**A multi-centre, pragmatic, parallel-group, randomised controlled trial of a programme to promote activity and independence, and prevent falls, for people with early dementia and mild cognitive impairment.**

**Version 2**
**16th July 2018**

**Short title:** **Promoting Activity, Independence and Stability in Early Dementia and Mild Cognitive Impairment**

**Acronym:** PrAISED 2

**Trial Registration:** ISRCTN reference: (pending)

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**Study co-ordination centre:**
University of Nottingham, Queens Medical Centre, Nottingham NG7 2UH

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**Sponsor**

Nottingham University Hospitals NHS Trust is the research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance Manager at:

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**Disclaimer**

This protocol describes the PrAISED 2 trial and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

## Contents

**GLOSSARY OF ABBREVIATIONS**

| | |
|---|---|
| AE | Adverse Event |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRN | NIHR Clinical Research network |
| CSRI | Client Services Receipt Inventory |
| DAP | Data Analysis Plan |
| DMC | Data Monitoring Committee |
| GCP | Good Clinical Practice |
| ICF | Informed Consent Form |
| MCI | Mild Cognitive Impairment |
| NHS | National Health Service |
| OT | Occupational Therapist |
| PI | Principal Investigator at a local centre |
| PIS | Participant Information Sheet |
| PT | Physiotherapist |
| REC | Research Ethics Committee |
| R&D | Research and Development department |
| RSW | Rehabilitation Support Worker |
| SAE | Serious Adverse Event |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |

**KEYWORDS:** Falls, prevention, dementia, mild cognitive impairment, randomised controlled trial, exercise, activity

**STUDY SUMMARY**

| | |
|---|---|
| **TITLE** | **Promoting Activity, Independence and Stability in Early Dementia and Mild Cognitive Impairment (PrAISED 2)** |
| **DESIGN** | Multi-centre, pragmatic, parallel-group, randomised controlled trial, with internal pilot trial, and embedded process and economic evaluations.<br><br>Web-based randomisation, using a dynamic adaptive algorithm, stratified for centre and other variables to 1) active intervention or 2) standard brief falls assessment and advice. An internal pilot trial will recruit the first 50 participants. |
| **AIMS** | To test the clinical and cost-effectiveness of a therapy intervention designed to promote activity and independence and reduce falls, amongst people with early dementia or mild cognitive impairment |
| **INTERVENTION** | Assessment, tailored strength and balance exercise programme, activity analysis and risk enablement advice, and assessment for environmental hazards. Tailored adherence support and supervision.<br><br>The control group will receive standard brief falls assessment and advice. |
| **OUTCOME MEASURES** | Primary outcomes will be disability in Activities of Daily Living (Disability Assessment in Dementia, DAD) measured 12 months after randomisation.<br><br>Secondary outcomes include rate of falls, quality of life, activity, cognition, time to first fall, fractures and injurious falls, hospital and care home admissions, days spent in hospital, affect, carer strain and cost-effectiveness.<br><br>Safety variables are intervention-related injury, injurious falls, hospital admission, and mortality. |
| **SETTING** | Memory Assessment Services (Memory Clinics), NIHR Join Dementia Research register, and community settings |
| **POPULATION** | 368 men and women aged over 65 with diagnosed mild cognitive impairment (MCI) or early dementia, and a family member or carer. |
| **ELIGIBILITY** | Diagnosis of dementia or MCI. Aged 65 or over. Montreal Cognitive Assessment (MoCA) 15-25; able to walk without human assistance, able to communicate in English; no co-morbidities that prevent cognitive assessment or exercise participation; likely to be available for intervention, and not terminally ill. Capacity to give consent and agreement to participate. A family member or carer, who has contact with the participant for at least one hour per week, willing to consent to be an informant. Vision, hearing and dexterity sufficient to complete neuropsychological tests. |
| **DURATION** | Total trial recruitment for up to 21 months.<br><br>Follow-up for 12 months and 15 months for falls data; each participant will take part for 15 months |

## 1. INTRODUCTION

### 1.1 BACKGROUND

Dementia is a syndrome of progressive and irreversible loss of memory and other cognitive functions including agnosia, apraxia, language and executive function, caused by a variety of brain diseases, and severe enough to interfere with daily function. Mild cognitive impairment is defined as measureable memory loss or other cognitive decline in the absence of interference with daily function, but which in about half of cases progresses on to dementia. Dementia affects 1% of those at age 65, 20% at age 80 and over 30% at 90, leading to a prevalence of about 850 000 in the UK. Numbers will double by 2030.

Dementia progressively reduces the ability to undertake activities, including personal care, domestic tasks, and social and leisure activities. This is in part due to features of dementia, such as forgetfulness or apraxia, but much is socially-determined through changes in opportunity, and restriction by self or others, often in the name of 'safety'. Individuals with dementia and their families may not access advice on how to change or adapt activities to enable their continuation. This can result in a 'spiral' of disengagement, isolation, deconditioning and decline. Of particular concern is risk of falls.

A fall is defined as unintentionally coming to rest on the floor or at a lower level, through whatever cause (WHO; Lamb 2005). Some definitions exclude falls associated with syncope or overwhelming force, or confine interest to fractures or injurious falls, but for research purposes there is risk of information bias with restrictive definitions. Consequences of falls include fractures, other injuries, hospital attendance, the 'fear of falling syndrome', immobility and loss of independence.

People with dementia and mild cognitive impairment are at high risk of falling with at least a two-fold increased risk of falls compared with cognitively normal older people (Muir 2012; Tinetti 1988; Delbaere 2012). This equates to an annual fall incidence of 60-80% (Shaw 2007; van Dijk 1993; Allan 2009; Taylor 2014). People with dementia also have a higher risk of fractures, hip fractures in particular, and poorer outcomes after fracture, compared with people who are cognitively intact (Kallin 2005; Tinetti 2005).

The Ministerial Advisory Group on Dementia Research identified research on falls prevention in dementia as a priority (Kennard 2011). Up to a third of emergency hospital admissions occur in an older person with dementia, and over half are associated with a fall (Goldberg 2012). Each year, in the UK there are 75 000 hip fractures, set to rise by half again in the next 10 years, and 200,000 other

fragility fractures. The combined cost of these is over £2 billion per year, and use 1.6 million hospital bed days. Half of hip fractures occur in someone with dementia (House 2000).

There has been extensive research into falls and fall prevention in older people in general (Gillespie 2012). Multifactorial interventions including medication review, balance training, visual corrections and environmental modifications can reduce falls by up to a third (Gillespie 2012, British Geriatrics Society 2011). However, these interventions have not been shown to reduce falls in people with dementia (Shaw 2003, Oliver 2007). The usual opinion amongst falls prevention clinicians is that standard intervention is ineffective for people with dementia (Shaw 2007). People with dementia have more 'conventional' falls risk factors than people of similar age without dementia (Shaw, 2007), including motor impairments, impaired vision, functional impairments and medications (Harlein 2009). In addition, there are specific risk factors associated with dementia, including those that manifest as part of the disease (such as abnormalities of executive or visuo-spatial function), which might account for increased falls risk (Kearney 2013).

## 1.2 RATIONALE FOR CURRENT STUDY

There has been extensive research into falls prevention in older people. Risk factors are muscle weakness, neurological disease, medications, poor vision and environmental factors. Multi-factorial interventions reduce risk [Gillespie 2012; British Geriatrics Society 2011], but these interventions have not been shown to reduce falls in people with dementia or MCI [Shaw 2003, Oliver 2007, Guo 2014, Booth 2016]. Falls guidelines recommend that cognitive function is assessed, but do not say how to respond [NICE 2013]. A systematic review of interventions concluded that they were poorly adapted to the needs of people with dementia [Hauer 2006].

People with dementia have dementia-specific risk factors including: type and severity of dementia, specific cognitive and gait deficits, behavioural disturbances, psychotropic and cardiovascular drugs [Taylor 2014, Harlein 2009, Taylor 2012]. Recent studies highlight the importance of attention, and dual-task cost (increased risk when concentrating on two things at once) [Beauchet 2009], manifestations of impaired executive function (ability to form, maintain, and shift mental set [Suchy 2009]). Abnormalities in executive function and gait predict falls [Kearney 2013, Muir 2012, Segev-Jacubovski 2011]. Dual-task and gait abnormalities are found early in Alzheimer's disease [Taylor 2014, Hausdorff 2005, Wittwer 2010, Soumare 2009, Montero-Odasso 2012] and MCI [Verghese 2008] beyond what would be

considered 'normal ageing'. Potentially reversible risk factors provide opportunities to intervene before inevitable deterioration occurs.

Systematic reviews have considered the impact of strength and balance training in older people, with and without dementia [Guo 2014, Chan 2015, Sherrington 2008 & 2011, Power 2013, Lui 2009, Booth 2016]. Moderate-intensity exercise, 2-3 times a week, improves strength, gait speed, and ability in activity of daily living [Heyn 2004, Blankevoort 2010, Potter 2011, Forbes 2013, Rao 2014]. There may be additional benefit in slowing cognitive decline [Heyn 2004, Forbes 2013, Lautenschlager 2008, Law 2014, Forte 2013, Cassilhas 2007, Burgener 2008] although the size of this effect appears small (on global cognition measures). The recent NIHR HTA DAPA trial of four months of moderate intensity group exercise was negative for both cognitive and activity of daily living outcomes [Lamb, 2017, personal communication]. Training can improve executive function, dual-task performance and gait parameters [Lui-Andrews 2008, 2010a & 2010b, Trombetti 2011, Schwenk 2010, Silsupadol 2009]. Functionally-orientated therapy can improve cognition and ability in Activities of Daily Living [Graf 2006, Rebok 2014, Clemson 2012, Law 2014]. There is insufficient evidence to confirm reduction in falls, improved mood, behaviour or carer strain for people with dementia [Guo 2014, Hauer 2006, Heyn 2004, Potter 2011, Forbes 2013, Winter 2013]. Customary levels of physical activity are low among older people [Illife 2008].

A recent Finnish trial of 12 months of twice-weekly, supervised exercise at home for people with established dementia and their co-resident spouse, significantly reduced the rate of decline in ADLs, and halved the rate of falling ('FINALEX' trial [Pitkala 2013]). This study was the first to show convincingly that falls risk can be reduced in dementia. Hospital admissions and overall costs were reduced. This demonstrates that intensive exercise is achievable, sustainable with the right support, and cost-effective. The challenge is how to achieve sufficient participation, adherence and persistence in the NHS and UK cultural environment.

A new intervention must be able to produce changes in individuals that are physiologically and neuro-psychologically credible, but must also take account of aspects of health psychology [Michie 2011, Simek 2012, Davis 2014, French 2014]. We know from previous work that an intervention will need to overcome *barriers to uptake* with the intervention (e.g., unwillingness to be thought of as being incapable or at risk of falls [Peach 2017, Yardley 2005]; and also *barriers to long-term adherence* (e.g. forgetfulness, planning problems, practical support). The utility of current approaches to behaviour change (e.g. behaviour change wheel [Michie 2011]) in the context of dementia is unknown, but provides a framework for further investigation.

This trial forms part of a programme of work including the development, refinement, feasibility testing of the intervention, and investigation of the impact on carers, barriers and facilitators to success, economic evaluation and necessary steps for implementation in the NHS, public health or civic society.

## 2. STUDY OBJECTIVES

### 2.1 PURPOSE

To determine the clinical and cost-effectiveness of a newly-developed therapy programme to promote activity and independence, and prevent falls, suitable for people with early dementia and mild cognitive impairment.

### 2.2 PRIMARY OBJECTIVE

To determine if the intervention reduces disability in activities of daily living (ADL) after 12 months follow-up.

### 2.3 SECONDARY OBJECTIVES

Over 12 months of follow-up, to determine if the intervention:

a) decreases rate of falling and increases time to first fall (months 3-15)

b) improves quality of life

c) increases level of habitual activity

d) improves cognition

e) reduces the rate of fractures and injurious falls (months 3-15)

f) reduces the rate of hospital and care home admissions, and days spent in hospital

g) reduces carer strain

h) is cost-effective, within the trial period, over the anticipated remaining lifespan, and using a social return on investment model.

i) reduces apathy

## 3. STUDY DESIGN

### 3.1 TYPE OF STUDY

Individually randomised, multi-centred, pragmatic, parallel-group, randomised controlled trial with process and economic analyses.

**Internal pilot trial**

We are undertaking a feasibility RCT which will answer feasibility questions and acts as an external pilot trial (to complete April 2018). We will run a further internal pilot trial of 50 participants recruited over six months from all sites, using the full trial documentation and methods. This is to confirm recruitment, randomisation, data collection and follow-up are adequate across all sites. We will use ACCEPT criteria for inclusion of pilot data in the main dataset [Charlesworth 2013], and the methodology of Wittes and Brittain (1990) for sample size re-estimation, if necessary.

**Number of participants**

The trial will recruit 368 participants together with a family member or carer acting as informant, including those in the internal pilot, and making an allowance for attrition.

For process evaluation, we will aim to interview 10 participants at each site. In additional, we will invite all participants who withdraw from the study to be interviewed to explore reasons for withdrawal.

**Randomisation & Blinding**

Participants will be individually randomised, stratified by site, co-resident carer and history of previous falls, using a dynamic, adaptive allocation algorithm (Russell 2011) accessed by a secure web portal to the system held at the NWORTH Clinical Trials Unit, Bangor University. The randomisation system will be maintained by a statistician independent of the analysis and research teams.

Recruitment will be by a study research assistant or a Clinical Research Network Clinical Studies Officer, who will also undertake the baseline assessment. Randomisation will be web-based, therefore

concealed from the researcher. Clinical researchers will inform the participant about the treatment and follow-up plan. Access to the study website will be password protected and only accessible by authorised individuals.

Blinding of intervention is impossible for participants and therapists administering the intervention. In the feasibility study, we have found that blinding researchers at outcome assessment was virtually impossible, as participants invariably made comments which unblinded the researchers, even when specifically asked not to. We believe that a 'case manager' system for recruitment and data collection (having a single person doing all assessments and contacts for a given participant) will improve support to participants, and will result in better retention. Specific anti-bias training will be given to all researchers and CSOs to mitigate risk of bias.

Statistical analysis will be blind to allocation.

**Maintenance of randomisation codes and procedures for breaking code**

Patient participants and carers will not be blind to treatment allocation. There is no need for procedures to break randomisation codes.

Treatment allocation will be represented by a binary variable in the database, which will be used for final and any interim analyses.

Trial statistician will prepare six monthly safety reports by unattributed allocation group. These will be unblinded if the Trial Data Monitoring and Ethics Committee (DMEC) requests it.

**Study Duration**

Internal pilot trial will recruit 50 participants (approximately six months), with follow-up for 15 months.

Main trial recruitment will be for a further 12 months, with a facility to increase this to 15 months if needed.

Active treatment and follow-up will proceed together. Follow-up for falls will be between months 0 and 15 (with the first three months data monitored for safety only, as reduction in falls is not expected immediately).

An individual takes part for 15 months.

The end of the study will be at the final follow-up of the last participant.

**Process Evaluation.**

As recommended for complex intervention trials (MRC 2008), a formal process evaluation will be conducted in accordance with MRC guidance (Moore 2014).

This will address objectives:

1) Investigate if the intervention is operating as planned

2) Identify facilitators and barriers for intervention delivery, and longer-term adherence

3) Examine the delivery of elements of the intervention (fidelity and 'dose')

4) Assess intervention acceptability to participants and their carers

5) Enhance interpretation of results

6) Support dissemination and implementation.

The process evaluation will explore the implementation of the intervention, the mechanisms of impact and contextual factors.

*Implementation*

For the implementation of the intervention we will record number and lengths of training sessions for clinicians, attendance and completion rates of training tasks.

For the delivery of the intervention we will record number and lengths of intervention visits as well as goals set for the participants and video-record intervention visits (participant information sheets and consent form attached to the application).

*Mechanisms and contextual factors*

For the exploration of mechanisms and contextual factors, we will conduct interviews and assess personality traits. We will aim to interview 10 participants at each site as well as the clinicians delivering the intervention. In additional, we will invite all participants who withdraw from the study to be interviewed to explore reasons for withdrawal. Furthermore, a personality questionnaire (BFI-10, see assessments) will be included in the baseline and follow-up assessments to examine the role of personality traits in adherence to the intervention.

## 3.2 INTERVENTION AND CONTROL

The trial will compare active intervention with a standard care control.

**Active intervention**. The therapy programme will be tailored to individual abilities, co-morbidities, interests and goals, and will include progressive strength and balance exercise, activity and risk analysis, training and advice, environmental assessment, and will identify opportunities to continue the programme outside of supervised sessions and after the period of supervision has finished.

The intervention is described in a manual. The therapy programme includes:

*Assessment*

Therapists will make a clinical assessment, including conventional falls risk factors (using the Guide to Action tool, Robinson 2010), balance, gait and activities of daily living. Clinical measurement scales (such as Berg or Tinetti balance scales) will be used if appropriate.

*Activities, exercise, information and advice*

A programme of activities and exercises will be developed with the patient and carer and set out in a workbook, including:

1) Functional activities such as shopping, climbing stairs, hanging out washing, decorating, gardening, hobbies, cooking. Dual-task challenges will be introduced into functional activities. Pacing will be used to avoid fatigue.

2) Gait re-education, muscle strengthening, balance-challenging and resistance exercises with dual-task challenge. Previous literature has consistently established that 3h per week is the minimum effective exercise 'dose', over six-12 months, to prevent falls (Sherrington, 2016). Participants are encouraged to perform exercises three times a week, and spouses, partners, family members or carers will be asked to support, by telephone if necessary, or to participate as well.

3) Advice on avoiding risk, taking risks, planning for risks, planning for falls including practice getting up from the floor. Risks that are identified will be discussed and agreement reached on how to manage them in a positive way, only restricting activity if absolutely necessary (Manthorpe, 2010).

4) To encourage persistence after professional supervision ceases patients will be introduced to local exercise or activity classes, encouraged to start a diary of activities.

5) Periodic reassessment, review and progression.

*Supervision*

People with dementia struggle to remember and to plan. One potential solution to this is to provide supervision. We will determine each participant's needs to enable them to sustain the programme, using a stratification tool, with up to 50 visits from therapists and rehabilitation support workers over 52 weeks if required, tapered to encourage habit-formation and the continuation of self-directed exercise between supervised sessions and after the programme has completed. An option to pause or suspend supervision will be introduced to account for individual circumstances (such as holidays, intercurrent illness or bereavement).

**Control.** A falls prevention assessment by a therapist, and up to two further visits if required.

**Concurrent treatment.** All other interventions will be permitted, in both study arms, including Cognitive Stimulation Therapy, use of acetylcholine inhibitor drugs or memantine, or referral to standard falls prevention services.

## 3.3 STUDY OUTCOME MEASURES

**Primary endpoint**

Primary outcome will be disability in ADL, which is informant-reported (Disability Assessment in Dementia, DAD, Gélinas, 1999). This is as recommended in a recent NIHR systematic review [Webster 2017].

**Secondary endpoint**

1) Self-reported ADL using the Nottingham Extended ADL Scale [Nouri and Lincoln 1980]
2) Falls rate in months four-15 from randomisation (defined as 'unintentionally coming to rest on the ground or at a lower level, however caused', and ascertained by monthly diary)
3) Quality of life (EQ5D3L and EQ5D5L proxy [EuroQol Group 1990]; DemQol and DemQol proxy, including Demqol-u weights [Smith 2005; Mulhern 2013])

4) Mood or 'Affect' (HADS [Zigmond and Snaith 1983]; AES [Marin, Biedrzycki and Firinciogullari 1991])
5) Physical activity (LASA physical activity questionnaire [Stel 2004], pedometers)
6) Cognition (three scales from CANTAB [Cambridge Cognition, 2015]; Montreal Cognitive Assessment [Nasreddine 2005], verbal fluency (from MoCA).
7) Time to first fall (diary)
8) Rate of fractures and injurious falls (diary)
9) Rate of hospital and care home admissions, and days spent in hospital (diary, hospital administrative records)
10) Carer strain (Carergiver Strain Index [Robinson 1983]).
11) Carer health-related quality of life (EQ5D-5L [EuroQol Group 1990])
12) Personality (Big Five Personality Inventory– short [BFI-10, Rammstedt and John 2007])

Costs from NHS and personal social services perspective, including care home admission, will be collected using the Client Service Receipt Inventory [Chisholm 2000] and routine health service records.

**Safety endpoints**

1) Intervention-related injury (recorded by therapists, diary, or research follow-up)

2) Injurious falls (diary)

3) Hospital admission (diary, hospital administrative records)

4) Mortality (carer report, hospital administrative records).

## 3.4 ADDITIONAL STUDIES

An MRI sub-study will be conducted on a sample of participants. A supplementary protocol is available, and separate ethical approval will be sought.

## 4. PARTICIPANT ENTRY

### 4.1 SELECTION OF PARTICIPANTS

**Recruitment**

We will recruit patient participants and a willing family member or carer.

**Sites**

Participants will be recruited from Memory Clinics (Memory Assessment Services), in at least four sites.

**Approach**

Initial approach will be from a member of the patient's usual care team, and information about the trial will be on display in the relevant clinical areas. The investigator or a nominee (from the research team, a clinical research network Clinical Studies Officer or a member of the participant's usual care team), will inform the participant and a carer, of all aspects pertaining to participation in the study, will assess capacity, take consent and make arrangements for baseline data collection.

Patients are being encouraged around the country to register with the NIHR Join Dementia Research initiative. Where this is in place, subsequent contact may be directly from a member of the research team or CSO.

**Population vulnerability**

The population is vulnerable because of cognitive limitations, and the psychological trauma of receiving a life-changing diagnosis. They may fail to understand what is proposed, or be vulnerable to coercion. We will explicitly test capacity to consent to participation, and we will only recruit those who do have such capacity. Both patient participants and family members or carers will give informed written consent.

**Voluntary participation and data management in the event of withdrawal**

It will be explained that: entry into the trial is voluntary and that their routine treatment and care will not be affected by their decision; they can withdraw at any time, without giving a reason, and that any such decision will not affect future treatment or care; participants who withdraw from treatment will be asked to continue to provide falls and activity data, and attend the final follow-up visit; data on withdrawn participants will be used in the final analysis, and routine healthcare data will be

scrutinised for mortality, hospital admissions and fractures, unless the participant has specifically declined permission for this.

For those who do withdraw, data will be retained to enable an audit-trail of a participant's participation up to their point of withdrawal.

## 4.2 PRE-REGISTRATION EVALUATIONS

Diagnosis of MCI or dementia; Montreal Cognitive Assessment (MoCA) score 15-25 (or Addenbrooke's Cognitive Assessment ACE-III of 60-80 if that is used locally).

## 4.3 INCLUSION CRITERIA

Inclusion criteria:

1) age 65 or over (no maximum)

2) a diagnosis of dementia or MCI (of any subtype, except Dementia with Lewy Bodies)

3) Has a family member, carer or friend who knows the participant well (defined as having contact with them for at least one hour per week via internet, telephone or in person), and is willing and able to act as an informant

4) Able to walk without human help

5) Able to communicate in English

6) Able to see, hear and have dexterity sufficiently to perform neuropsychological tests

7) Capacity to give consent to participate, and consenting to do so.

## 4.4 EXCLUSION CRITERIA

1) Co-morbidity preventing participation (e.g. severe breathlessness, pain, psychosis, Parkinson's, Dementia with Lewy Bodies, or other severe neurological disease)

2) Unavailable over the next year (e.g. plans to relocate or go on a long holiday, or has a life expectancy of less than a year)

## 4.5 BASELINE ASSESSMENT

Those agreeing to take part will be screened for suitability and a baseline assessment undertaken at home, or in a clinic setting if preferred. This will include:

1) Demographic and contact details, carer demographic and contact details

2) Medical and falls history, including previous fractures, recent hospitalisation, and drugs taken

3) Blood pressure, sitting and standing

4) Montreal Cognitive assessment (MoCA), CANTAB neuro-psychological assessment, verbal fluency.

5) Outcome variables (DAD and NEADL activities of daily living scales, EQ5D3L, EQ5D5L-proxy and DemQol quality of life scales, HADS and AES measures of affect, LASA physical activity questionnaire, frailty).

6) Berg balance and timed up and go tests.

7) Carer strain (caregiver strain index).

8) Carer health related quality of life (EQ5D-5L)

9) Personality (BFI-10)

## 4.6 EXPECTED DURATION OF PARTICIPANT PARTICIPATION

Each participant will take part for 15 months, starting with the taking of consent and baseline assessment, and finishing with the final diary record.

## 4.7 WITHDRAWAL CRITERIA

**Removal of participants from therapy or assessments**

Individual participants will discontinue intervention if:

1) they withdraw consent or otherwise no longer wish to take part

2) the therapist overseeing their care decides they are no longer able to take part (for example due to intercurrent illness or injury, progression of their disease or inability to adhere despite adjustment and tailoring of the programme)

3) Otherwise at the discretion of the Investigator (e.g. risk to safety of staff).

Participants may opt not to take part in individual therapy sessions or a series of sessions (e.g. because of holidays or intercurrent illness) without withdrawing from the trial.

Withdrawn participants who have been randomised will not be replaced (sample size calculations make allowance for dropout). Abrupt termination of study treatment will not affect participant safety.

## 5. ADVERSE EVENTS

We will follow procedures developed for the HTA FEMUR trial, a trial of rehabilitation after hip fracture, supported by NWORTH CTU.

Adverse event (AE) monitoring will begin when a participant has signed the consent form and will continue for 12 months.

The intervention is in keeping with current national exercise guidelines, will be individualised by experienced therapists and supervised by rehabilitation support workers. Likelihood of harm caused by the intervention is low.

Intercurrent illness, progression of dementia, loss of function, falls, hospitalisation and death are expected in both intervention and control groups. Expected SAE's given the frailty of the participant population include: falls; fractures; infections; pneumonia; strokes; dehydration; renal failure; myocardial infarction; heart failure, deep vein thrombosis; pulmonary embolism; cardiac arrhythmia; increased confusion; delirium. Mortality will also be expected for some participants given their age and frailty at the point of commencing the study.

The intervention group will have more contact with professional staff than the control group, and therefore greater opportunity to report Adverse Events (AEs). This represents a potential bias. We will assess all reported AEs. For the purposes of comparison of the safety of trial arms we will consider "deaths", "hospital admissions" and "falls" to be core AEs (as agreed by the Data Monitoring and Ethics Committee). We have mechanisms to ascertain these which are equivalent across arms and therefore free from bias.

Adverse events may be volunteered spontaneously by the participant during therapy sessions or discovered by clinicians during therapy sessions or telephone conversations. To reduce potential bias

between the intervention and control groups all participants will be asked to record new symptoms and hospital admissions in their monthly calendars.

Medical judgement will be exercised in deciding whether an AE is serious, expected or causally related.

## 5.1 DEFINITIONS

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria below. Hence, a severe AE need not necessarily be serious.

**Adverse Event (AE):** an incident, injury or symptom related to therapy sessions, or exercise undertaken independently. The most likely adverse events are fatigue, musculo-skeletal symptoms or injuries such as muscle stiffness, or sprains, or increased falls though increased activity. Some conditions such as arthritis or angina may be exacerbated by exercise. All such events, whether expected or not, should be recorded.

**Serious Adverse Event (SAE):** any untoward and unexpected medical occurrence or effect, during or caused by the intervention, that:

**a) Results in death**

**b) Is life-threatening** – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

**c) Requires hospitalisation**

Hospitalisations for elective treatment of a pre-existing condition do not need reporting as an SAE.

**d) Results in persistent or significant disability or incapacity.**

**Causality**

**a) Not related or improbable**: a clinical event including laboratory test abnormality with temporal relationship to trial intervention which makes a causal relationship incompatible or for which other treatments, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

**b) Possible**: a clinical event, including laboratory test abnormality, with temporal relationship to trial intervention which makes a causal relationship a reasonable possibility, but which could also be

explained by other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

**c) Probable**: a clinical event, including laboratory test abnormality, with temporal relationship to trial intervention which makes a causal relationship a reasonable possibility, and is unlikely to be due to other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

**d) Definite**: a clinical event, including laboratory test abnormality, with temporal relationship to trial intervention which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

With regard to the criteria above, medical and scientific judgement shall be used in deciding whether prompt reporting is appropriate in that situation.

## 5.2 REPORTING PROCEDURES

The reporting procedures outlined in the adverse event reporting Standard Operating Procedure should be followed. Any questions concerning adverse event reporting should be directed to the central co-ordinating administrator in the first instance:

**Melanie Heeley, Email: m.heeley@nottingham.ac.uk, Tel 0115 8466545**

All adverse events should be reported, as soon as possible – Serious Adverse Events within 24 hours of the PI becoming aware of the event.

The adverse event should be reported by the team member who is first informed of the event.

SAEs will be reported to the Yorkshire and Humber – Bradford Leeds REC if, in the opinion of the Chief Investigator, the SAE is considered:

- ‘related’, i.e. resulted from the administration of any of the research procedures; **and**
- ‘unexpected’, i.e. an event that is not listed in the protocol as an expected occurrence

Related and unexpected SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event, using the “NHS HRA Non-CTIMP Safety Report to REC” Form.

Principal investigators should report any SAEs as required by local Trust policy and procedures.

SAE reports will be notified to the sponsor (NUH) by the CI or delegated person by e-mail to rdspon@nhs.nuh.uk, or by fax to: 0115 8493295, and by phone to the R&I Dept on 0115 9709049, to confirm arrival.

## 6. ASSESSMENT AND FOLLOW-UP

Participants will complete a daily falls activity and service use calendar from months 0-15, to be returned monthly. The nominated carer will be asked to prompt and oversee this. Telephone calls will be made to prompt or support as needed.

At 6 months, carers will be asked to complete questionnaires via post (EQ5D-5L proxy, DEMQOL-U items from DEMQOL, and a short CSRI). Telephone calls will be made to prompt or support as needed.

Participants will be asked to wear a pedometer for a week at baseline and week 52, in order to measure activity. These will be posted back, or collected if required.

Participants will be visited at home 12 months (+/- 4 weeks) after randomisation, to collect outcome data.

### 6.1 PROCESS EVALUATION ASSESSMENT

Semi-structured interviews will be conducted with a sample of participants from each site to explore their experiences of taking part in the intervention. When participants notify the study team of their wish to withdraw, they will be invited to take part in an interview to explore their reasons for withdrawal. Clinicians will be interviewed about their experiences of delivering the intervention, and this will form a part of their job role.

Minutes of PrAISED activity completed by participants per day will be collected by calendars, as described above. Therapists will record number and lengths of intervention visits as well as goals set for the participants. Therapy sessions with participants will be video-recorded. Participants and carers involvement in video-recording is will be listed as an optional box on their consent form. Video recording will be part of the job role of clinicians delivering the intervention. We will record the number and lengths of training sessions for clinicians, attendance and completion rates of training tasks.

## 7. STATISTICS AND DATA ANALYSIS

A data management plan will be drawn up by NWORTH CTU as part of trial set up, following that used in the feasibility trial. Data will be entered locally using the MACRO data entry system. All appropriate documentation will be stored for a minimum of seven years after the completion of the study, including the follow-up period.

### 7.1 STATISTICAL ANALYSIS PLAN

A Statistical Analysis Plan will be agreed between the CTU study statistician, and chief investigator before completion of data collection, and presented to the DMEC and PSC for ratification.

Data management and analyses will be undertaken by the CTU. Analyses will be performed blind to allocation.

### 7.2 SAMPLE SIZE AND JUSTIFICATION

Primary outcome is disability at 12 months. A sample size of 184 participants per group, including 23% attrition (based on previous studies (Blankevoort 2010, Pitkala 2013), has 80% power to detect changes in the disability outcome, DAD, with effect size 0.5 (11 points on a baseline of 70, standard deviation 22, data from [Blankevoort 2010, Rao 2014]). This will be rechecked using data from the feasibility study.

We have also assessed the power of a study of this size to detect a reduction in falls, based on a negative binomial distribution (over-dispersed compared with Poisson; we did not assume a normal distribution). If the mean fall rate in the control group is 2.0 falls/year, with a two-sided significance level of 5%, a study of this size has 80% power to detect a 25% reduction in the fall rate. Taylor (2014) followed-up a similar population (80% MMSE>18, 49% MMSE >24); mean fall rate was 2.1/year.

### 7.3 BASELINE COMPARISON

Baseline variables will be described in both groups using means, medians or proportions as appropriate:

age, sex, education, CANTAB and MoCA cognitive function, co-morbidity score, previous falls, DAD and NEADL disability, baseline EQ5D and Demqol, physical functioning (BP, TUGs and Berg Balance), fear of falling, frailty, physical activity, affect (HADS, AES), personality, and carer strain, health and comorbidity.

## 7.4 ASSESSMENT OF EFFICACY

The primary outcome is disability in ADLs. We will compare the DAD ADL scale between intervention and control groups, adjusting for stratifying variables and any baseline imbalances in a regression/ANCOVA model.

Rate of falls will be compared using the incidence rate ratio, with 95% CIs and statistical significance determined in a negative binomial regression model, adjusted for baseline imbalance or variables with prognostic importance. Previous studies (eg Logan et al (2010), Robertson et al (2005)) recommend using negative binomial regression to account for the over-dispersed Poisson data that has been encountered in their studies.

Other secondary outcomes will be compared using proportions, means and analysis of covariance to adjust for baseline imbalance or variables with prognostic importance. Secondary outcomes include fractures, hospital admissions, cognition and quality of life.

Participants who die will have follow-up time censored. If there is an (unexpected) mortality difference between arms we will perform a sensitivity analysis with death included as an end-point (to avoid survivor bias).

The process evaluation analysis will be descriptive [MRC guidelines, Moore 2014].

## 7.5 ASSESSMENT OF SAFETY

Safety variable are intervention-related injury, injurious falls, hospital admission and mortality, and will be compared using proportions/odds ratios, means and regression analysis to adjust for baseline imbalance or variables with prognostic importance.

### 7.6 PROCEDURES FOR MISSING, UNUSED AND SPURIOUS DATA

Data will be checked and cleaned using logical and manual checks and reference to original documents. We will use multiple imputation after description and testing the assumption of MAR.

### 7.7 DEFINITION OF POPULATIONS ANALYSED

Safety set: All randomised participants who receive at least one treatment.

Full Analysis set: All randomised participants, for whom a post-baseline assessment of the primary endpoint is available.

Per protocol set: All participants in the Full Analysis set who are undertook >75% of the treatment sessions.

Analysis will be by intention to treat with multiple imputation for missing data. A complete case analysis will be undertaken as a sensitivity analysis.

An exploratory per protocol efficacy analysis will be undertaken if there is no significant difference on the main analysis.

### 7.8 PROCESS EVALUATION

The process evaluation of the trial will follow Medical Research Council guidelines for the Process Evaluation of Complex Intervention (2011) to explore the implementation of the intervention, the mechanisms of impact and contextual factors. A process evaluation analysis plan will be developed and agreed between the chief investigator and process evaluation work-package leaders.

## 8. REGULATORY ISSUES

### 8.1 ETHICS APPROVAL

The Chief Investigator will obtain approval from a Research Ethics Committee and the Health Research Authority, including capacity and capability assessment at each participating NHS Trust. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

## 8.2 CONSENT

In accordance with the Mental Capacity Act 2005, research should not be undertaken on patients lacking capacity when the research question could be answered by including participants who have capacity to consent. For this research question, we believe that this to be the case, so potential participants lacking capacity will not be included.

Researchers and CRN Clinical Studies Officers will be trained in assessing mental capacity and taking consent from those with cognitive impairment. All participants and a family member or carer will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. The researcher or CRN Clinical Studies Officer will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The researcher or CRN Clinical Studies Officer will answer any questions that the participant has concerning study participation, and assess understanding and ability to use information to make a decision about participation. The right of the participant to refuse to participate without giving reasons will be respected. A brief and simplified PIS will be provided to facilitate understanding and capacity.

Informed consent will be collected from each participant before they undergo any baseline assessment (apart from MoCA which is part of suitability screening), data collection or interventions related to the study. One copy of the consent form will be kept by the participant, and one will be kept by the Investigator.

If participants lose capacity to consent during the course of the study, they will continue in the study so long as the family member or carer is happy for them to do so, in the role of 'personal consultee' (under Mental Capacity Act section 5).

Should there be any amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

## 8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study. The patient's GP will be informed of participation.

### 8.4 INDEMNITY

Standard NHS Indemnity applies.

### 8.5 SPONSOR

Nottingham University Hospitals NHS Trust will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

### 8.6 FUNDING

NIHR-CCF are funding this study. Expenses will be reimbursed. There will be no other inducements.

### 8.7 AUDITS

The study may be subject to inspection and audit by Nottingham University Hospitals under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

The NWORTH Quality Assurance Manager will provide support and advice on regulatory and quality assurance aspects of the study.

## 9 STUDY MANAGEMENT

### 9.1 MANAGEMENT STRUCTURE

This trial forms part of an NIHR Programme, which will be under the overall direction of a Programme Management Board. The Programme Management Board will meet monthly.

The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator.

The trial will be led by a work-stream lead, in collaboration with the CI.

A Trial Management Group will comprise the Chief Investigator, Trial Manager, and statistician, and other researchers, service managers or clinicians as required, and will meet fortnightly. TMG will report to the PMB.

A Programme Steering Committee will be constituted including an independent chair, two PPI representatives, sponsor's representative, two other clinician representatives, CI, statistician and trial manager. The PSC will meet before commencement and six monthly thereafter, including considering the final report, or at the request of the PSC chair or CI. PSC will report to the PMB. Terms of Reference will be in line with 1998 MRC guidelines.

A Data Monitoring Committee will be a subcommittee of the PSC, but will include only independent members and an independent statistician in order to consider statistical reports. Terms of Reference will be in line with 1998 MRC guidelines.

Monthly progress reports will be submitted to the PMB. The PSC will report 6 monthly to the PMB. Adverse events will be reported as detailed in section 5.

## 9.2 CRITERIA FOR TERMINATING TRIAL

The trial would discontinue if the Programme Management Group (PMG) decided that:

1) the intervention was deemed likely to be harmful beyond reasonable doubt

2) conduct of the trial become non-viable (poor recruitment, inability to deliver the intervention).

The trial would discontinue in a single centre if the PMG decided that:

1) recruitment rate or retention was so poor as to make it not worth deploying trial or network resources at that site

2) the intervention became impossible to deliver.

In reaching these decisions the PMB will take into account the advice of the Programme Steering Committee.

## 10 PUBLICATION POLICY

The published output will form part of the dissemination of the programme, and will include:

1) Details of the intervention and its development

2) Intervention manual

3) Trial protocol

4) Main results (efficacy) paper

5) Papers relating to fidelity and context

6) Interim and final reports to NIHR.

Authorship will follow standard ICMJE guidelines, on behalf of the study group.

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**APPENDIX 1. SUMMARY OF INVESTIGATIONS, TREATMENT AND ASSESSMENTS**

| | Pre-treatment | Monthly, months 0-15 | 6 month | Week 52 |
|---|---|---|---|---|
| Baseline measures | X | | | |
| Diary (falls, exercise, service use) | | X | | |
| Pedometers (wear for 7 days) | X | | | X |
| Postal outcome variables (quality of life, service use) | | | X | |
| Follow-up assessment, outcome variables | | | | X |

## APPENDIX 2. AMENDMENT HISTORY

| Amendment No. | Protocol version no. | Date issued | Author(s) of changes | Details of changes made |
|---|---|---|---|---|
| 1 | 2 | | | Addition of MRI sub-study (supplementary protocol available).<br><br>Addition of short postal informant-completed health economics questionnaire after 6-month<br><br>Revision of questionnaires at baseline and follow-up, in light of feasibility study<br><br>Addition of items on personality<br><br>Clarification on SAE reporting |