p<0.05$, and inflation to account for therapist effects using an ICC of 0.01 (i.e. design effect of 1.04), with the assumption that there will be on average 5 patients within each group session.

The number of cases needed for final analysis at 12 months is 375. We have inflated to account for a loss to follow up of 20%, including 10% attrition attributable to death, yielding a target sample size of 468 participants. The trial has satisfactory power (>=80%) to detect clinically important differences in the secondary outcomes.

2.5 Eligibility Criteria

2.5.1 Inclusion criteria

Potential participants will be eligible for inclusion if they meet each of the following criteria:

1. Probable dementia according to the Diagnostic and Statistical Manual, 4th Edition (DSM IV) criteria:

   a. Memory impairment with cognitive disturbance in at least one of the following domains - aphasia (language), apraxia (motor activities), agnosia (object recognition) or executive functioning (planning, sequencing, abstracting)

   b. Functional decline: increasing impairment in functional ability (social, occupational, personal/self-care) related to cognitive deficits.

2. Probable dementia of mild to moderate severity (MMSE >10).

3. Are able to participate in a structured exercise programme:

   a) able to sit on a chair and to walk 10 feet without human assistance;
   b) no serious unstable illness (e.g. unstable angina)

4. Live in the community, either alone or with a relative, friend, or carer, or in sheltered accommodation.

2.5.2 Exclusion criteria

1. People with severe dementia (MMSE ≤10) will not be eligible for inclusion.

2. Acute, unstable or terminal illness which would make participation in the exercise group impractical.

3. People living in residential nursing homes will not be eligible for inclusion.

2.6 Informed Consent

The main ethical issue in this trial is that some people with mild to moderate dementia will lack the necessary mental capacity to give informed consent. As is routine in dementia trials, however, patients who lack capacity to consent can agree to participate and, in compliance with the Mental Capacity Act (2005), advice is obtained from a personal consultee. For those relatively few participants unable to give informed consent, and for whom no personal consultee is available, an attempt will be made to find a nominated consultee. The most common route for a nominated consultee might be an independent mental capacity advocate (IMCA). Experience in other trials suggests IMCAs are rarely willing to consider this role. If this is the case, an alternative professional (e.g. GP) who is entirely independent of the trial may be approached. If one attempt to find a nominated consultee is unsuccessful, we will not attempt further to recruit the participant.

The initial approach to potential participants/carers will come from the patient's responsible clinician or a member of the healthcare team in the clinic. Those individuals who provide outline permission will be contacted by a research nurse, who will assess eligibility and obtain consent. All research nurses will be trained in informed consent, including methods for assessing competence for consent, agreement to participant and obtaining advice from carers.

If the participant demonstrates a lack of capacity or competency to consent to this research and does not object, then the researcher will obtain advice from the carer, on whether the person who lacks capacity should take part in the project and what their past and present wishes and feelings would have been about taking part. All research staff taking consent will receive specific training on this issue.

Carers will also be invited to participate in the trial for the collection of data on carer burden. Their willingness to participate will not affect the inclusion or consent of the person with dementia (PWD) as a participant.

At each assessment visit the researcher will check that the participant still agrees to take part in the study

2.7 Recruitment and Randomisation

Design: The main trial is a multi-centred, randomised parallel group controlled trial with economic analysis. The unit of randomisation will be the individual patient, stratified by site and dementia severity (MMSE >10 for mild and moderate dementia). Participants will be randomised to (1) best practice usual care, or (2) best practice usual care plus a four-month group exercise intervention with a physical activity maintenance component.

Participants and settings: We will identify potential participants from the clinic attendances and review lists of Dementia Services across England. Potential participants will be people with mild to moderate dementia currently or recently receiving services (assessment and/or treatment) from primary care, secondary care services for dementia and Alzheimer cafes. This will include those newly diagnosed and those being followed up longer term. Potential participants will be screened for initial eligibility (from medical notes, clinic records and/or clinical consultations) and, if appropriate, given information about the trial. This

will involve an initial approach from a member of the clinical team in secondary or primary care. Potential participants will be referred to the study research worker who will arrange an appointment to discuss the trial, answer any questions, take informed consent, undertake baseline assessments, arrange randomisation and appropriate follow on treatments as determined by the allocation.

Subjects will be randomised strictly sequentially, as subjects are eligible for randomisation. Subjects will be randomised using a 2:1 allocation in favour of the intervention.

Randomisation will be undertaken by the Randomisation service at WCTU. This is a telephone service available for randomisations during standard working hours Tel: 024 765 150402 (Mon-Fri, 9am to 5pm).

Carer participants will not be randomised; their inclusion is for observational purposes only.

2.8 Post-randomisation withdrawals and exclusions

Subjects may be discontinued from the trial treatment and/or the trial at any time without prejudice. Unless a subject explicitly withdraws their consent, they will be followed-up wherever possible and data collected as per the protocol until the end of the trial.

Participants who become unable to participate in the exercise intervention will withdraw from the intervention but will continue to be followed up at 6 and 12 months as per protocol.

Carers as participants may withdraw from the trial without this affecting the inclusion of the participant with dementia.

Documentation will be completed on withdrawal to confirm the date and reason for withdrawal.

2.9 Blinding

2.9.1 Methods for ensuring blinding

Randomisation, allocation concealment and masking: The random allocation sequence will be generated by an independent statistician using a random number generator, and implemented by a central telephone registration and randomisation service at the Warwick Clinical Trials Unit. Research workers will register participants after confirming eligibility and obtaining consent, thus ensuring allocation concealment. Neither intervention providers (DAPA physiotherapists) nor participants can be masked to treatment allocation. We will arrange for follow-up assessments to be conducted by different research workers to ensure investigator masking, and all study personnel involved with data entry, management and analysis will be masked until the final analysis is complete. We will undertake assessments of the success of masking.

2.10 Trial Intervention / Treatments

2.10.1 Trial Treatment(s) / Intervention

Research methods

We propose to conduct a series of studies in preparation for the main trial. We will update a systematic review (authored by our group), undertake a pilot study and evaluate operational procedures, trial materials, and the acceptability of the intervention and its implementation.

Pre-pilot project

Six people with mild to moderate dementia will be approached to participate in a pre-pilot of the intervention. We will measure cognitive impairment at baseline and characterise health and fitness as part of the intervention planning (i.e. exercise prescription). Participants will attend for up to 6 weeks, and their informal opinion of the programme will be sought.

Maximal commitment from participants will be as follows:

To read and consider approach.

To provide consent (or declaration via personal consultee).

To allow physiotherapists to check that the exercise intervention is suitable for them this will take place during the home visit, which will last between 1-1.5 hours and will include administration of the ADAS-Cog [Mohs etal 1997].

To participate, if willing, in the exercise intervention, which will involve an initial pre-exercise assessment (lasting 1 hour) and six weeks of 2x weekly exercise classes for 1 hour (plus social time).

To consider participating in community health walk (1-2 hours).

To provide informal feedback.

- The main trial will evaluate the effects of adding the exercise/physical activity package to usual care for patients with mild to moderate dementia. Economic and qualitative studies will run parallel to the main trial. We describe research methods for the main trial first.

- Outcomes will be assessed at 6 and 12 months, to reflect the short-term and sustained effects of DAPA.

Planned interventions

- *Best practice usual care:* All participants will receive care as usual from the clinical service they attend. All of the services participating in our study provide best practice care in accordance with national guidance, including the relevant NICE guideline.

- *Exercise intervention:* The exercise intervention will be delivered in a group format, with up to 14 participants in each group. The programme will be provided in two, 1-hour sessions per week for 4 months, supplemented with between-session at-home exercises of at least one hour per week. Each participant will receive a brief assessment prior to entering the exercise class to determine initial dose. The intervention will be delivered in a secure environment, for example day centres where

dementia respite care is provided already. This ensures adequate access and appropriate security. We will train physiotherapists to deliver the intervention, as although therapists are more expensive than exercise trainers, they have the specialist expertise to deal with dementia. Physiotherapists will be supported by a technical assistant as the groups are likely to be challenging to deliver.

- We have developed the training programme for physiotherapists, and have engaged substantial amounts of user input into the development of the intervention, which included a consultation forum co-ordinated by the Alzheimer's Society in Coventry. Subsequently we have undertaken a rigorous process evaluation alongside the implementation of the intervention within the OPERA study, which has included participant and carer observation and interviews to assess the acceptability of the intervention and its implementation.

- The most significant challenge is to develop a physical activity programme that people can adhere to after they have finished the structured part of the intervention. This will form an appreciable part of the pilot phase. We will link people to activities they enjoy and using behavioural strategies appropriate for people with memory impairment to promote adherence. Carers will play an important role, and many will want to assist in promoting adherence. However, we need to respect that not all carers will want to or be able to do this, and we will seek alternative options for these individuals. It is likely that we will use a counselling session at the end of the exercise programme, backed up with regular (up to monthly) phone calls to encourage adherence.

Pilot study, and evaluation of pilot and main study phases

Pilot study

The issues that need to be addressed by the pilot study are:

1. Is the size of the groups optimal, and do we need a physiotherapist and technical assistant for all classes?
2. Is the upper intensity level of the OPERA intervention sufficient to deliver a moderate aerobic challenge to participants?
3. Does the structured programme result in changes in physiological intermediary variables indicative of improved strength and aerobic conditioning?
4. Can we help participants make a successful transition to a sustainable pattern of physical activity at the end of the programme?
5. What is the participant and carer experience of the exercise programme, and how can we improve this?
6. Do the outcome measures capture issues important to users, and what is the likely uptake of the invitation to participate?

We will conduct a randomised pilot, and recruit at least one group of people with dementia to participate. As part of the process evaluation we will sample physiological data relating to cognition, aerobic strength and other physiological variables to determine the size and timing of response, and will evaluate physical activity levels using activity monitors during the structured programme, and afterward. All of the proposed measures will be sampled and will be undertaken during or immediately after the class.

Qualitative evaluation

Pilot evaluation

We will interview and observe participants and their carers to inform the development and evaluation of the intervention, gaining insight into barriers and facilitators to engagement, the experience of the intervention and acceptability. For this qualitative component, a researcher will observe the sessions, conduct short informal interviews with participants and carers, and those delivering the sessions. To further evaluate the intervention and its supporting materials, brief face to face or telephone interviews will be conducted with participants and their carers. In the pilot phase, we will include those with low or no attendance. Interviews will be recorded and transcribed verbatim. Data will be coded thematically using NVivo software, and analysed using framework analysis (Green et al 2004).

Main study evaluation

During the main phase of the trial, we will record the number of sessions each individual attended, and the intensity of exercise achieved. We will interview participants (approx n=15) of the intervention arm of the main trial 3 months after completion. Their main carer will also be invited. Ideally the interview with the participant and carer will be undertaken separately, although it is likely that most will want to be interviewed jointly (Powell et al 2010*).* These interviews will focus on the impact of the intervention on living with dementia including changes in wellbeing, maintenance of exercise between group sessions and after completion of the intervention. In the main study we will only include participants who have good attendance. Transcription and analysis will mirror processes in pilot phase (above).

More details on the exercise intervention we will test

We have developed a comprehensive exercise programme to prevent and manage depression in older people living in long term care settings, and this is being tested in the OPERA study (HTA 06/02/01). Many of the mechanisms targeted for the management of depression are similar to those used to target dementia, and we will use the OPERA intervention as the foundation for the DAPA trial. The intervention is designed for group-based implementation by a physiotherapist, and has three levels of difficulty to fit with the requirements of those who cannot stand well alone, those who can stand with support, and those who are mobile and functioning relatively well. It is likely that the individuals we will recruit in the DAPA study will fall into the upper functioning cohort.

In the pilot study we will test to ensure a sufficient aerobic challenge, and refine this further if required. The OPERA intervention is delivered to music, which is known to stimulate compliance within sessions and enhance enjoyment. The intervention is delivered by physiotherapists who are experienced in managing people with dementia. For the DAPA study, we will supplement each session with a technical assistant because the participants are likely to be more mobile, and potentially more difficult to manage in a group.

The DAPA intervention will include the addition of an element to ensure self-sustaining exercise in the community. In the pilot study we will evaluate whether participants can be matched to existing community programmes. Generally exercise on prescription, health walks and similar schemes do not cater for people with significant levels of cognitive

impairment. Exercise programmes are provided by some local branches of voluntary organisations, but provision is sporadic. We need to explore the acceptability of a home based activity programme implemented in collaboration with carers, family and friends, and to design the motivational materials needed to ensure compliance.

Much time and cost will be saved by building on the materials, manuals, CDs, training programme and expertise gained in the OPERA intervention. The OPERA exercise programme has been delivered to over 300 older residents of care homes, the majority of whom scored in the cognitive impairment range on MMSE which we will be using for this study. There have been no adverse events resulting from participation, and most people report enjoying sessions.

2.10.2 Compliance/Contamination

During the main phase of the trial, we will record the number of sessions each individual attended, and the intensity of exercise achieved.

We will periodically observe the consent process and baseline and follow-up assessments. The clinical research fellow based at Warwick will have responsibility for quality control of the interventions. The clinical research fellow will periodically make quality control visits to observe the group exercise sessions and will ensure quality control for the implementation of organisational change. Quality assurance checks will be undertaken by the WCTU to ensure the integrity of randomisation, study entry procedures and data collection.

3. Methods and assessments

3.1 Schedule of intervention and data collection

Table 1 Trial events

Visit	**1**	**Supervised Exercise**	**Unsupervised Exercise**	**2**	**3**
Visit Window (No. Weeks ± No. Days)	**Baseline assessment**	**32 sessions twice weekly for 4 months**	**1 hour per week for first 4 months then 3 hours per week for the subsequent 8 months**	**6 m (± 1 m) After Visit 1** **Main Trial only**	**12 m (± 1m) After Visit 1** **Main Trial only**
Informed consent	✓				
Medical history	✓				
Inclusion/exclusion criteria	✓				
Intervention		✓	✓		
Demographic data	✓ (main trial only)				
Cognitive/ Function ADAS-Cog BADL	✓			✓	✓
Quality of Life EQ5D	✓			✓	✓
Dementia Quality of Life/NPI	✓			✓	✓
Carer Burden ZBI	✓			✓	✓
Serious Adverse events		✓	✓	✓	✓

4. Adverse event management

4.1 Definitions

4.1.1 Adverse Events (AE)

An adverse event is defined as any untoward medical occurrence in a subject which does not necessarily have a causal relationship with this treatment.

4.1.2 Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Events

A serious adverse event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition.

4.2 Reporting SAEs

We will define as reportable any serious adverse event as any fracture, death or hospitalisation that occurs as the result of an incident during, or within two hours of completing the exercise sessions or follow-on physical activities.

SAEs and SUSARs will be reported using the SAE form. The Exercise Physiotherapist for each exercise intervention must report any SAEs and SUSARs to the Trial Co-ordinating Centre within 24 hours of them becoming aware of it. The SAE form should be completed and faxed to 02476 150549. The trial co-ordinator will liaise with the clinician to compile all the necessary information. The Trial Co-ordinating Centre is responsible for reporting adverse events to the sponsor and ethics committee within required timelines.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the Chief Investigator(s) and this will be recorded on the SAE form.

All SAEs will be recorded in the trial database and reported to and reviewed by the Trial DMEC throughout the Trial.

All SAEs will be followed up to resolution.

4.3 End of Trial

The trial will end when 468 patients have been recruited and completed their 12 month follow-up. The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring and Ethics Committee (DMEC)
- Funding for the trial ceases

The Main Research Ethics Committee (MREC) will be notified in writing if the trial has been concluded or terminated early.

5. Data management

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act.

Participants will be identified using a unique trial number. The trial number for the participant with dementia (PWD) and the carer as participant will be linked for cross identification purposes.

Personal identifying information will be held at WCTU, when received in response to the invitation. Personal contact details of trial participants and their carers will be needed to organise the baseline and follow-up meetings and send information about dates, venues and timings for exercise classes. This information will be filed separately from all other trial information and each participant and their carer will be assigned a unique trial number. We will retain paper records of participant & carer details.

5.1 Data collection and management

The Case Report Forms (CRFs) will be designed by the Trial Co-ordinator in conjunction with the Chief Investigator, Co-investigators and Statistician. Original copies will be sent to WCTU, with copies of CRFs held by physiotherapists in relation to the exercise intervention. Data will be entered onto a WCTU database by a member of the Trial team. Data will be subject to validity checks and additional data checking procedures to assure quality of data entry.

5.2 Database

The database will be set up by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer, statistician and trial co-ordinator.

5.3 Data Storage

All essential documentation and trial records will be stored by WCTU in compliance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

5.4 Archiving

Trial documentation and data will be archived for at least five years after completion of the trial.

6. Statistical analysis

A fully specified data analysis plan, including frequency of analyses and pre-planned sub-group analyses, will be developed in the early phases of the trial and approved by the DMEC. Data will be summarised and reported in accordance with CONSORT guidelines for randomised controlled trials (Shultz et al 2010), and we will use intention-to-treat analyses.

Treatment effects: Hierarchical regression models will be used to estimate the treatment effects (with 95% confidence intervals), and will be adjusted for important co-variates (age, sex and baseline MMSE). We will include estimation of and adjustment for therapist effects. Pre-specified sub-group analyses will examine the interaction of treatment assignment with severity of cognitive impairment (MMSE ≥20 and <20) and gender will be conducted using formal tests of interaction (Brookes et al. 2001). We will explore dose dependency in a secondary analysis, by reporting effect across quartiles of dose received, and will test for trend in the effect across the doses.

We will estimate the group effects in the trial, if this is possible. Hierarchical analyses adjusting for group effect will give us insight into whether the group structure is contributing to the treatment effect.

Economic analysis: The most significant formal costs associated with dementia are the costs of social and long term care (Quentin et al 2010). Hospitalisation costs are also likely to occur, particularly related to falls and injuries (Rizzo et al 1998). The economic analysis will therefore focus on the following major components of costs: NHS primary and secondary care, local authority care, the costs to other agencies or organisations, costs associated with institutional care and home care support (summarised in Table 2). Intervention costs will reflect the costs necessary to implement the DAPA physical activity, including development and training, overheads, equipment, and staff-related expenses.

Two economic evaluations will be undertaken – *a within trial evaluation* will compare the outcomes and cost during follow up and, secondly, *a decision analytic cost effectiveness model* will be used to estimate the expected incremental cost per quality-adjusted life year (QALY) gained for the DAPA interventions in comparison to best practice usual care. For both analyses, the perspective will be that of the UK NHS and social services. The potential impact of adopting a societal perspective on incremental cost-effectiveness ratios will be tested in sensitivity analyses using data on informal and indirect costs provided by carers at 6 and 12 months.

The within trial analysis will compare the costs and outcomes between the study arms at the end of follow up. The primary outcome measure will be the QALY. Utility weights will be taken from the UK General Population tariff for the EQ-5D (Dolan 1997, Kind et al 1999). Unit costs will be taken from national databases including the NHS reference costs and the PSSRU costs of health and social care. Where national unit cost estimates are not available unit costs will be estimated using established accounting methods in consultation with Trusts recruiting to the study. In line with current recommendations for best practice in economic analyses, costs and outcomes will be discounted at 3.5% per annum. Probabilistic sensitivity analysis will be undertaken using the non-parametric bootstrap. We will use the Client Services Receipt Inventory as a framework for resource data capture (Beecham & Knapp 1992).

The decision analytic cost effectiveness analysis model will use a lifetime time horizon to capture the full impact of any mortality and health-related quality of life differences on

the long term cost effectiveness. It is likely that the model will have a semi-markov structure to capture the time trend in the underlying risk of mortality, health related quality of life, and costs of care. The methods for estimating health related quality of life and utility, unit costs and discounting will be the same as for the within trial analysis. Probabilistic sensitivity analyses will be undertaken using Monte Carlo simulation techniques. The outputs reported from the analysis will be the same as for the within trial analysis.

7. Trial organisation and oversight

7.1 Ethical conduct of the trial

Ethical arrangements: The study will obtain all necessary ethical permissions and NHS Research and Development approvals before commencing. All data will be stored securely and anonymised in accordance with Data Protection Act, and the trial will be conducted in compliance with the principles of MRC GCP guidelines, the Declaration of Helsinki and other requirements as appropriate. Our team has considerable experience of research involving people with dementia (e.g. DOMINO- AD, and OPERA) and in developing appropriate consent procedures in accordance with legal and regulatory requirements.

Risks and benefits: All participants will have access to usual care, and thus no treatment will be withheld from trial participants. There is some limited evidence of a very small increased risk of injury as a result of becoming more physically active. In our physical activity programme, however, healthcare professionals tailor progressive exercises to individual need/ability, and deliver the programme to small groups of participants in a supervised and safe context.

All participants may benefit from the provision of additional 'usual care' monitoring. Intervention participants may also benefit from the wide range of positive effects associated with increased physical activity. A successful trial will also yield substantial benefits for others. Either we will demonstrate that DAPA is clinically effective and that its wider implementation would benefit patients, carers and society more generally, or we will demonstrate that DAPA is ineffective or not cost-effective, thus allowing NHS resources to be re-directed to other more effective interventions.

Informing potential participants of risks and benefits: The patient information leaflets will provide potential participants with information about the possible risks and benefits of taking part in the trial. Potential participants will be given the opportunity to discuss the trial with the research nurse. We will inform participants, their carers and GPs/consultants if new information comes to light that could affect their willingness to participate in the trial.

Research Governance The trial will be conducted in accordance with the Standard Operating Procedures of Warwick Clinical Trials Unit. A Trial Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC) will be convened, and each will have at least 3 independent members. In addition, each committee will have a lay member with relevant experience of dementia and dementia care services.

7.2 Sponsor

The University of Warwick will act as Sponsors for the trial.

7.3 Indemnity

Staff employed by the NHS will be covered by the Clinical Negligence Scheme for NHS Trusts. Staff employed by the University of Warwick will be covered by the University's trial insurance. Negligent harm cover will be provided by standard NHS arrangements (HSGG(96)48). NHS Indemnity does not give indemnity for compensation in the event of non−negligent harm, so no specific arrangements exist for non−negligent harm for this trial.

7.4 Trial timetable and milestones

Recruitment rate

In the main study, we have planned for a recruitment period for each site of 12 months, giving an overall target of 8.5 patients per centre per month. This will be moderated according to the size of the centre, and phase of the trial.

Table 2: DAPA recruitment targets

Month	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Date	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14
Target	2	6	38	52	63	70	86	91	103	122	160	180	199	215	232	249	266

Month	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Date	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15
Target	283	300	314	328	342	356	370	384	398	412	426	440	454	468

Project timetable and milestones

This project will require 54 months to complete (Table 3). We are confident to progress into delivering the intervention in the pilot study early on – the highest level of the OPERA intervention should result in the correct training stimulus, and we can monitor and moderate this as we progress. We will update the reviews ahead of the project, and at the same

time as conducting the pilot exercise classes. We need to test the feasibility of transferring to community and other sustainable types of exercise, and this will occur at about 9 months in the overall project plan. At this point we will triangulate the information, from reviews and our experience of delivering the intervention, and make any necessary amendments to the intervention training manual and materials. We will also have evaluated how many people are likely to accept the invitation to participate in the trial and have refined the projections for the trial. The feasibility of the study would be known at this point, and we can agree with the funders whether it is desirable to continue.

Our timetable is quite tight, and we have assumed an immediate roll forward. We will launch the main trial at 12 months. We have a bank of experienced therapists who have already been trained in delivering the OPERA intervention, although we will need to identify and train therapists at more remote sites. The trial will recruit participants from month 12, finishing by month 42Final 12 month follow up will be complete by up to month54. Data analysis, and report writing will be from month 54 onward. Summary results will be presented to DMEC, TSC and user groups for comment, a full report will be prepared and submitted to HTA, and other dissemination activities will be undertaken.

7.5 Administration

The trial will be coordinated at Warwick Clinical Trials Unit. A trial coordinator will be responsible for the day to day management of the trial. A clinical research fellow will be responsible for the day to day work to update the systematic reviews, refine the intervention, train the physiotherapists and ensure there are sufficient numbers of therapists available, ensure the quality of the intervention, and collect data and report on fidelity of the intervention. A second research fellow will be appointed to assist with these activities, the qualitative study, and fidelity modelling during the main trial. Clinical guidance will be provided by Dr Sheehan (Consultant and Clinical Lead, John Radcliffe Hospital), Dr McShane (Clinical Lead, Thames Valley DeNDRoN) & Mrs Nicola Atherton (Research Fellow, the University of Warwick).

7.6 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and investigators involved in the day-to-day running of the study, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the TSC or Investigators, as appropriate.

7.7 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced dementia personnel and trialists as well as 'lay' representatives. The TSC will have an independent Chairperson and a minimum of three independent members. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMEC
- Informing and advising on all aspects of the trial

7.8 Data Monitoring and Ethics Committee (DMEC)

The Data Monitoring Committee will consist of independent experts with relevant clinical research, and statistical experience. During the period of recruitment into the trial, interim analyses of the accumulating data will be supplied, in strict confidence, to the DMC, along with any other analyses that the committee may request. The frequency of these analyses will be determined by the committee.

7.9 Essential Documentation

A Trial Master file will be set up and held securely at the coordinating centre, in accordance with WCTU SOPs.

8. Monitoring and Quality assurance of trial procedures

The trial will be conducted in accordance with the Standard Operating Procedures of Warwick Clinical Trials Unit. A Trial Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC) will be convened, and each will have at least 3 independent members. In addition, each committee will have a lay member with relevant experience of dementia and dementia care services.

The Sponsor will that ensure investigator(s)/institutions will permit trial-related monitoring, audits, REC review and regulatory inspections, providing direct access to source data/documents.

A risk assessment of the project will be undertaken by the trial team and a Data Monitoring Plan produced. Monitoring will be conducted in accordance with this Data Monitoring Plan throughout the trial. A Data Management Plan will also be followed throughout the trial.

9. Dissemination and publication

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the TSC before submission for publication, on behalf of the collaboration. The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.(39) The main publications will be the report to the funding body (HTA Monograph) and a journal publication. In addition, the results will be presented at international conferences.

A policy for authorship of trial publications will be drafted and agreed by the investigators, in accordance with the WCTU Standard Operating Procedure 22 (Publication and Dissemination).

At final contact during the study participants will be informed that results will be posted on study websites. If they request to have further details we will endeavour to accommodate this.

10. Financial support

The trial is funded by the NIHR Health Technology Assessment Programme, grant number 09/80/04.

11. Protocol amendments

Amendment 1 – approved 31/05/2012

Since favourable opinion was granted, our primary focus has been to refine the exercise and physical activity intervention for people with mild to moderate dementia. We have now refined the intervention which remains consistent with the proposal in the original DAPA application, i.e. 2 weekly, group exercise, focused at cardiovascular and strength training. The major refinement is that we propose to use exercise bicycles and weighted body vests as opposed to free standing cardiovascular exercises and strap weights. We believe these to be safer (there is substantially less possibility of falling), more effective and easier to manage logistically. We have also reduced the number of people in the sessions and increased the staffing levels to ensure a better ratio of staff to participants. We have refined the methods of assessment, prescription and progression.

We are seeking permission through substantial amendment (as advised by the Chair), to conduct a pre-pilot project. This would be an additional small project. We wish to gain experience with the intervention and check that our assumptions about the time and skill it takes are correct. We want to go into the randomised pilot for the main trial (which already has approval) with a well-functioning intervention, and we want the physiotherapists who will ultimately be responsible for training the larger group of therapists to deliver the intervention in the main trial to have the opportunity to gain experience and make final changes before we do this. This would maximise the possibility that we can use incorporate the pilot data into the main trial, and ensure we maximise efficiency in terms of recruitment and cost of the main trial.

The most practical route for us to achieve this, in a timely manner, is to work with local Alzheimer's Society, with whom we have an established relationship, have previously completed projects with, and who already run exercise classes. Up to 6 participants would be recruited via the Alzheimer's Society in Coventry. Participants would be identified by two routes (1) Flyers which advertise the project would be distributed and displayed at the Alzheimer's Society premises and (2) seeking volunteers .The Alzheimer's café co-ordinator would approach individuals whom he considers may be interested and will introduce the idea of the project. If interest has been lodged via the Alzheimer's café coordinator, the coordinator will ask to take their contact details and if agreed by the participants, pass these to the trial team. A physiotherapist from the trial team will contact those interested via telephone to further explain the purpose of the project and answer any questions the potential participant or their carer may have. If the potential participants are interested in taking part, the physiotherapists will make an appointment to visit their home. A letter confirming the home

visit appointment and the participant information sheets will be posted to the potential participant. A flyer, appointment letters for the home visit, pre-exercise assessment and class are enclosed for review. All of the materials we have developed for the pre-pilot have been based on the previously approved patient information sheet, personal consultee information leaflet, participant consent form and consultee declaration form, but with removal of references to randomisation and follow-up. These are also enclosed.

The home visits will be carried out by trained physiotherapists and will take approximately one to one and half hours. During this visit we will gain written consent from the participant and/or their carer, check cognitive status using the ADAS-cog [1] and collect health and fitness related information required to ensure safe participation in the groups.

The exercise classes will be run twice weekly. The exercise will be individually tailored – i.e. the starting levels will be prescribed according to the capacity of the individual, such that individuals who are weaker or less fit start at lower levels of exercise. The exercise classes will be held at a local Cardiac Rehabilitation facility (Atrium Health, Watch Close, Coventry, CV1 3LN). A risk assessment of this venue will be undertaken by the trial team prior to the first session. We have also ensured the appropriate insurance is in place.

We may also invite participants to take part in a supervised walking session, provided the physiotherapists view that they are sufficiently capable and fit to do so.

We will not collect any outcome data, although physiotherapists will in the course of running the classes, seek the informal opinion of participants about how the experience might be improved and identify areas which participants find challenging. Although we do not anticipate any serious adverse events, these will be reported to the ethics committee and will be reviewed by the Data Monitoring Committee should they occur.

Recruitment to the main DAPA trial has not been mentioned in the pre-project PIL (V1.0-15/05/2012) as identification and recruitment routes for this pre-pilot project and the pilot/main trial phases are not linked. GPs will not be notified of participation in the pre-pilot i. If serious health concerns are identified during the project, participants and their carers will be advised to see their GP and inform them of their participation at that stage.2

Amendment 2 –approved 17 July 2012

The intervention is delivered as group based exercise classes. In order to fill the classes as efficiently as possible the randomisation ratio will now be 2:1 (treatment : control). The main advantage of this is that the time taken to fill exercise groups will diminish meaning that participants will not have lengthy waits until the treatment starts. This is an accepted strategy in those trials that have a group based element to them. The trial statistician confirms that the sample size calculation will remain as 728 but n=485 participants will now receive the intervention (treatment arm) and n=243 participants will continue with usual care (control arm). Imbalance of randomisation will increase the chance of the participant being allocated to the intervention arm and this has been explained in the letter of invitation (and reminder letter) and the information sheets for participants and consultees (personal and nominated) and also for the carer. The consent and declaration forms have been updated to reflect version changes for the information sheets.

We also request approval for use of the DAPA trial logo; 4 versions of this logo are attached for opinion; (i) coloured, ii) black & white, iii) greyscale and iv) logo with no text.

Amendment 3 – approved 17/07/2012

One of the co-primary outcomes for DAPA is cognition. Our current proposal states that this will be measured using the Standardised Mini Mental State Examination (sMMSE). However on-going discussion with co-applicants and emerging evidence now strongly suggests that the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) [1] would be the most appropriate outcome measure in this patient group. The sMMSE although widely used in clinical evaluation is a very global, relatively insensitive measure of cognitive function. In contrast the ADAS-Cog has the following advantages:

1. The ADAS-cog is acknowledged to be more sensitive in detecting cognitive change in individuals with mild to moderate dementia than a variety of other measures, including the sMMSE [2]. The ADAS-cog is able to characterise different domains of cognitive performance better than other measures.

2. It has been recommended by an expert task force as the cognitive outcome measure of choice for research using participants with moderate cognitive impairment [2]. This is our target population.

3. Unlike many other tests of cognition the ADAS-Cog has an expert agreed minimal clinically important difference [2].

This means that we can use a valid but more sensitive primary outcome measure, with the possibility of being able to reduce the sample size of the study at some point in the future. We have checked the sample size estimates carefully, and do not propose to change the sample size at this stage. Rather we will wait until we have accumulated data on 200 participants, and then check the underlying assumptions of the sample size. The study is currently based on a sample size of 728, using the sMMSE. The potential efficiency saving using the ADAS-cog is substantial (sample size of approximately 480). This estimate is based on published literature: A study of cognitive decline in patients with Alzheimer's disease showed a 12-month decline of 4.46 points (SD 6.32) on the ADAS-cog in the control group [3]. An overall difference of 2-2.5 change points on the ADAS-Cog points is considered to be a clinically worthwhile target [4], [5]. A systematic review of Cholinesterase inhibitors in patients with Alzheimer's disease showed differences of 1.5-3.9 points on the ADAS-cog [6]. This estimate is calculated at 80% power, alpha $p<0.05$ with inflation for therapist effects based on an ICC of 0.01 as per the original application. Estimates of the ICC and SD at baseline will be used to revise the sample size estimate at an interim point of 200 patients. Eligibility criteria for the DAPA trial will continue to be assessed using the sMMSE as this is the standard clinical evaluation tool routinely used by clinicians within the NHS.

As the ADAs-cog takes up to 40 minutes longer (in most cases less) to administer compared to the sMMSE in order to reduce burden on the participants we have reconsidered the relative added value of the secondary outcomes and have decided to remove measurement of mood i.e. the Cornell Scale for Depression in Dementia (CSDD).

Amendment 4 – current amendment 07/07/2014

Protocol amendment 3 approved change of the primary outcome tool from the sMMSE to the ADAS-COG and highlighted a possible reduction in sample size for future consideration. In line with this, this amendment describes a change in sample size from 728 to 468 participants. We have used a between group difference of 2.45 points on the ADAS-COG, baseline standard deviation of 7.8 (equating to a standardised effect size of 0.31), 80% power, $p<0.05$, and inflation to account for therapist effects using an ICC of 0.01 (i.e. design effect of 1.04), with the assumption that there will be on average 5 patients within each group session.

The number of cases needed for final analysis at 12 months is 375. We have inflated to account for a loss to follow up of 20%, including 10% attrition attributable to death, yielding a target sample size of 468 participants. The trial has satisfactory power (>=80%) to detect clinically important differences in the secondary outcomes.

Section A31 of the NHS REC form: We request opinion to reduce the amount of time patients and carers require to decide to participate in the trial from 1 week to up to 48 hours. Our experience after approaching over 200 participants is that patients and carers frequently state that 1 day is a sufficient amount of time to understand trial information and make their informed decision to progress further. We have support from co-applicants in DeNDRoN that 48 hours for consideration of information is appropriate duration for people with dementia.

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13. Appendices

Table 3. Project timetable

Project Activity (Trial month)	<0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Recruit research staff	*			*															
Ethics appraisal	*				*														
Update systematic review	*	*																	
Design sustainable physical activity prog.	*	*																	
Pilot study		*	*	*	*														
Structured exercise		*	*																
Physical activity			*	*															
Pilot study evaluation				*	*														
Site set-up/approvals			*	*	*														
Recruit / train DAPA providers				*	*														
Main trial					*	*	*	*	*	*	*	*	*	*	*	*			
Recruitment period					*	*	*	*	*	*	*	*							
Exercise groups					*	*	*	*	*	*	*	*	*						
6-month follow-up							*	*	*	*	*	*	*	*					
12-month follow-up									*	*	*	*	*	*	*	*	*		
Data analysis			*	*	*											*	*	*	*
Economic appraisal			*	*	*											*	*	*	*
DMEC meeting			*			*			*			*			*			*	
TSC meeting				*			*			*			*			*			*
Monitoring reports			*		*		*		*		*		*		*		*	*	*
HTA monograph/pubs					*	*												*	*