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Evaluation of Exercise on Individuals with Behavioural and Psychological Symptoms of Dementia and Their Carers: A Randomized Controlled Trial

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I Arlinda Cerga Pashoja, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. I joined the EVIDEM team in 2008 and was therefore present in the early meetings between the Principal Investigator Dr James Warner and the Trial Manager Dr David Lowery and was able to have input into the trial design, refining and writing up the protocol. I have also contributed in setting up the Steering Group and organising its meetings. I wrote the standard operating procedures, put together study Case Report Forms and completed the R&D and ethics applications. The trial was granted ethical approval by the Outer North East London Research Ethics Committee, REC reference number: 09/H0701/67. I coordinated participant recruitment and carried out data collection through face to face interviews with participants. I set up the study database in Epidata, entered data and carried out the data analysis with support from Mark Griffin (statistician).

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ABSTRACT

There are over 840,000 people in the UK with dementia, most of whom will experience Behavioural and Psychological Symptoms of Dementia (BPSD). Treatment options for BPSD are limited and often they have been managed with anti-psychotic medication, which increase mortality and the risk of stroke in people with dementia. Consequently, it is imperative to evaluate the impact that non-pharmacological interventions such as physical exercise have on BPSD. This research seeks to address this matter by: exploring the current state of knowledge through a literature review; designing a simple, measurable and safe physical intervention for BPSD; devising, carrying out and reporting findings on a methodologically robust trial of exercise; and discussing its impact and future directions.

A rapid appraisal of the literature showed that exercise programmes for people with dementia have often been poorly conceptualised and research methods had significant limitations; this was addressed with the design of EVIDEM-E. EVIDEM-E was a pragmatic, randomised, parallel group, single-blind, controlled trial that evaluated the effectiveness of exercise (planned walking) on the BPSD symptoms of 131 dyads (individuals with dementia and their carers). Physical exercise was delivered as an individually tailored regime of walking designed to become progressively intensive.

Regular walking did not produce a statistically significant reduction in BPSD. This exercise, however, attenuated carer burden significantly. It is not clear whether this was because of the exercise per se, increased psychosocial interaction between carer and person with dementia, or a Hawthorne effect. Further research should focus on the mechanisms by which exercise may affect carers' burden and whether reducing carer burden has long-term effects.

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TABLE OF TERMS

The following is a list of abbreviations used in this thesis.

AE	Adverse Events
BPSD	Behavioural and Psychological Symptoms of Dementia
CMHT	Community Mental Health Teams
CNWL	Central and North West London NHS Foundation Trust
CRF	Case Report Forms
DCR-10	Diagnostic Criteria for Research-10
DemReg	Dementia Registry
DLB	Lewy Body Dementia
ET	Exercise Therapy
Eth	Exercise Therapist
FRAT	Falls Risk Assessment Tool
FTD	Frontotemporal Dementia
GCP	Good Clinical Practice
GP	General Practitioner
HBM	Health Belief Model
IPA	International Psychogeriatric Association
IR	Independent Researcher
ITT	Intention to Treat
MCA	Mental Capacity Act
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MSS	Multi-sensory Stimulation

NIHR	National Institute for Health Research
NPI	The Neuropsychiatric Inventory
NT-DeNDRoN	North Thames Dementias and Neuro-Degenerative Diseases Research Network
OR	Odds Ratio
PI	Principal Investigator
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
RO	Reality Orientation
RPE	Rating of Perceived Exertion
RT	Reminiscence Therapy
RW	Research Worker
SAE	Serious Adverse Events
SLUM	Saint Louis University Mental Status
TAU	Treatment as Usual
TPB	Theory of Planned Behaviour
TRA	Theory of Reasoned Action
TRL	Trial Recruitment Log
TSC	Trial Steering Committee
TTM	Trans-theoretical model
TUSS	Timed Unsupported Steady Standing
VaD	Vascular Dementia
ZBI	Zarit Caregiver Burden Inventory

1 INTRODUCTION

1.1 What is Dementia

The word Dementia is derived from Latin (de=out from; mens= the mind) and means loss of mental abilities due to illness. Dementia is a syndrome that is defined as “progressive brain atrophy due to nerve cell loss leading to a characteristic worsening of memory and global intellectual deterioration without impairment of consciousness” (Rowley, 1994). Dementia is almost always an irreversible process that damages areas of the brain that control thinking, memory, reasoning, personality, perception and language. Some types of dementias are potentially reversible. The causes for these types of dementia can be: toxic reaction to medication, vitamin B12 deficiency, hormonal dysfunction, tumours and dietary deficiency. (Solomon and Budson, 2011). There are different types of dementia, which are discussed further in paragraph 1.1.3.

1.1.1 Historical context

King Lear, Act 4, Scene 7:60-70

LEAR: "Pray, do not mock me: I am a very foolish fond old man;
Four score and upward, not an hour more nor less;
And, to deal plainly, I fear I am not in my perfect mind;
Methinks I should know you, and know this man;
Yet I am doubtful: for I am mainly ignorant. What place this is; and all the skill I have;
Remembers not these garments; nor I know not where I did lodge last night;
Do not laugh at me; for, as I am a man, I think this lady to be my child Cordelia."

William Shakespeare wrote King Lear around 1606. He portrayed what we now know as dementia about 300 years before Alois Alzheimer's landmark description. Depictions of disorders of memory in older adults can be traced back to 2000-1000 BC in Egyptian and Greek civilizations (Berchtold and Cotman, 1998). References to dementia-like conditions can also be found in Roman, Indian and Chinese medical texts. In India the complementary physicians called Ayurvedic used the Sanskrit term *Smriti Bhransh* to describe loss of memory (Mishra et al., 2013). Also, in some parts of South India, the word *Chinan* is used to refer to a condition associated with ageing, deterioration in memory, abnormal behaviour and incontinence. The Chinese used the words *Zhi Dai Zheng* for dementia and *Lao Ren Zhi Dai Zheng* for senile dementia (Zhang et al., 2006).

The word 'démence' has existed in the French language since 1381 and implied a lack of ability to function on day-to-day basis. Apart from clinical implications 'démence' was introduced in the legal system during Napoleon's reign. This is represented in Article 10 of the Napoleonic Code 1808: *'There is no crime when the accused is in a state of dementia at the time of the alleged act'.*

Medical use of the term dementia evolved throughout the 19th century and was used to describe a degenerative memory disorder often associated with old age, distinguishing it from other mental health problems such as depression or psychosis (Berchtold and Cotman, 1998).

In 1907 Alois Alzheimer identified the 'senile plaques' and 'neurofibrillary tangles' that are common to the brains of people with Alzheimer's type dementia. Alois

Alzheimer was the first to identify and publish a clinical case of ‘pre-senile dementia’ (Figure 1.1), which was later named after Alzheimer by Kraepelin (1909/1910). The description below is a clear depiction of behavioural and psychological symptoms of dementia, which I will return to later (page 32).

Definitions of dementia have become more medically specific in the last three decades. Currently the diagnostic criteria for dementia (American Psychiatric Association, 2013) refers to the multiple cognitive and intellectual deficiencies and decline involving memory, new and previously learnt information and problems with language, impairment of motor skills, inability to recognize familiar people or objects and impairments in planning, organizing and abstract reasoning. The process of ageing has been considered dominantly under the disciplines of biology and medicine (biomedicine) (Estes and Binney, 1989), which is being discussed further in the next section.

“One of the first disease symptoms of a 51-year-old woman was a strong feeling of jealousy towards her husband. Very soon, she showed rapidly increasing memory impairments; she could not find her way about her home, she dragged objects to and fro, hid herself, or sometimes thought that people were out to kill her, then she would start to scream loudly. From time to time she was completely delirious, dragging her blankets and sheets to and fro, calling for her husband and daughter, and seeming to have auditory hallucinations. Often she would scream for hours and hours in a horrible voice.”

Figure 1.1 Extract from: Alzheimer, 1907

1.1.2 Biomedicalization of dementia

During this brief journey in the history of dementia, it is remarkable how its definition has changed but descriptions of the symptoms remain more or less the same. Our conceptualization of dementia has changed through time and it has been informed by very important medical discoveries. Development of medication for dementia helped bring dementia out of the shadows and foster discussion. However, it seems that the more is learned about dementia mechanisms and brain structural changes the more medical focus the definition takes and the further away it departs from important social and psychological factors. The biomedical model of dementia assumes there is a causal relationship between neuropathology and dementia. Kitwood (1989) and Lyman (1989) challenged the medical model of dementia as inadequate and as a way of medicalizing dementia by treating it strictly as a medical problem. The biomedical model describes the diagnosis of a disease process, attempts to explain its causation and offer (limited) management with pharmaceutical drugs. Thus, this account tends to lose sight of the person who suffers from the condition and overlooks essential social factors such as the carers and their wider social and family support systems.

The loss of cognitive functions can bring about distress in individuals who suffer from it, and amongst the people who care for them, usually family members. Lyman argues that being given the medical label of ‘dementia’ with a prognosis of progressive deterioration brings about feelings of helplessness and despair (Lyman, 1989). The labeling itself may limit the social engagements of those diagnosed and reduce social and functional expectations from carers, family and friends, thereby

imposing ‘learned helplessness’. ‘Learned helplessness’ is a condition when individuals believe they have no control over any situation, whatever they do (Seligman, 1991). Lyman (1989) suggests that while the biomedical model may be useful in terms of giving order to the care provided through introducing some predictability and control it can affect significantly the behaviour of the people diagnosed and their carers. Thus, activities which could be construed as “normal” such as walking may be interpreted by carers as signs of disease and be labeled or pathologised as ‘wandering’.

Kitwood (1993) proposed a model of dementia, called the Theory of Personhood that takes into account individual differences, social and psychological factors as well as neurological impairment. He puts forward the following equation:

SD = P + B + H + NI + SP

SD stands for the clinical symptoms of dementia; P for individual’s personality characteristics such as coping styles towards change and loss and help seeking attitude; B refers to individual life stories in terms of losses, bereavement, and weakening of their lifelong support systems; H represents physical health; NI neurological impairment and SP social psychology and its effect on person’s values and wellbeing.

Kitwood’s Theory of Personhood comprises a holistic, non-biomedical approach to the individual with dementia which alongside other psychosocial theories of BPSD (discussed in Paragraph 1.3.3) is a fundamental element of the EVIDEM-E study design as described in this thesis. The trial was carefully designed to tailor a non-

medical intervention to each participant with dementia and their carer in order to test the hypothesis that physical activity would improve Behavioural and Psychological Symptoms of Dementia (BPSD) and carer burden. We used a rigorous approach, which is distinctive of pharmacological trials, to test a non-medical intervention. The evidence-base of dementia research is characterised by poor quality studies of non-pharmacological interventions (Kverno et al., 2009; Thuné-Boyle et al., 2012).

1.1.3 Dementia sub-types

Dementia is an umbrella term for memory disorders and other cognitive changes in older adults, and is therefore a syndrome. Different types of dementia exist of which Alzheimer's disease is the most common and therefore quite often it is used in lay language as a synonym for dementia.

Primary neurodegenerative disorders: Alzheimer's disease, along with Parkinson's disease, Huntington's disease, Lewy Body dementia and a group of conditions referred to as Frontotemporal dementia (FTD), are conditions that result in progressive degeneration or death of nerve cells.

Vascular disorders: Vascular dementia is caused as a result of conditions such as atherosclerosis, stroke or vasculitis that impair blood flow to the brain.

1.1.4 Diagnostic criteria for dementia

Dementia is difficult to recognise clinically in its early phase (Vernooij-Dassen et al., 2005). The process usually includes taking medical and informant history, brain imaging, and neuropsychological testing, as well as other investigations depending

on the individual's presentation, as summarised in the Nice Guidelines (2006). The growing body of evidence about biomarkers has allowed them to be incorporated into the diagnostic research criteria, especially for Alzheimer's disease (Dubois et al., 2007).

A set of criteria is often used to help make an accurate diagnosis. There are two main criteria systems presently used: The International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health Organization, 1993), and the Diagnostic and Statistical Manual of Mental Disorders (5th Edition), also known as the DSM-V (American Psychiatric Association, 2013).

The DSM-V outlines a detailed set of criteria for the diagnosis of dementia under the category of Major Neurocognitive Disorder (NCD). According to DSM-V a diagnosis is made when there is established cognitive impairment in addition to memory deficits that significantly affect social functioning and are characterised by gradual onset and irreversibility.

The ICD-10 criteria is not worded as precisely as the DSM-V and has been criticised for being open to personal interpretations (Regier et al., 2013). Nevertheless, ICD-10 is widely used in both clinical and research settings (Naik and Nygaard, 2008). We chose to use ICD-10 instead of DSM-V because of a focus on emotional, behavioural and motivational decline (Table 1.1).

Table 1.1 Criteria for dementia diagnosis according to ICD-10 and DSM-V

Diagnostic Criteria	ICD-10	DSM-V
Memory impairment: recent or long term	X	X
Other cognitive disturbances aphasia apraxia agnosia executive functioning		X
Impairment of: abstraction judgement thinking planning/organizing	X	
Preservation of awareness/consciousness	X	
Decline in or change of : emotional liability irritability apathy coarsening of social behaviour	X	
Duration 6 month or more	X	

The accuracy of dementia diagnosis has been evaluated through post mortem identification of neuropathological sign especially senile plaques and neurofibrillary tangles. The diagnostic accuracy for Alzheimer's disease has been reported to range from 65–96% with a specificity (the percentage of healthy people who are correctly identified as not having dementia) of 23%–88% (Kazee et al., 1993; Lim et al., 1999; Varma et al., 1999). The positive predictive value (the chance that a person with diagnosis truly has dementia) has been reported as 80%-90% (Corey-

Bloom et al., 1995). However these values vary on the setting where the diagnosis is made and the exact clinical and neuropathological criteria used. There are two established neuropathological diagnostic criteria: Braak and Braak's criterion that evaluates the density and distribution of neurofibrillary tangles and is mainly used in research settings, and the Consortium to Establish a Registry for Alzheimer's disease (CERAD) criterion that evaluates the highest density of senile plaques and is most frequently used in clinical outcome studies (Murayama and Saito, 2004). Thus, diagnosis made at special memory clinics have been reported to have higher positive predictive values than diagnosis made in the primary care (Corey-Bloom et al., 1995). Neuropathological studies are susceptible to the selection bias because patients seen in a specialised memory clinic are more likely to receive an autopsy than those seen only in primary care (Nelson et al., 2003). Dementia is under-diagnosed by primary care general practitioners, who interestingly often over-estimate the prevalence of dementia syndromes (Turner et al., 2004). There is also a tendency to overestimate the prevalence of vascular dementia compared with Alzheimer's disease in some countries (Maeck et al., 2008).

Neuropsychological tests are standardized tests that measure a person's memory, concentration, problem solving, mood and behaviour, and language skills. Neuropsychological testing can aid diagnosis of dementia, can help track its progression and can also assess the effectiveness of medications or other interventions. Nevertheless, their reliability has been criticized because they may be influenced by respondent's level of education, through misclassifying poorly educated individuals as demented or by missing dementia in well-educated people

(Mackinnon and Mulligan, 1998). Informant (carer) reports, on the other hand, may be influenced by non-cognitive factors, such as the affective state of the person with dementia and the informant, their personality and the quality of their relationship (Jorm, 1996). Dementia assessments are heavily dependent on linguistic and cultural factors therefore cognitive tests developed with a specific population may not be appropriate and reliable when used with individuals from different cultural and ethnic backgrounds (Rahman, 2015). The way dementia is considered in particular cultures affects how it is experienced, expressed and communicated to health professionals. Dementia in some cultures can be either highly stigmatised or be seen as normal ageing (Seabrooke and Milne, 2009). Azam (2007) has reported that in some South Asian countries dementia is considered as a form of madness and that in most South Asian languages no word for dementia exists. Furthermore, in some South Asian cultures dementia may be seen as punishment for past life actions (Mackenzie, 2006). These cultural differences make it more difficult for dementia to be diagnosed accurately and in a timely way in ethnic minority communities.

1.1.5 Prevalence and incidence rates of dementia

Life expectancy is increasing especially in industrialised societies (Figure 1.2) and is expected to continue to rise. This has brought about an increase in the prevalence of dementia.

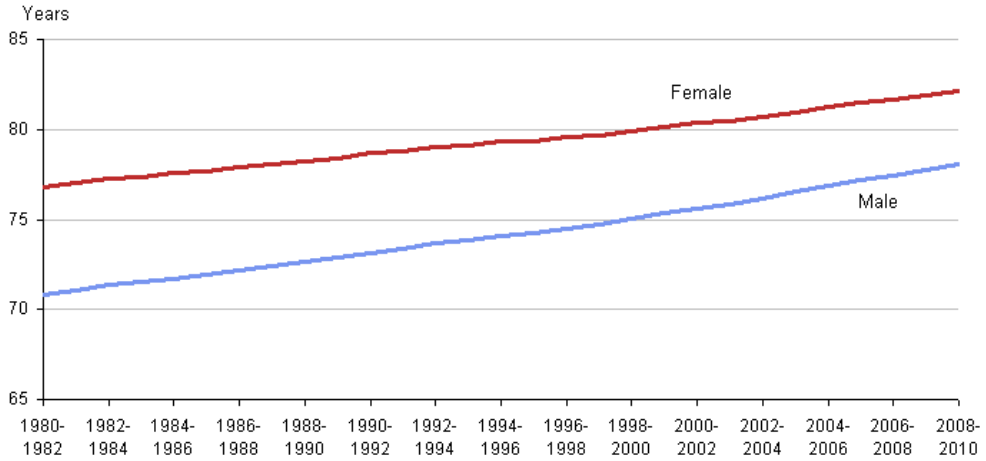


Figure 1.2 Life expectancy at birth, UK, from period life tables, 1980-82 to 2008-10 (Office for National Statistics 2011)

It has been estimated that more than 24.3 million people worldwide live with dementia, and 4.6 million new cases are diagnosed each year (Ferri et al., 2005). The prevalence of dementia is expected to double between 2001 and 2040 (Ferri et al., 2005).

Alzheimer's Society Report (2014) indicates that currently there are 850,000 people in the UK living with dementia. It also claims that 163,000 new cases of dementia occur in England and Wales each year, which means a new case arises every 3.2 minutes. Approximately 6% of people aged over 65 years have some form of dementia (Lobo et al., 2000), with the population prevalence rising to 20% in those aged over 80 years (Katz et al., 2012). However, recent epidemiological studies suggest that the incidence of dementia may be falling and that prevalence figures are inflated by as much as 25% (Matthews et al., 2013). Mathews et al. (2013) suggest that later-born populations have a lower risk of prevalent dementia than those born in the past century.

In recent years, in UK, the number of people being diagnosed with dementia has come under political as well as scientific attention. In 2013 UK hosted the first ever G8 summit on dementia. The political impetus centred around the perceived blockages in the dementia diagnosis pathway namely:

- Lack of health seeking behaviour by people with dementia and their families
- Lack of recognition in primary care and acute hospitals
- Lack of awareness of referral pathways when clinicians did identify dementia.

In 2011 in England just 42% of individuals estimated to have dementia were being diagnosed, therefore the government set an objective on dementia diagnosis according to which two thirds of the estimated number of people with dementia should receive a diagnosis by 2015 (Department of Health, 2012a). A year later (2012) dementia diagnosis had risen to 59% and the government issued a specific mandate to NHS England for 2015/16 that included a commitment to improve diagnosis (Department of Health, 2013a). As a consequence of these campaigns the proportion of people in UK diagnosed with dementia exceeded 66% of expected prevalence in 2015 (Alzheimer's Society, 2015).

1.1.6 The impact of dementia

The Dementia Report (2014) reveals that dementia costs the UK economy about £26 billion a year, which is more than the cost of cancer and heart disease combined. Thus, dementia has been described as "the greatest medical challenge of the 21st century" (Alzheimer's Research Trust, 2010). Investments in dementia

research, however, remain relatively modest. Combined government and charitable investment in dementia research, in 2010, was 12 times lower than spending on cancer research. Over £590 million is spent on cancer research each year, while just £50million is invested in dementia research. The discrepancy between dementia costs and research investments may partly be explained by the lack of awareness about the degree of the problem and dearth of statistics. On the other hand, this may represent a vicious circle where the less attention dementia gets, less research is carried out and consequently less evidence about the depth of the problem that dementia represents is available. This vicious circle can perpetuate the stigma Dementia seems to have been out of the public awareness for a long time, but recently the Department of Health (2009) and consequently the Dementia Report (Lakey et al., 2012) have focused on raising awareness and transforming the dementia services in order to provide a more effective system of diagnosis and treatment of the condition. Government funding of dementia research across the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) has increased by nearly a third (31%) in 2010/11. The prime minister has promised to double UK government investment in dementia research from £66 million in 2015 to £122 million in 2025, and similar increases are expected from the commercial and charitable sectors (Department of Health, 2012b, 2013b).

There are 6.5 million people in the UK who provide unpaid care and support to older people with dementia (Office of National Statistics, 2011). This number is predicted to reach 9 million by 2037 (Buckner and Yeandle, 2011). According to the Dementia Report (2010) 25 million people or 42% of the UK population know someone close

to them who has been diagnosed with dementia. Carers are typically partners, relatives and family members and the majority of them are women (Office of National Statistics, 2011). The Alzheimer's Research Trust (2010) reports that 1.4 million of these carers provide more than 50 hours per week unpaid care, thereby, saving the UK economy £8 billion per year.

Caring for people with dementia comes at a price for the carers. Carers of people with dementia experience more physical and mental health problems (Moise and Schwarzinger, 2004; Pinquart and Sörensen, 2007) and get more distressed (Schulz and Martire, 2004; The Princess Royal Trust for Carers, 2011) than their counterparts who look after older people without dementia. Despite the fact that carers bring huge savings to the economy, 75% of them report that they are worse off financially as a result of caregiving (Carers UK, 2008). Carers have reported that because of their caring responsibilities they have had reduced income or working hours, missed out on the chance of a promotion, or were forced to give up work (Carers Week, 2013).

Caring for a person with dementia has a profound impact not just on individual families but on the society as a whole. Thus, caring for a person with dementia costs the UK economy about £27,647 per year. This is more than the combined cost of care for or people with cancer, stroke and heart disease (cancer-£5,999, stroke £4,770 and heart disease £3,455 per year) (Carers Week, 2013).

1.2 Behavioural and Psychological Symptoms of Dementia

Behavioural and psychological symptoms of dementia (BPSD) are also known as neuropsychiatric or non-cognitive symptoms and are common and distressing features of the condition. Psychological symptoms can include anxiety, depressed mood, hallucinations and delusions while behavioural symptoms refer to aberrant motor behaviour, verbal and physical aggression, screaming, restlessness, agitation, swearing, wandering, apathy, culturally inappropriate behaviours, disinhibition and hoarding (Desai and Grossberg, 2001). Unlike cognitive functioning of people with dementia that progressively deteriorates, BPSD symptoms typically fluctuate over the course of dementia (Ballard and Howard, 2006; Lawlor, 2004).

1.2.1 Phenomenology, prevalence and incidence of BPSD

Although non-cognitive symptoms of dementia have historically been described as core features of the condition (Table 1.2) they have not been given the appropriate recognition until the last twenty years. The term Behavioural and Psychological Symptoms of Dementia was introduced in 1999 by the International Psychogeriatric Association (IPA) which has been at the forefront of raising awareness about BPSD and has been publishing and updating educational packs for the management of the symptoms.

Table 1.2 Common Behavioural and Psychological Symptoms of Dementia (Grossberg and Desai, 2003)

Symptoms	
Aggression	Screaming
Verbal	Cursing
	Agitation
Physical	Hitting
	Biting
	Kicking
	Scratching
	Grabbing
Non-aggressive behavioral symptoms	Repetitive questioning
Verbal	Complaining
	Wandering
	Pacing
	Hoarding
Physical	Rummaging
	Hiding
	Taking other people's belongings
	Shadowing
	Resistance to care
	Intrusiveness
	Mannerism
Thought and perception	Delusions
	Hallucinations
	Illusions
	Misperceptions
	Mania
Affect-Mood	Depression
	Anxiety
	Apathy
	Irritability
	Elation
	Persecution
Sleep disturbances	Insomnia
	Increased daytime napping
	Sundowning
Sexual	Hypo-sexuality (inhibited sexual excitement)
	Hyper-sexuality (increased sexual urges)
	Sexual disinhibition
Appetite	Poor food intake
	Hyperphagia (excessive hunger)

It is estimated that over 90 percent of people with dementia are likely to experience BPSD such as changes of personality and behaviour (Aalten et al., 2003; Overshott et al., 2004) and sleep disruption (Boeve et al., 2002). People with dementia are four times more likely to experience BPSD than older adults without dementia (Lyketsos et al., 2000). Prevalence estimates for BPSD vary because of the heterogeneity of sample populations studied, diverse settings and type of dementia, different study designs, sample sizes, different instruments used to measure the symptoms and the different definitions used for BPSD (Aalten et al., 2007; Finkel et al., 1996; Ikeda et al., 2004; Lyketsos et al., 2002a; Savva et al., 2009). The prevalence of BPSD is more common in nursing homes than in community settings (Australian Medicines Handbook, 2006).

Table 1.3 BPSD point prevalence in adults with dementia[1]

Symptoms	Aalten et al. (2003) Netherlands (*n* = 199)	Benoit et al. (2003) France (*n* = 255)	Byrne (2003) 12 European Countries (*n* = 138)	Saz et al. (2009) Spain (n=223)	Lyketsos et al. (2002b) USA (n=362)	Savva et al. (2009) UK (n=587)	Steinberg et al. (2008) USA (n=408)	Weighted mean[2] (n= 2,172)
Apathy	59.3	63.5	48.9	46.7	35.9	50.3	51	**50**
Depression	57.3	42.7	45.3	38.2	32.3	20.5	47	**37**
Agitation	28.6	44.3	30.9	44.4	30.3	Not reported	24	**33**
Sleep	18.1	12.9	12.9	43.3	27.4	42	Not reported	**30**
Irritability	39.7	25.0	31.7	17.9	27	28.8	27	**28**
Delusions	34.7	24.7	19.4	26	18	Not reported	38	**28**
Anxiety	39.2	46.3	33.8	39.3	21.5	8.9	32	**27**
Aberrant Motor Behaviour	34.7	29.8	18.7	Not reported	16	Not reported	29	**25**
Appetite	24.6	24.3	12.9	28.4	19.6	Not reported	Not reported	**22**
Hallucinations	13.1	7.8	7.9	5.4	10.5	15.1	24	**14**
Disinhibition	12.6	13.3	14.4	Not reported	12.7	Not reported	15	**14**
Euphoria	7.0	9.8	5.0	Not reported	3.1	9.5	1	**6**

[1] This table was adapted from Robert et al. (2005) with additional data (Savva et al., 2009; Saz et al., 2009; Steinberg et al., 2008) added and calculated (http://www.rapidtables.com/calc/math/weighted-average-calculator.htm) by the candidate.
[2] Overall mean taking into account the relative contribution of the size (n) of each study.

The above table (Table 1.3) presents findings from six, large, cross-sectional, population based studies that have reported prevalence of BPSD worldwide. The variability between the reported prevalence rates may be due to differences between study designs, utilized measures, geographical and cultural settings, population samples and severity of dementia. Thus, Benoit et al. (2003) reported on individuals with Alzheimer's disease only, while all the other studies included different dementia types. Aalten et al. (2008) and Benoit et al. (2003) recruited patients from specialized memory clinics where BPSD prevalence is expected to be higher, as opposed to the other studies that recruited community based samples. Another characteristic of Benoit et al. (2003) is that it reported on individuals with moderate/severe dementia only (MMSE 11-20) who may experience more BPSD symptoms than individuals with mild dementia. All but two of the above studies i.e. Savva et al. (2009) and Saz et al. (2009) have utilized the Neuropsychiatric Inventory to measure BPSD. The other two studies used the Geriatric Mental State Interview (Copeland et al., 2009), which uses a different taxonomy to the NPI, therefore some data is missing from these two studies. In spite of the high level of heterogeneity between the reported studies, the reported prevalence estimates of BPSD are consistent between studies. Apathy, depression and agitation are the most frequent symptoms followed by sleep problems, irritability, delusions and anxiety. Participants seem less likely to experience hallucinations, disinhibition and euphoria.

1.2.1.1 Depression

The World Health Organisation (2014) defines depression as "…. *a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration*."

Depression frequently co-exists with dementia. This can exacerbate the effects of dementia, making it even harder for affected people to remember things, leading to increased confusion and anxiety. It may also cause behavioural changes such as walking aimlessly, aggression, social withdrawal and reduced appetite (Alzheimer Society, 2008).

1.2.1.2 Anxiety

Up to 71 percent of people with dementia show signs of anxiety (Ballard, Neill, et al., 2000; Chemerinski et al., 1998; Lyketsos et al., 2001; Wands et al., 1990). In older adults without dementia, anxiety is associated with reduced quality of life, functional limitations, poorer physical health and reduced activities (de Beurs et al., 1999; Wetherell et al., 2004). Until recently, little attention has been paid to anxiety symptoms in dementia despite their high prevalence. This may be due to difficulties in defining anxiety in this population because of the overlap between symptoms of anxiety, agitation, depression and dementia. However, there is some evidence that anxious mood is associated with poorer quality of life and behavioural disturbances in dementia, even after controlling for depression (Seignourel et al., 2008).

1.2.1.3 Apathy

Apathy refers to a loss of motivation and is marked by diminished initiation (difficulty in initiating purposeful activity), poor persistence, lack of interest, indifference, low social engagement and blunted emotional response (Landes et al., 2001). The incidence of apathy increases with the severity of dementia and is the most common behavioural disturbance with reported prevalence rates as high as 80 percent (Onyike et al., 2007) with an average mean prevalence across studies of 56 percent (Robert et al., 2005). Apathy is also associated with decreased function (Yeager and Hyer, 2008). Patients with apathy are nearly three times more likely than those without to be impaired in dressing, bathing, transferring from bed to chair, using the toilet, walking or eating (Freels et al., 1992). Apathy and depression have some overlapping characteristics, like loss of interest or pleasure from activities and both are associated with functional and cognitive decline. As a result, these conditions can be conflated and many patients are perceived as having apathy and depression simultaneously (Onyike et al., 2007; Robert et al., 2006).

1.2.1.4 Aggression/Agitation

It is important to note that aggressive behaviours and agitation may be a sign of pain and discomfort (Husebo et al., 2011). It is therefore imperative to rule out pain before engaging the person in interventions to reduce BPSD. Indeed, the aetiology of aggression in dementia is complex but includes feeling frightened or humiliated; feeling frustrated at being unable to understand others or make themselves

understood; the physical effects of dementia eroding judgement and self-control; boredom; physical discomfort or pain and; loss of inhibitions and decreased awareness of rules about appropriate behaviour (The Alzheimer's Society, 2008). Behaviour can be seen as a form of communication and establishing what the person with dementia is trying to communicate may prevent them from feeling frustrated and acting aggressively. However, dealing with aggressive behaviour can be difficult and multiple solutions such as consistent routine, regular stimulation or use of music may be required (Desai and Grossberg, 2001).

1.2.1.5 Repetitive behaviours

The aetiology of repetitive behaviours include: memory loss causing the person not to remember that they have already asked a question; perseveration (repetition of a particular response) due to frontal lobe damage; side effects from medication resulting in repetitive movements or restlessness, and; psychotropic medication causing the person to have akathisia (inner restlessness) or tardive dyskinesia (repetitive body movements) (The Alzheimer's Society, 2010).

There may also be environmental causes such as: separation from the carer which leads to the person with dementia to repeat questions about their whereabouts; misrepresentation of sounds or sights, which may cause anxiety; overwhelming stimuli (e.g. movement, noise); inability to judge time causing the person to think the carer has been away for a long time; misunderstanding what is happening, causing the person to constantly ask questions; inability to express needs such as hunger, thirst, or needing to go to the toilet.

1.2.2 BPSD and types of dementia

BPSD does not occur uniformly and different dementia types are characterised by specific BPSD symptoms (Kar, 2009).

- People with Alzheimer's disease (AD) have been said to present with depression symptoms in the early stages of the condition and sometimes low mood symptoms can precede cognitive impairment (Geerlings et al., 2000). BPSD symptoms become more frequent with the severity of dementia (Steinberg et al., 2008) in AD. Other common BPSD symptoms reported for AD are apathy (Benoit et al., 2003), anxiety, phobias (Chiu et al., 2006) and agitation (Lyketsos et al., 2001).

- Lewy body dementia (DLB) is said to be characterised by the presence of visual hallucinations, which are less prevalent in other dementia types (Chiu et al., 2006). Delusional misidentification and hallucinations can happen in the early stages of DLB (Ballard et al., 2014) and worsen over the course of dementia. Anxiety and aggression have also been reported as the most common BPSD symptoms followed by depression, apathy, agitation and sleep disorders (Borroni et al., 2008; Chiu et al., 2006). DLB is marked by motor disabilities such as muscle jerking, loss of dexterity, limb stiffness and a shuffling gait (Gnanalingham et al., 1997). These symptoms cause balance problems for people with DLB and put them at increased risk of falls compared to people with other dementia types (Ballard et al.; Härlein et al., 2009).

- People with vascular dementia (VaD) are reported to be primarily affected by affective disturbances such as depression and apathy (Kindermann et al., 2002; O'Brien et al., 2003). Kar (2009b) argues that people with VaD, who unlike people with other dementia types maintain a significant degree of insight for a long time during the course of the condition, react to the awareness of their prognosis by experiencing depression and anxiety symptoms.

- The most prominent aspects of Frontotemporal dementia (FTD) are verbal outbursts and inappropriate activities (Chiu et al., 2006; Mendez et al., 1998). Inappropriate activities have been reported as disinhibition and complex compulsive behaviours (time consuming preoccupation with ideas and/or activities such as wandering, pacing and/or hoarding) which often occur at the early stages of the condition and precede cognitive deterioration (Rosso et al., 2001). Another unique feature of FTD is a change in appetite and major dietary changes (Miller et al., 2001).

The above descriptions provide an overview of the distinct features of BPSD in different dementia types. However, these characteristics can become indistinct in cases of mixed aetiology and any people with any type of dementia can experience any of the BPSD symptoms (Desai and Grossberg, 2001). The variety of symptoms across dementia subtypes encouraged us to design an intervention for people with dementia of any type, rather than for a specific sub-type. We will return to this topic on 'EVIDEM-E trial design and methods' Chapter (3) on page 106. Notwithstanding the differentiation of dementia subtypes and the importance of this in terms of management and prognosis the study group felt that clinicians

particularly in primary care would not place too much emphasis on subtype. We therefore thought it was important in terms of generalizability of the study to include all subtypes.

1.2.3 Methods for screening and diagnosing BPSD

A number of scales have been developed as tools to assess BPSD (Table 1.4, Table 1.5). However, only some of these tools are validated and widely used at present. Most of the measures are developed specifically for people with Alzheimer's disease, therefore symptoms typical to other dementia types such as hallucinations and disinhibition are not included (e.g. BEAM-D, BEHAVE-AD, BSSD, Pittsburgh Agitation Scale). Some of the more widely used instruments are: the Neuropsychiatric Inventory which screens for a wide range of behavioural and psychological symptoms; The Cohen-Mansfield Agitation Inventory (CMAI), which focuses on aggression and agitation behaviours; The Behavioral Pathologic Rating Scale for Alzheimer's Disease (BEHAVE-AD) which is used in detecting delusions and sleep disturbances; and The Consortium to establish a Registry in AD (CERAD) Behavioural Scale, which like the NPI, rates a range of non-cognitive symptoms of dementia.

Table 1.4 presents the set of measures that were not considered to be used as a primary outcome for EVIDEM-E and the reasons for their exclusion. The main reasons for not considering these instruments were that: they screened for specific symptoms only such as sleep (Leeds Sleep Evaluation Questionnaire), depression (Dementia Mood Assessment Scale, Cornell Scale for Depression in

Dementia); or the scales were not validated for people with dementia (Brief Psychiatric Rating Scale, Sandoz Clinical Assessment – Geriatric).Table 1.5 displays a more detailed analysis of the BPSD measures considered for use in this trial and their psychometric properties.

Table 1.4 Excluded measures

Measure	Reason for exclusion
Blessed Dementia Scale (Blessed et al., 1968)	Used as a dementia diagnostic tool rather than as a measure of BPSD. The rate consists of 22 items that evaluate performance of everyday activities, changes in habits and changes in personality interests and drive. Not BPSD specific.
Brief Agitation Rating Scale (BARS) (Finkel et al., 1993)	Assesses agitation and physical aggression in elderly nursing home residents. This scale is not dementia or BPSD specific.
Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962)	Developed to evaluate symptoms' change in psychiatric patients. Not validated with dementia patients.
Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield et al., 1989)	Developed to measure agitation and aggression in nursing home residents. Primarily useful with severely demented institutionalised patients. It does not assess the full BPSD spectrum.
Cornell Scale for Depression in Dementia (Alexopoulos et al., 1988)	Designed to assess depression only in dementia patients.
Dementia Behavior Disturbance Scale (DBD) (Baumgarten et al., 1990)	Assesses challenging behaviour in Alzheimer's patients. It does not include psychological symptoms such as apathy and depression and is not validated for different dementia types just AD.
Dementia Mood Assessment Scale (DMAS) (Sunderland et al., 1988)	Designed to assess depression only in dementia patients, omits other symptoms.

Measure	Reason for exclusion
Dysfunctional Behavior Rating Instrument (DBRI) (Molloy et al., 1991)	Assesses challenging behaviour such as demanding, acting out, withdrawing, psychotic, paranoid, disruptive, repetitive, and inappropriate behaviours. It does not include psychological symptoms such as depression, anxiety, apathy, irritability, dishinibition.
Global Assessment of Psychiatric Symptoms (GAPS) (Raskin and Crook, 1988)	Developed to evaluate psychiatric symptoms in geriatric psychiatric inpatients. It is not validated for dementia patients and it does not cover a wide range of BPSD symptoms.
Irritability/Apathy Scale (Burns et al., 1990)	This scale measures Irritability (5 items) and Apathy (5 items) only.
Leeds Sleep Evaluation Questionnaire (Parrott and Hindmarch, 1980)	This questionnaire assesses sleep disturbances only.
Sandoz Clinical Assessment – Geriatric (SCAG) (Shader et al., 1974)	This assessment is developed to assess psychopathology for and with geriatric populations and is not validated for people with dementia.

Table 1.5 Characteristics of measures that were considered for use as the primary outcome in Evidem-E

Measure	Population	Informant	Frequency	Severity	Reliability	Validity	Comments
Behavioral and Emotional Activities Manifested in Dementia (BEAM-D) (Sinha et al., 1992)	45 Alzheimer Disease (AD) outpatients	Patient/ carer	Present/ absent	4 point scale indicating severity and intensity of behaviour	Interrater reliability for target symptoms r=0.95 and for inferred behaviours r=0.85 Test-retest not reported	Has construct, content and convergen t validity	Omits apathy, and disinhibition. Assesses symptoms characteristic of AD outpatients only, not other dementia types. **Excluded**
Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) (Reisberg et al., 1987)	57 AD outpatients mild to severe	carer	No frequency measure	Ratings differ for each item	Interrater reliability for item severity ratings r= 0.76-1.00 Test-retest R=0.96	Has content and construct validity when compared with patient records	Excludes apathy, irritability and disinhibition. Developed with AD outpatients only, no other dementias included. **Excluded**
Behavioural Syndromes Scale for Dementia (BSSD) (Devanand et al., 1992)	Based on interviews of carers of 106 AD patients	Carer and clinician	Most items are not rated for frequency	There are no guidelines for severity	Interrater interclass correlation coefficients for scores on five domains range from r= 0.76-0.95	Has content and construct validity	Excludes anxiety and depression symptoms. Assesses symptoms characteristic of AD outpatients only, not other dementia types. **Excluded**
Caretaker Obstreperous Behavior Rating Assessment	Developed on 25 community dwelling and nursing home	carer	0-4 scale	Severity measured as impact on carer	Interrater r=0.73-0.99; Test-retest r=0.73-0.95	Validation studies have not been	Excludes apathy, anxiety, depression, and hallucinations. Complicated scoring and

Measure	Population	Informant	Frequency	Severity	Reliability	Validity	Comments
(COBRA) (Drachman et al., 1992)	patients with mix dementias			4 point scale		reported	small study sample size. **Excluded**
CERAD Behavior Rating Scale for Dementia (Tariot et al., 1995)	Developed from literature review and expert pannel. Piloted in 303 AD outpatients	carer	4 point scale	Not measured	Interrater k=0.77-1.00 Test-retest r=0.70-0.89	Has content and construct validity	The frequency rating does not distinguish between symptoms that happen several times daily and once every two days. It does not provide assessment of severity. These properties limit its usefulness in assessing subtle changes. **Excluded**
Gottfries-Bråne-Steen Scale (Gottfries et al., 1982)	Long-term nursing home residents (only 30% with dementia)	Nurses, psychiatrists, psychologists	Not measured	7 point scale	Interrater for three subscales: motor- 0.83-0.93; cognitive- 0.81-0.97; emotional- 0.57-0.87 No test-retest reliability reported	Not validated with dementia patients	Not validated for dementia patients. Informants have to be highly trained professionals. **Excluded**
Manchester and Oxford Universities Scale for the Psychopathological Assessment	32 dementia patients	carer	3 point scale 1-less than once a week to 3-four or	3 point scale 1-mild to 3-severe	Interrater k=0.56-1.00 Test-retest K=0.43-0.93	Has face validity	Small sample size. Content and construct validity information absent. Not widely used. **Excluded**

Measure	Population	Informant	Frequency	Severity	Reliability	Validity	Comments
of Dementia (MOUSEPAD) (Allen et al., 1996)			more times a week				
Neurobehavioral Rating Scale (NRS) (Levin et al., 1987)	HIV positive, head injury and dementia patients	patient	Present-absent	6 point scale 0-'not present to 6-'extremly severe'	Reliability not reported for dementia patients	Has construct and content validity for AD and vascular dementia.	Observer rated, requires clinical expertise and training. Frequency rating does not distinguish between high and low rate of symptom occurrence. **Excluded**
Neuropsychiatric Inventory (NPI) (Cummings et al., 1994)	Elderly dementia patients	carer	4 point scale 1-less than once a week to 4-several times a day	3 point scale 1-'mild' to 3-'severe'	Interrater r=0.53-0.98 (frequency); r=0.51-1 (severity) Test-retest k=0.79-0.86	Has construct and content validity and convergent validity with HAM-D and BEHAVE-AD. Validated for telephone interviewing.	Use of screening questions minimizes time of administration. Includes wide range of BPSD. Widely used in clinical trials. Has been validated for telephone interviewing. **Included**
Pittsburgh Agitation Scale (Rosen et al., 1994)	AD psychiatric inpatients or nursing home residents	Direct observation of behaviour	Not measured	4 point scale different criteria for each domain	Interrater r=0.82 No test-retest reliability reported	Has construct, content and internal validity for AD psychiatric	Requires constant observation and evaluates only disruptive behaviours. It does not provide assessment of frequency. Not validated for other dementias, just

Measure	Population	Informant	Frequency	Severity	Reliability	Validity	Comments
						inpatients and nursing home residents only.	AD. **Excluded**
Revised Memory and Behavior Problems Checklist (Teri et al., 1992)	201 geriatric outpatients with possible depression or cognitive impairment (roughly half had AD)	carer	4 points scale 0=none to 4=daily	Not measured	Interrater r=0.86 Test-retest r=0.88	Has construct, content and convergent validity in depression, cognition, carers' burden and carers' depression.	It does not measure severity of symptoms. The scale omits core symptoms such as apathy, appetite and perceptual disturbances. **Excluded**

1.2.3.1 The Neuropsychiatric Inventory

The NPI was chosen in preference to other measures because it includes a broader range of BPSD symptoms. The NPI is an established, validated measure that is widely used in similar research studies, which makes the study findings more easily comparable with other research results. This measure is the only instrument that includes commonly experienced personality change such as apathy and irritability. Furthermore, the NPI incorporates symptoms that are rare in AD but common in other dementia types, such as euphoria and disinhibition (as in frontotemporal dementias), making the tool valid for a wide range of dementias. Another strength of the NPI is that it attempts to avoid symptom overlaps. For example, to avoid overlap when assessing symptoms of depression and dementia the authors have included in the depression/dysphoria scale just the key emotional aspects of depression such as sadness and tearfulness (Cummings and McPherson, 2001). Ease of scoring is also one of the positive features of NPI, as it takes account of both frequency and intensity of behaviours. However, its intensity scoring has been criticized because it is based on carers' subjective interpretation of how difficult symptoms seem to be for the patient, whereas frequency ratings have been described as more objective reports (Gallo et al., 2009). The NPI is flexible and easy to administer even by less clinically experienced professionals without affecting scale validity or reliability (Fernandez et al., 2008). Being reliant on carers' reports, NPI assessment does not require the input of individuals with dementia and can be inclusive of everyone with dementia no matter what stage of dementia they are at (Connor et al., 2008).

The main psychometric features of the NPI are described below:

- Content validity of an instrument refers to the degree to which it includes all the items necessary to represent the concept being measured. A Delphi panel[3] evaluated the content validity of each domain of the NPI as well assessed (Cummings et al., 1994). A score of 1 meant that the domain was well assessed and a score of 4 meant that the domain was poorly assessed. The mean scores ranged from 1.2 (disinhibition) to 2.0 (aberrant motor behaviour).

- Test re-test reliability assesses the agreement between results of the same measure that is being repeatedly tested. The measure is reliable when there is close agreement over repeated tests given that the variables being measure remain the same. The NPI has optimal test-retest reliability for both frequency (Cohen's Kappa = 0.79) and severity (Cohen's Kappa = 0.86) testing, and overall Cohen's Kappa = 0.88. The NPI validation study (Cummings et al., 1994) included telephone interviewing in its assessment suggesting that the NPI can be used as a telephone interview.

- Inter-rater reliability indicates how well different raters agree in the way they administer and score an instrument. The inter-rater reliability of the NPI has been reported to very good with correlations ranging from 0.53 (irritability) to

[3] A Delphi panel is a board of experts who participate in a reiterative process of evaluation and/or discussions that usually involves several rounds that aims to achieve convergence of opinions.

0.98 (hallucinations) for the frequency measure, and from 0.51 (anxiety) to 1 (hallucinations) for the severity testing (Cummings et al., 1994). Overall inter-rater reliability coefficients have not been reported.

- The internal consistency of a measure is concerned with the extent to which items comprising the measure fit together. Cummings et al. (1994) reported a high level of internal consistency reliability (Cronbach's alpha = 0.88).

- The NPI has good concurrent validity with other similar measures such as BEHAVE-AD and the HDRS with all correlations reaching 0.05 significance level; and good convergent validity (individual items of the NPI have been subjected to convergent validity studies with MRI, PET and other studies) (Cummings et al., 1994).

Although Cummings did not provide a conceptual framework for the design of the NPI, the tool can be considered as grounded on the biomedical model whereby the disease leads to certain symptoms (behaviours) and a specific measure such as NPI is applied to determine the symptoms' response to treatment. The NPI quantifies the problematic behaviours of individuals with dementia, and their carers' distress. The measure fails to consider the meanings of these behaviours and possible alternative triggers such as changes to physical or psychosocial environments or the quality of the relationship between the person with dementia and their carer. This may lead to detection biases because of the arbitrary attribution of behaviours as neuropsychiatric symptoms. On the other hand, determining the cause of problem behaviours in people with dementia can be a

very complicated and time consuming process, and avoiding identification of the underlying meaning of the non-cognitive symptoms can make them easier to capture (Lai, 2014). Further information about the NPI domains and how the scale is scored is provided in paragraph 3.4.1, pp 134.

1.2.4 Impact of BPSD

The development of BPSD is associated with a worse prognosis and faster rate of dementia progression (Paulsen et al., 2000). Untreated BPSD brings about reduction in the quality of life for the person suffering from the condition and causes significant distress (Chan, 2007; Cohen-Mansfield, 1995; Finkel et al., 1996). Once symptoms are ameliorated functional impairment may partially resolve, reducing patient and carer distress and improving quality of life.

BPSD symptoms increase carer stress (Ornstein and Gaugler, 2012) and have a negative effect on their quality of life (Ballard, Lowery, et al., 2000). Behaviours that challenge carers especially depression and low-mood are reported to have a consistent and powerful negative impact on the psychological health of carers (Hooker et al., 2002). Behavioural and Psychological Symptoms of Dementia cause distress for carers and can contribute to the breakdown in care at home leading to relocation to a care home (Banerjee, 2003; Donaldson et al., 1998; Finkel, 2000; Lawlor, 2002). Specific BPSD symptoms such as sleep disturbances (i.e. nightly restlessness and wandering) also contribute to carer distress (Hope et al., 2001) and are predictors of relocation to a nursing or residential home (Schur and Whitlatch, 2003) because of the increased burden that is placed on the carer

(Lindsay and Anderson, 2004). Caring for dementia comes at a financial cost for family carers who reduce working hours to look after their family members, which inevitably results in lower incomes for carers (Covinsky et al., 2001).

Untreated BPSD can also cause stress to nursing staff in residential facilities (Draper et al., 2000; Rodney, 2000) and increase financial costs (Cohen-Mansfield, 1995; O'Donnell et al., 1992; Smith et al., 2005).

Several studies indicate that treatment of BPSD with antipsychotics almost doubles the risk of mortality for patients (Banerjee, 2009; Food and Drugs Administration, 2011) and increases by 9-fold risk of stroke in the first four weeks (Kleijer et al., 2009). The following section will discuss this topic further.

1.3 Aetiology of BPSD

Different theoretical frameworks have been proposed to explain the aetiology of BPSD. These theories are divided into two major groups, neurobiological and psychosocial, and have driven various and distinct interventions for BPSD that will be discussed in detail in the following sections.

1.3.1 Neurobiological/genetic theories of BPSD

The neurobiological/genetic theories of BPSD are predominant within medicinal research and practice, and assert that BPSD are the direct cause of cognitive decline, brain dysfunction, imbalance of neurotransmitters and genetic characteristics (Kar, 2009). Thus, agitation in people with dementia has been linked to frontal lobe dysfunction (Boyle and Malloy, 2004; Senanarong et al.,

2004). People with BPSD have been reported to have lower metabolism and perfusion in the frontal and temporal lobes than those without BPSD (Hirono et al., 2000). Boyle and Malloy (2004) have claimed that apathy is triggered by an interaction between cholinergic deficiency and neuropathological changes in frontal brain regions. Agitation and psychosis are reported to be specifically correlated with a high burden of neurofibrillary tangles (Barber et al., 1995; Tekin et al., 2001). Parnetti et al. (2001) suggest that specific brain regions that regulate emotional activities (parahippocampal gyrus, dorsal raphe, locus coeruleus) and cortical hypometabolism contribute to BPSD. Genotypes such as transmitter receptor polymorphisms of the serotoninergic, cholinergic, and dopaminergic systems have also been proposed as predisposing factors for BPSD (Assal et al., 2004; Holmes et al., 1998; Nacmias et al., 2001; Sukonick et al., 2001). Irritability and aberrant motor behaviour in Alzheimer's have been associated with dopamine transporter gene 3'-untranslated region variable number tandem repeat polymorphism (DAT1 3'-UTR VNTR) (Pritchard et al., 2008). Pritchard et al. (2007) also reported that serotonin transporter SERT may cause susceptibility to the development of psychosis and aggressive symptoms.

While this specific framework is very useful in understanding possible mechanisms of BPSD and in planning specific pharmacological interventions, there are a few pitfalls to be aware off, especially if this approach is considered in isolation to other psychological and social factors. Pharmacological therapies have significant limitations such as serious adverse side effects (discussed further in the following section), interaction between drugs and limited efficacy (Hersch and Falzgraf,

2007). Psychotropic medicines can have sedating effects which may contribute to further cognitive decline, non-compliant behaviour, restlessness and dyskinesia (Lindsey, 2009). The neurobiological approach disregards possible psychosocial or environmental factors influencing the expression of particular BPSD symptoms, which may serve as signals to communicate particular needs (Cohen-Mansfield, 2001). Cohen-Mansfield (2001) argues that medication may instead conceal the real need by eliminating important signal symptoms. Furthermore, there is a tendency to interpret an association with a cause: for example just because dopamine levels go up or down it does not necessarily mean that dopamine causes the symptoms associated with it.

1.3.2 Conventional treatments for BPSD

Conventionally, a pharmacological approach has dominated the clinical management of BPSD. Common forms of treatments include mood stabilisers, anxiolytics, hypnotic and antipsychotic medications and more recently, cholinesterase inhibitors. Antipsychotic medications (e.g. haloperidol, risperidone, olanzapine) have been overly used to manage behavioural problems such as agitation and aggression (Ballard, Hanney, et al., 2009; Banerjee, 2009) but there are long-standing concerns that treating aggressive behaviour with pharmacological methods suppresses behaviour without addressing its cause (The Alzheimer's Society, 2008; The Royal College of Psychiatrists, 2006). Evidence is also beginning to accumulate suggesting that excessive sedation with antipsychotics may reduce symptoms such as restlessness and aggression at the expense of the person's mobility and coherence, with the perverse consequence of

accelerating the rate of decline of cognitive capacity and quality of life for the person with dementia (Ballard, Hanney, et al., 2009; Schneider et al., 2006). Other side effects of antipsychotics include excessive sedation, dizziness and unsteadiness, which can lead to increased falls and injuries, as well as parkinsonism and restlessness.

Use of antipsychotics in dementia increases the likelihood of stroke and premature death which has led the health authorities of both the United States (Food and Drugs Administration, 2011) and the UK (National Institute for Health and Clinical Excellence, 2006) to issue guidance directing clinicians to avoid the use of these drugs in dementia (Ballard, Hanney, et al., 2009; Banerjee, 2009). In the UK, the NICE/SCIE guidelines encourage clinicians to treat BPSD with non-pharmacological methods in the first instance, unless the patient is severely distressed and there is an immediate risk of harm to themselves or others (Clark, 2011).

In 2012, an audit of prescriptions of antipsychotic drugs by GP practices in England reported that antipsychotic prescriptions for people with dementia reduced by 52 per cent between 2008 and 2011 (Health and Social Care Information Centre, 2012).

Other pharmaco-therapeutic interventions are sometimes used but may present similar challenges to antipsychotics. Cholinesterase inhibitors may in fact worsen BPSD symptoms (Howard et al., 2007). Memantine is another option but is relatively high cost (McShane et al., 2006). Hypnotic and anti-depressants may

potentially worsen symptoms or have negative side effects (Boeve et al., 2002; Glass et al., 2005). Further, most classes of medication are designed for short term use (especially hypnotics, anxiolytic medications). Long-term psychosocial strategies may be a better way to achieve the best quality care possible for people with dementia and those whom support them. Therefore, non-pharmacological alternatives are now being considered as first-line management of BPSD (Hersch and Falzgraf, 2007).

1.3.3 Psychosocial theories of BPSD

As Kitwood (1989) proposed, individual differences, social and psychological factors need to be taken into account alongside neurological impairment in order to provide effective, holistic, individualised interventions for BPSD. Three psychosocial models of BPSD have been proposed by Cohen-Mansfield (2000):

- The unmet needs model
- Learning/behavioural model
- Environmental vulnerability/reduced stress-threshold model

The Unmet Needs model suggests that the dementia process affects both the ability of the person with dementia to use the environment appropriately to meet their needs and their ability to communicate their needs effectively (Algase et al., 1996; Cohen-Mansfield, 2000; Hancock et al., 2006). These impaired abilities, in interaction with longstanding habits and personality, physical and mental states and unfavourable environmental conditions, can give rise to BPSD (Figure 1.3).

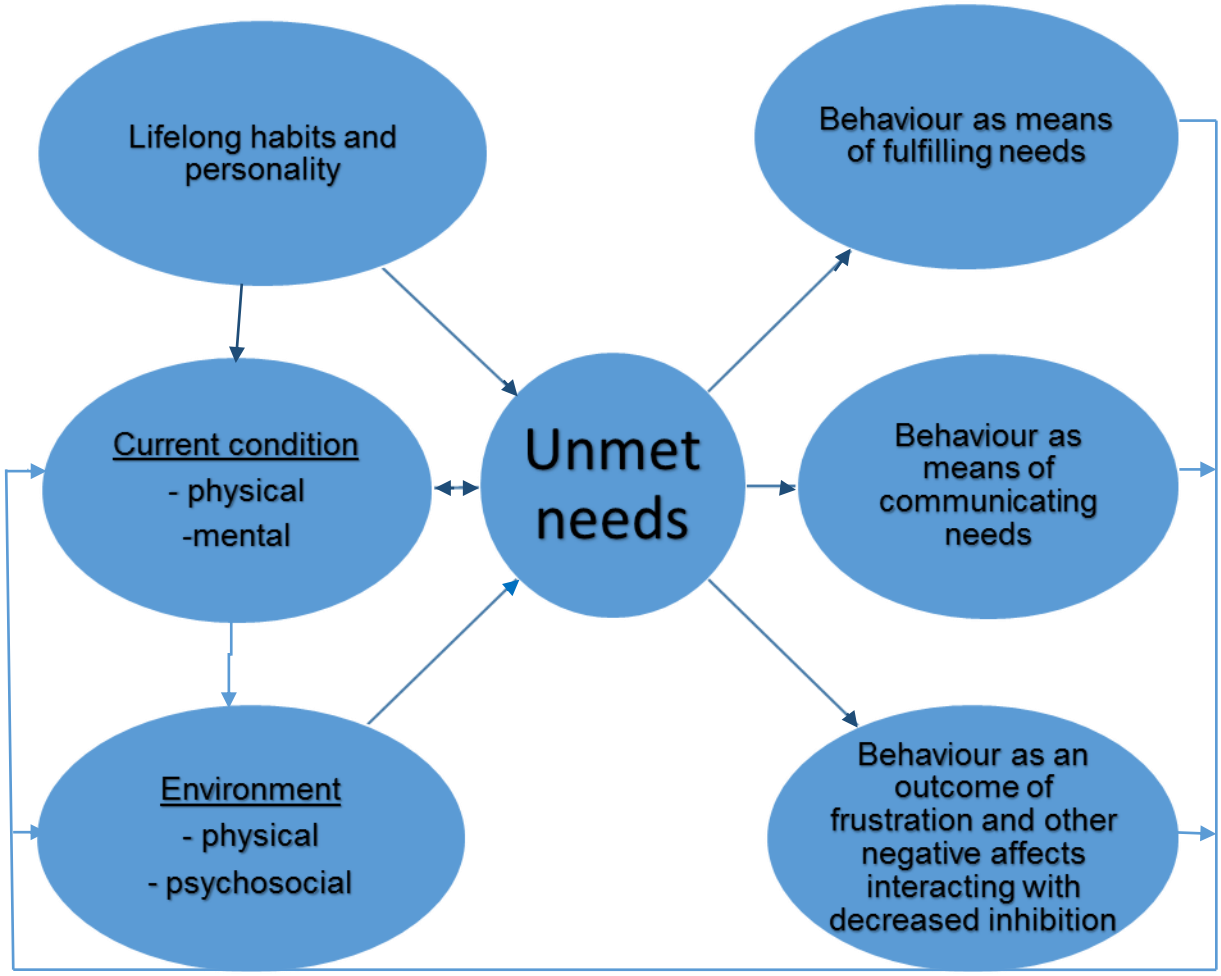


Figure 1.3 Unmet needs model (Cohen-Mansfield, 2000)

According to this model BPSD can result from unmet needs as a way of:

- ✓ meeting a specific need (e.g. pacing to provide stimulation when bored)
- ✓ communicating a need (e.g. repetitious verbalisations to communicate an unmet need)
- ✓ as an outcome of having an unmet need (e.g. screaming when in pain or constipated)

According to the unmet needs model an imbalance in the interaction between personality, physical and mental health and environmental circumstances results in BPSD.

Premorbid personality problems have been correlated with a higher incidence of BPSD. Thus, premorbid neuroticism has been correlated with anxiety (Archer et al., 2007), delusions, aggressiveness and affective disturbance (Low et al., 2002). Poor physical and mental health especially pain and discomfort have a two way interaction with unmet needs (Cohen-Mansfield, 2000). Symptoms like agitation and aggression can be a way of communicating distress and physical pain. For example, Hurley et al. (1992) reported an increase of verbal challenging behaviours when people with dementia experienced fevers. A positive association has also been reported between aggression and urinary tract infections (Huffman and Kunik, 2000). Sleep disturbances and fatigue have been related to increased agitation in dementia (Cohen-Mansfield and Marx, 1990). Mental health problems can be both a cause and effect of unmet needs. Affective disorders, for instance, have been associated with increased agitation in nursing home residents with dementia (Volicer et al., 2012). Agitation on the other hand, can develop as result of loneliness or limited social contact (Cohen-Mansfield and Werner, 1995, 1997; Salzman et al., 2008).

Environmental circumstances are essential to this social constructionist model of BPSD and include both the physical and the social context of the environment. Social constructionism is a theoretical approach according to which our realities are shaped through our experiences and our interactions with others (Burr, 2003).

Physical environments can be under-stimulating or over-stimulating for people with dementia. BPSD symptoms result when the balance between under and over-stimulation is compromised (Kovach et al., 2004). Overstimulation such as excessive noise and large number of staff can cause irritation and agitation (Cleary et al., 1988). On the other hand, monotonous environments that do not offer activities and frequent stimulation can also result in agitated behaviours (Cohen-Mansfield et al., 1992).

The Learning/Behavioural model assumes that BPSD happen as the direct result of conditioning. The basis of conditioning is that a reward following a particular response acts as a reinforcer and increases the likelihood that the response will be repeated. This model proposes an ABC paradigm= Antecedents -> Behaviour -> Consequences; where particular BPSD symptoms that are related to specific antecedent stimuli are reinforced by certain consequences. For example: under-stimulation in a nursing home (bored, lonely) -> triggers agitation in a person with dementia -> staff engage more and try to calm and pacify the resident, which fulfils the social need of the person with dementia; on the other hand this attention reinforces agitated behaviours. According to this model many challenging behaviours are learned through reinforcement by carers, therefore behaviour change can only happen when reinforcement contingencies are modified. This model relies on the assumption that learning occurs with dementia, however impaired learning is one of the most prominent features of the condition. Cohen-Mansfield (2000) suggests that the fundamental element of this model is not direct

learning but fulfilment of social needs through increased attention or provision of attention.

The Environmental Vulnerability/Reduced Stress-Threshold model suggests that a person's needs and abilities need to match the environmental demands (Cohen-Mansfield, 2000). Lawton's (1982) seminal work conceptualized the role of an individual's home environment on physical functioning performance through a 'press-competence' model, according to which an individual with a given competence interacts with an environmental condition having a given "press" or demand. Lawton and Simon (1968) postulated that individuals with lower competence are more sensitive than those with higher competence to the demands of their environment. If environmental demands are either too strong or too weak in relation to the individual's level of competence, negative mood and problematic behaviour may occur (Tomey and Sowers, 2009). A related hypothesis is the 'Reduced Stress Threshold', according to which individuals with dementia gradually lose their coping abilities and consequently perceive their environment as increasingly stressful (Hall, 1994). Cohen-Mansfield (2000) drew into these earlier frameworks to develop the Environmental Vulnerability model which brings together the 'press-competence' and 'reduced stress threshold' models. This model maintains that considering the decreased level of competence of people with dementia their likelihood of being disturbed by the environment increases. Therefore, environmental stimuli that are inappropriate and exceed the individual's threshold for tolerating stress results in negative mood and challenging behaviours (BPSD).

The three psychosocial models described above may be complementary and are not mutually exclusive. Different models may also account for different BPSD symptoms in different individuals. These models have provided the grounding for different non-pharmacological interventions for BPSD, which will be described in detail in the next section.

1.3.4 Non-pharmacological interventions for BPSD

The growing recognition of the importance of BPSD symptoms and the rising concern regarding their treatment with antipsychotic drugs have triggered a surge of interest in developing and applying non-pharmacological interventions as treatments for BPSD. Table 1.6 presents my summary of non-pharmacological interventions for BPSD. The main headings represent the category under which individual interventions have been included. Most of the individual therapies may be categorised under more than one heading, for example reduced sensory stimulation can be classified as sensory manipulation as well as environment manipulation and social contact. However, for ease of description individual interventions have been categorised under one heading.

Table 1.6 Non-pharmacological therapies for BPSD

Sensory manipulation/ relaxation	Massage/touch Aromatherapy Music Snoezelen therapy/multi-sensory stimulation --- Decreased sensory stimulation --- Balancing arousal control excesses
Social contact	Pet therapy Reminiscence therapy Simulated Presence Therapy
Psychological therapies and emotion oriented approaches	Differential reinforcement (behavioural) Reality orientation/ Cognitive stimulation therapy Validation therapy
Environmental interventions	Stimulus control Signposting Use of Mirrors Wandering areas Enhanced environments Light therapy
Training and psychoeducation for carers	Educational programmes for staff and family carers
Structured activities	Recreational activities Physical activities (outdoor walks, Tai Chi, strength and flexibility training, etc.)

1.3.4.1 Sensory manipulation

Sensory manipulation treatments are primarily used with people with moderate to severe dementia and have been focusing on both stimulation enhancement and reduction. Stimulation enhancement approaches have been used to provide meaningful stimulation, reduce anxiety/agitation and improve mood and are based on the 'unmet needs' and 'environmental vulnerability' models, which propose that BPSD may result from periods of sensory deprivation (Cohen-Mansfield, 2001). Massage therapies have included hand massage with essential oils (Kilstoff and Chenoweth, 1998; Kim and Buschmann, 1999; Rowe and Alfred, 1999), electrical nerve stimulation (Scherder et al., 1995) and craniosacral therapy[4] (Gerdner et al., 2008). All these studies, apart from Scherder et al. (1995) have indicated decrease on agitation, wandering and fidgety behaviours, however, they are quite small with samples varying from 14-30 participants and the methodologies used are not robust (not blinded, no control group) (Kverno et al., 2009).

Aromatherapy involves the use of essential oils such as lavender, thyme and melissa (lemon) balm for treatment of agitation in people with dementia. These oils have been applied in different ways such as by diffusion in communal areas (Holmes et al., 2002), bedside diffusers (Lin et al., 2007), applied to the skin (Ballard et al., 2002) and as sachets (Snow et al., 2004). Most of these studies have reported significant reduction in agitation and excellent compliance with the intervention (Douglas, 2004). The study from Ballard and colleagues (2002) is a

[4] An alternative medicine approach that aims to relieve pain and tension by gentle manipulations of the skull.

randomised controlled trial (RCT) that reported not only significant reductions in agitation but also excellent compliance with the intervention. However, the intervention itself was more than just aromatherapy as it also involved increased social contact whereby Melissa balm was applied twice a day on participants' faces and arms, which may also be considered as massage. Therefore, the benefit of aromatherapy is still under investigation and it has been reported as one of the fastest growing complementary therapies (Burns, 2002; Forrester et al., 2014).

Music interventions have been quite heterogeneous, ranging from listening to music for relaxation and anxiety reduction (Holmes et al., 2006; Sung et al., 2010), during mealtimes (Chang et al., 2010; Hicks-Moore, 2005) or bath-times (Clark et al., 1998), to dancing, singing, playing musical instruments, or participating in composition and improvisation sessions (Cohen-Mansfield, 2001; Ledger and Baker, 2007; Sherratt et al., 2004). All of the above studies reported some benefits in terms of decreased agitation, reduction of aggressive behaviours and grater positive engagement. The main disadvantage of music intervention studies is that most of them have very small sample sizes (ranging from 10-46 participants); have employed within-participants experimental design; and use direct observational methods which are susceptible to rater bias and Hawthorne effect. Therefore the chance of obtaining significant results is reduced and the findings remain inconclusive (Vasionytė and Madison, 2013). White noise (environmental sounds) has also been used to induce relaxation and sleep, and consequently reduce verbal agitation and wandering (Burgio et al., 1996). Different music interventions feed into different psychosocial theories. For example listening for relaxation is

based on the unmet needs and environmental vulnerability hypotheses; music use during bath and mealtimes is based on the above mentioned hypotheses as well as the learning/behavioural theory.

Multi-sensory stimulation (MSS) or Snoezelen therapy, which is also considered as an emotion-oriented approach, combines relaxation and exploration of sensory stimuli such as lights (e.g. fiber optics), sounds and tactile sensations (cushions, vibration pads). This therapy is usually delivered in dedicated rooms and sessions are tailored to individual needs (Douglas, 2004). Multi-sensory stimulation is primarily used to reduce apathy in people with advanced dementia. Baker et al. (2001) examined the effects of MSS on 25 participants with moderate to severe dementia through an RCT and found significant reduction in dysphoric mood. However, when the same authors (Baker et al., 2003) ran a second, bigger trial (n=65) they did not find any significant differences between the control and intervention arms. The cost and complexity of MSS rooms can be a barrier to using them especially as evidence in their favour is not very robust.

Decreased sensory stimulation interventions are based on the 'reduced stress threshold' model, which suggests that BPSD can result as a consequence of over or inappropriate stimulation. This approach has been applied in care or residential homes where the levels of over-stimulation are higher than family homes. Two small studies (Cleary et al., 1988; Meyer et al., 1992), with samples of 11 participants each, explored benefits of "quiet" interventions in agitation symptoms. Meyer et al. (1992) introduced a 'quiet week' which included turning off the television, lowering voices and reducing fast movement by staff at a day centre,

and found a significant decrease in agitated behaviours. Cleary et al. (1988) took a more holistic approach by removing sources of stimulation such as TVs, radios and telephones as well as by manipulating the environment (introducing: smaller tables for eating and activities or neutrally painted walls), educating carers and training staff. These authors also reported decrease in agitation. Overall, there is limited evidence about the effectiveness of these interventions on BPSD.

Kovach et al. (2004) has taken a noteworthy approach to the subject of stimulation and its relationship to BPSD. These authors propose a model called Kovach's Model of Imbalance of Sensoristasis, which describes the importance of keeping in balance sensory-stimulating and sensory-calming activities as this imbalance can give rise to or exacerbate agitation in advanced dementia. This model is consistent with Cohen-Mansfield's (2000) environmental vulnerability/reduced stress-threshold model.

1.3.4.2 Social Contact

The next group of interventions include interventions that focus on real or stimulated social contacts and are based on the 'unmet needs' model of BPSD. Several studies suggest beneficial effect of pet therapy on agitation and verbal aggression (Churchill et al., 1999; Fritz et al., 1995, 1996; Zisselman et al., 1996).

Reminiscence therapy (RT) uses materials (e.g. old newspapers, photographs and household items), music and art to stimulate memories and enable people to relive past experiences that are highly significant to them. This approach was originally but unsuccessfully utilised as an intervention for improving cognitive

symptoms of dementia, but it has been shown to improve level of psycho-social wellbeing of people with dementia (Brooker & Duce, 2000; Lai, Chi, & Kayser-Jones, 2004; Woods, Spector, Jones, Orrell, & Davies, 2005). Reminiscence therapy is flexible and can be adapted to groups as well as individual needs. However, there is limited evidence of a significant impact of RT in BPSD (Woods et al., 2005).

Simulated presence therapy is grounded in the unmet needs and environmental vulnerability theories and entails use of videos or audio recordings of family members sharing conversations and memories with the person with dementia. This intervention has been used in care and residential homes. Two studies have reported reduction in physical and verbal agitation and greater frequency of happy expressions during treatment, however, these benefits do not seem to last beyond exposure time (Camberg et al., 1999; Garland et al., 2007).

1.3.4.3 Psychological therapies and emotion oriented approaches

Differential reinforcement aims to reduce or eliminate maladaptive behaviours by using positive reinforcement in a structured way to increase desirable behaviour and is based on the 'learning/behavioural model'. Rogers et al. (1999) applied behavioural rehabilitation to reduce disruptive behaviour in nursing home residents with dementia. Doyle and colleagues (1997) also used reinforcement of quiet behaviour and environmental stimulation to decrease noise-making in 12 long-term-care residents with severe dementia. There have not been any reports of more recent interventions of differential reinforcement**.**

Reality orientation (RO) is based on the idea that impairment in orientation and confusion prevent people with dementia from functioning well and is supported by the environmental vulnerability and the unmet needs models. RO facilitates re-orientation through: reminding people with dementia of facts about themselves; and through environmental manipulation (such as using signposting, clocks, calendars, newspapers, television, pictures, personal belongings). The efficacy of RO has been criticised by several authors who found RO classes non-efficacious (Hanley et al., 1981); with little long-term effect (Hitch, 1994); or argued that RO can have a negative effect on mood through reminding people of their prognosis (Baines et al., 1987; Goudie and Stokes, 1989). Dietch and colleagues (1989) claimed that insensitive use of RO through incessantly correcting and challenging people with dementia could result on demeaning and confrontational experiences for this vulnerable population. However, more recent reviews (Spector, Davies, Woods, & Orrell, 2000; Spector, Orrell, Davies, & Woods, 2001) have been quite favourable to RO and its outcomes. In fact it seems as though, after a loss of interest for this approach in the nineteen eighties, interest in RO has been reawakened (Spector et al., 2001; Woods, 2002) under the new term Cognitive stimulation therapy (CST).

Cognitive stimulation therapy, unlike RO, is grounded in person-centred care (Kitwood, 1997) and its key principles are to appropriately and sensitively use multi-sensory stimulation to re-orient people with dementia and strengthen relationships with carers (Spector, Orrell, & Goyder, 2013). This approach is

predominantly used in group of patients with mild to moderate dementia, as participants need to be able to carry out meaningful conversations and participate in group activities.

Validation therapy (VT) is based on the Rogerian humanistic psychology argument that BPSD symptoms are strategies used by people with dementia to avoid stress, boredom and the painful reality of their condition (Hitch, 1994). Validation therapists propose that empathic communication with individuals with dementia is essential rather than their orientation to the present. Neal and Barton Wright (2003) evaluated validation therapy through a Cochrane review and concluded that evidence about the efficacy of validation therapy is insufficient.

1.3.4.4 Environmental interventions

Environmental interventions include modifications of the factors that may cause or exacerbate BPSD such as: excessive noise (reduced stress threshold model), lack of routine (unmet needs model), inadequate lighting (environmental vulnerability model), confusing surroundings, and excessive demands by staff in residential settings (learning/behavioural model) (Gauthier et al., 2010). Many of these approaches have focussed exclusively on assisted-living facilities. Some of the environmental interventions include:

Enhanced environments - Several non-randomised trials have investigated the effect of environment manipulation on agitation symptoms and exit-seeking behaviours of people with dementia in residential settings. Different approaches entailed: painting two dimensional grids on the floor in front of exit doors (Chafetz,

1990; Hewawasam, 1996; Hussian and Brown, 1987); painting murals over doorways (Kincaid and Peacock, 2003); and placing blinds and cloth barriers over doors or door handles (Dickinson et al., 1995; Namazi et al., 1989). Chafetz (1990) concluded that the two-dimensional grid is ineffective, however, the other authors reported on reduced exiting behaviours and ambulation.

Wandering areas/ Removal of restraints – A few authors have criticised the reduced autonomy in institutionalised patients, and have argued that these settings exacerbate or even cause BPSD. Two studies found that unlocking exit doors in a residential home, and release from mandatory confinement in an acute unit reduced agitation as well as both physical and verbal aggression (McMinn and Hinton, 2000; Namazi and Johnson, 1992).

Light therapy – Light therapy has been utilised to improve circadian rhythms, which are impaired in people with dementia (Vitiello and Borson, 2001). This approach is supported by the 'unmet needs' model as it attempts to improve sleep (Mishima et al., 1994; Okawa et al., 1991) and consequently reduce agitation (Lovell et al., 1995; Lyketsos et al., 1999). The above studies have reported benefits on sleep and agitation, but other studies have reported no effect (Koss and Gilmore, 1998; Thorpe et al., 2000). Overall, the support for this approach remains inconclusive as the reported studies are small non-RCTs (Cohen-Mansfield, 2001; Forbes et al., 2014; Skjerve et al., 2004).

1.3.4.5 Training and psychoeducation programmes for carers

This approach focuses on improving carers' knowledge of dementia and BPSD, improving communication with people with dementia, and on providing potential management strategies for BPSD. Reduced agitation has been reported after training staff on communication skills (McCallion et al., 1999), empathy (Williams, 1994), tailored and focused care (Matteson et al., 1997; Mentes and Ferrario, 1989; Wells et al., 2000). Psychoeducation interventions with family carers have also resulted in improved mood (Hébert et al., 2003) and decreased or delayed institutionalisation (Eloniemi-Sulkava et al., 2001; Mittelman et al., 1996). All the above studies report improved outcomes immediately after the intervention, however this effect ceases not long afterwards, indicating that educational programmes should be of an ongoing nature rather than a one-off intervention (Livingston et al., 2005).

1.3.4.6 Structured activities

Recreational activities such as sewing, dancing, games, playing instruments have been reported to have a positive effect on agitation (Aronstein et al., 1996) and wandering behaviours (Groene, 1993; Kolanowski et al., 2009). These findings, however, are based on a small number of non-randomised studies.

Physical activities include various types of physical exercises such as outdoor walks (Calkins et al., 2007; Detweiler et al., 2008), Tai Chi (Tadros et al., 2013), strength and flexibility training (Steinberg et al., 2009), walking, cycling, chair

based exercise (Heyn et al., 2004). These interventions will be covered at length in the Literature Review chapter.

1.4 Exercise and its putative mechanisms of improving BPSD

1.4.1 Working definition of exercise

The terms physical activity and exercise have been used interchangeably to describe interventions that involve bodily movements (Caspersen et al., 1985). Caspersen and colleagues (1985) have argued that although these concepts have common elements, they are quite distinct from each other. They state that even though both physical activity and exercise involve bodily movements that result in consumption of energy, exercise differs because unlike physical activity it is a planned, structured, and repetitive action for the purpose of improving health. This classic definition of exercise has been recently validated (Chodzko-Zajko et al., 2009) and is still being widely used in research, particularly in dementia studies (Bowes et al., 2013; Cedervall, 2014; Farina et al., 2014; Law et al., 2014), therefore it was decided to be applied in the conceptualization and design of the intervention in Chapter 3.

1.4.2 How exercise interventions might effect BPSD

According to BPSD theories the most fundamental elements that give rise to these symptoms are physical and mental health status and environmental circumstances (Cohen-Mansfield, 2000).

1.4.2.1 Physical health

Physical wellbeing is strongly associated with physical activity, absence of which is established as a major risk factor for ill health and mortality (Kokkinos, 2012; Lee et al., 2010; Scarmeas et al., 2011). Increased physical activity levels can improve general cardiovascular health (Balady et al., 2004), can reduce the risk of high blood pressure (Rossi et al., 2012), some types of cancer (Meyerhardt et al., 2006), osteoporosis and fracture risk (Rizzoli et al., 2009) and Type 2 diabetes (Knowler et al., 2002). Improved cardiovascular system and general physical health is characterized by lower arousal at rest which can induce relaxation, and positive engagement.

Physical activity has been strongly related to pain and discomfort caused by physical conditions such as arthritis, constipation, musculoskeletal diseases, cancer and vascular diseases, on a two way interaction as both cause and effect of these health problems (Dukas et al., 2003; De Schryver et al., 2005). For instance, physical inactivity can be a sign of experiencing pain or constipation but these conditions can also result from prolonged periods of immobility creating thus a vicious circle of inactivity and ill-health (Plooij et al., 2012). Physical pain often results in low mood, apathy, irritation and aggression, which can be wrongly diagnosed as BPSD and subsequently treated with antipsychotics (Ballard, Corbett, et al., 2009; Husebo et al., 2011). In order to address this issue NICE guidelines state that the first step to treating BPSD is to assess and treat any contributory physical or mental health problems (Clark, 2011).

Physical activity can improve strength and balance, and help to counteract the fear of falling (Allan et al., 2009). Improved physical function contributes in maintaining muscle strength and joint flexibility and reduces the risk of osteoporosis (a disease that affects the bones, making them weak and more likely to break) (Borer, 2005; Rizzoli et al., 2009). This can be a way of helping people maintain independence for longer by reducing their dependency in activities of daily living. Functional independence is essential for individuals' maintenance of self-efficacy, sense of control, self-esteem and ability to participate in social activities, all of which are strongly linked with depressive symptoms (Boström et al., 2014; Yang, 2006).

1.4.2.2 Cognitive decline

Exercise has been reported to be an important and effective protective factor against cognitive decline and subsequently of BPSD (Ahlskog et al., 2011; Laurin et al., 2001). BPSD such as apathy, agitation, disinhibition, irritability, and aberrant motor behaviour worsen with the progress of dementia (Tanaka et al., 2015). Ahlskog and colleagues (2011) describe regular exercise as 'neuroprotective therapy'. Recent studies suggest that exercise may have positive effects on brain neuroplasticity, which is a fundamental mechanism for learning, memory, and cognition (Ahlskog et al., 2011; Vaynman et al., 2004). Exercise has been reported to result in increased size of hippocampus and improved memory (Erickson et al., 2011; Morra et al., 2009). Functional brain MRI studies have reported significantly improved cognitive networks after exercise (Ruscheweyh et al., 2011; Voss et al.,

2010). The cognitive decline is critical for development of BPSD and regular exercise may provide a buffering effect.

1.4.2.3 Depression and anxiety

Exercise has been reported to improve mental health, specifically depression and anxiety in general population (Craft and Perna, 2004; Gogulla et al., 2012) as well as in individuals with dementia (Conn, 2010; Dunn, 2010). Cooney and colleagues (2013) carried out a Cochrane review of exercise interventions for depression and concluded that exercise was more effective than antidepressants and psychological therapies alone in reducing depressive symptoms. The mechanisms underlying the antidepressant effects of exercise can be multifactorial including physiological and psychological elements. The **'thermogenic' model** is one of the earlier physiological hypotheses, which claims that exercise brings about increases in the temperature of specific brain regions that can lead to relaxation and reduction in muscular tension and improvement of anxiety and depression (Szabo et al., 2013).

Another putative physiological model is the **'monoamine' hypothesis**, according to which exercise leads to an increase of brain neurotransmitters (e.g., serotonin, dopamine, and norepinephrine) that are reduced in individuals with depression (Tang et al., 1981). Although animal models back up this theory (Dishman, 1997), no studies involving humans have been reported so far due to the use of invasive procedures necessary in obtaining samples such as spinal taps for cerebrospinal fluid.

The **'endorphin' hypothesis** is another influential physiological model, which proposes that exercise has a positive effect on depression due to increased release of β-endorphins following exercise. According to this theory, β-endorphins act as internal psychoactive agents that can trigger feelings of euphoria and improve mood (Craft and Perna, 2004). This model has been criticized because peripheral endorphin levels may not necessarily reflect endorphin activity in the brain and even if they do they are not necessarily directly associated with a change in mood or feelings of depression (Farrell et al., 1982). It remains unclear if elevations in β-endorphins are directly linked to a reduction in depression.

Several psychological mechanisms have also been proposed. They include the **'self-efficacy'** and the **'distraction'** hypotheses. Craft and Perna (2004, pp108) define self-efficacy as the "*belief that one possesses the necessary skills to complete a task as well as the confidence that the task can actually be completed with the desired outcome obtained"*. Bandura (1997) describes that individuals with low self-efficacy often experience negative self-evaluations, negative ruminations, and faulty styles of thinking, which lead to depression and anxiety. Self-efficacy can be enhanced through improving feelings of mastery by promoting self-monitoring behaviours, goals' setting, and utilization of social support. Exercise interventions include all these elements as individuals learn to monitor exercise behaviours, set short and long-term exercise goals, and receive positive support from trainers and other carers. The relationship between exercise and self-efficacy in depressed patients has not been studied extensively and findings have been equivocal (Craft, 2005).

The distraction hypothesis suggests that exercise serves as a distraction from worries, anxiety, and depressing thoughts. This hypothesis is based on the styles theory proposed by Morrow and Nolen-Hoeksema (1990) according to which negative thinking leads to negative attributions about the self and the world, and prevents individuals from behaving in a manner that elicits positive reinforcement. Exercising can break this cycle through keeping individuals focused on training goals or somatic changes such as their breathing, heart rate, sore muscles and by providing positive reinforcement by meeting exercise goals and receiving social rewards from carers and trainers.

1.4.2.4 Sleep problems

Poor or inadequate sleep is a risk factor for depression (Riemann and Voderholzer, 2003). Although sleep problems increase with age, people with dementia have been reported to experience more difficulties than their peers without dementia (Grace et al., 2000; Prinz et al., 1982). Physical inactivity may be related to sleep disturbances and ‘sundowning’ (symptoms of agitation that are observed in some people with dementia during late afternoon and evenings) (Loprinzi and Cardinal, 2011). Exercise can improve sleep by promoting daytime activity. Daytime activity reduces sedentary behaviour and results in increased social contact, light exposure, timely suppression of melatonin secretion, and stronger circadian rhythms (Ancoli-Israel et al., 2003; McCurry et al., 2005).

1.4.2.5 Environmental factors

Physical and social environmental factors, such as lack of social interaction, enclosed spaces, isolation, visual and auditory sensory deprivation may all contribute to or cause BPSD (Hersch and Falzgraf, 2007). Regular exercise outdoors can be a way of counteracting all the above (Thuné-Boyle et al., 2012).

1.4.2.6 Delusions and hallucinations

There is a paucity of research on plausible mechanisms by which exercise might affect psychotic symptoms such as delusions and hallucinations. This was taken into account during the design of EVIDEM-E (Chapter 3).

It can be concluded that aetiology of BPSD may be described as the result of a complex interplay of psychological, social, and biological factors. Considering these factors at isolation can result in ineffective and even unsafe treatments. It has been recommended that BPSD is managed through a combination of non-pharmacological approaches and careful use of pharmacological interventions (Clark, 2011). As discussed earlier, non-pharmacological interventions for BPSD are based on three main psychosocial theories: 'The unmet needs model', the 'Learning/behavioural model' and the 'Environmental vulnerability/reduced stress-threshold model'. These interventions, unlike pharmacological therapies, vary greatly in their approach, population target, dose, and treatment objectives (Hersch and Falzgraf, 2007). Exercise interventions, for example, have been quite heterogeneous involving different activity types, frequencies, intensities, duration, and settings. Nevertheless, exercise interventions have the hypothetical potential

to affect BPSD, especially as they are already established as effective interventions for physical health and mood disorders in the general population (NICE, 2009).

1.5 Barriers to exercising and theories of behavioural change

Despite the multiple potential benefits of exercising it is difficult to induce individuals to start exercising and adhere to exercise regimens (Resnick et al., 2000; Salmon et al., 2003). Key barriers to participating in physical activity for the general population are pre-existing health problems (physical health conditions, medication intake; deteriorated physical abilities), cultural issues, environmental factors, demographic factors (lower socioeconomic status, living alone); psychological factors (worse cognitive ability, depressive symptoms), stress and a lack of time (Picorelli et al., 2014; Rasinaho et al., 2007; Schutzer and Graves, 2004). People with dementia, especially those living in residential care facilities, face additional barriers including stigma, staff availability, negative attitudes about the capability of people with dementia and a culture of risk aversion in care of older people (Benjamin et al., 2014; Tak et al., 2012).

Introducing exercise regimens in a person's life means initiating significant lifestyle and behavioural changes. Therefore, being able to predict and influence health behaviour is essential in order to achieve and maintain compliance with the intervention. Different theories have proposed various putative models of health behaviour change. I will describe the four most influential theories of behavioural change, which are based on Bandura's social cognition theory of behaviour:

- The Health Belief Model
- The Theory of Reasoned Action
- The Theory of Planned Behaviour
- Trans-theoretical model (Stages of change)

The Health Belief Model (HBM) suggests that social, economic and environmental factors guide individual's perceptions about the likelihood of threat to their health if they do not engage in the particular behaviour (e.g. exercise or smoking cessation), and the perceived expectations if they do. If individuals do not accept the diagnosis or the severity of their illness, or do not think that the health behaviour will be feasible and/or beneficial they will not change their behaviour (Strecher and Rosenstock, 1997). Tanner-Smith & Brown (2010) reported weak support for the HBM's ability to explain and predict perceptions of risk. Armitage & Christian (2003) concluded that the model offers poor construct definition and weak predictive validity of the HBM's core psychological components. This model has been criticised for its limitation in considering "contextual constraints". Thus, even if perceived health-threat susceptibility and severity may be high, if one is struggling with critical issues such as poverty, actions to assure health are not undertaken as this is not perceived as a high priority in the hierarchy of needs (Tanner-Smith and Brown, 2010). Although descriptions of the HBM include demographic and socioeconomic variables, reviews of its practice indicate that these elements have not been utilised effectively (Taylor et al., 2007). This can be another factor that may explain HBM's low ability to predict perceptions of risk.

The Theory of Reasoned Action (TRA) proposes that behaviour change can be predicted by a person's intentions (Fishbein and Ajzen, 1975). According to this theory, intentions are determined by the person's attitude towards the behaviour, and beliefs regarding carers' support of the behaviour. For example, people may believe that exercising will improve BPSD symptoms; however, they may also feel that it is painful, tiring and can cause falls. The pros have to outweigh the cons for behaviour to change. People are influenced by significant others whose opinions are valued (Schutzer and Graves, 2004). For example, if a man believes that his wife wants him to exercise, and he values her opinion, he would be more likely to engage in exercise. The Theory of Reasoned Action has been criticised because it neglects the social factors that affect human action (Werner, 2004).

To overcome TRAs limitations Ajzen (1991) proposed a new model called **The Theory of Planned Behaviour** (TPB). This model is very similar to the original TRA, with the added element of perceived behavioural control that is driven by perceived self-efficacy and self-confidence. Perceived behavioural control is an individual perception about the feasibility for a specific behaviour to be performed (such as exercising). TRA and TPB have some limitations in predicting behaviour (Werner, 2004). The first limitation is that intention determinants are not limited to attitudes, subjective norms, and perceived behavioural control. There may be other emotional factors, which these two models overlook, such as fear, mood and negative or positive feeling that influence behaviour. Empirical studies have reported that only 20% - 40% of the variance of behaviour could be explained using TRA or TPB (Ajzen, 1991; Werner, 2004). However, when compared to

HBM, the TRA and the TPB have been described as more parsimonious (they have fewer, more precisely defined, components) in design (Taylor et al., 2007).

The Transtheoretical model (TTM). Unlike the previously mentioned models that focus only on the mechanisms of behaviour change, TTM takes account of both processes as well as stages of change by including a temporal dimension (Prochaska and DiClemente, 1983; Prochaska and Velicer, 1997). This model assumes that for a healthy behaviour to be adapted or an unhealthy one to be eliminated certain consecutive stages have to occur. According to this model people progress through five phases related to their willingness to change: pre-contemplation (not ready), contemplation (getting ready), preparation (ready), action, and maintenance. Different intervention strategies have to be applied at each level in order to help people progress to the next stage. Progression through the stages can occur in a linear fashion, but nonlinear progression is also common and so is regression from later stages to earlier ones (Burkholder and Nigg, 2002). Several reviews have reported that TTM based approaches applied in exercise promotion are no more likely to be effective than alternative (rationally designed) interventions in achieving desired behavioural change outcomes (Adams and White, 2005; Riemsma et al., 2002; Taylor et al., 2007). Van Sluijs and colleagues (2004) reviewed 29 trials concerning the effect of stages-of-change-based interventions in primary care on smoking, physical activity, and dietary behaviour. They concluded that TTM application was effective on dietary behaviour but not smoking cessation and physical activity. Several authors have questioned the internal validity of the TTM, and have raised concerns about misclassifications in

self-report of stages of change (Adams and White, 2005; Riemsma et al., 2002; Taylor et al., 2007). Marshall and Biddle (2001) carried out a meta-analysis of 71 papers concerning the application of the TTM to physical activity. They concluded that stage membership is associated with different levels of activity and perceptions of self-efficacy. However, they were unable to confirm whether physical activity changes can be staged, or should be regarded as positioned on a continuum. This model, same as the other models described, has also been criticised for not including measures of health related social, economic and environmental variables (Buchan et al., 2012; Taylor et al., 2007).

Models of behaviour change are applied in the field of health promotion for interventions that are evidence based. These models have been utilised in the fields of smoking cessation, physical activity, diet and HIV risk control. TPB and the TTM appear to be the most extensively employed models and they can both predict health related behaviour with greater effect than the HBM and TRA (Taylor et al., 2007). This effect however remains quite low with this model explaining just 20-40 per cent of observed behaviour (Armitage and Conner, 2000). The body of evidence relating to the effectiveness of health behaviour change interventions based on all of the above models is varied and remains inconclusive (Taylor et al., 2007). The design of EVIDEM-E intervention (described in Chapter 3) was primarily pragmatic and not theory based, although elements of the above theories such as carer's perception of self-efficacy were fundamental to the study design and in the recruitment of dyads.

The following chapter will explore current (time limitations apply) evidence about the effect of exercise on BPSD.

2 LITERATURE REVIEW

A rapid appraisal method, which adopted a critical interpretive approach (Dixon-Woods et al., 2006) was carried out in order to synthesise the evidence of exercise on improving BPSD (Thuné-Boyle et al., 2012). Critical interpretive synthesis is an adaptation of meta-ethnography and grounded theory techniques, which involves an iterative approach of refining the research question by using theoretical sampling. Papers are searched and selected through this iterative process. Quality of selected papers is assessed using relevance in terms of contribution to theory development rather than methodological characteristics (Gough, 2007).

The critical interpretive approach is ingrained in qualitative methods and draws on interpretive synthesis methods (Noblit and Hare, 1988). Dixon-Woods and colleagues (2006) argue that the Critical Interpretive Synthesis is more useful than the Systematic Review, when exploring complex questions. They claim that Systematic Reviews are well-fitted to test theories through aggregative synthesis, but the Critical Interpretive Synthesis enables generation of theories that are grounded in research and hold stronger explanatory power. Using a critical interpretive approach, we synthesized the evidence of physical activity on improving BPSD and proposed a research agenda.

2.1 Aims and objectives

The purpose of the literature review was to synthesize the evidence in order to understand the efficacy of exercise programs for people with dementia in relation

to various outcomes: psychological, behavioural, and mood and sleep disturbance. Three questions were addressed:

1. Does exercise improve symptoms of BPSD?

2. How has exercise been conceptualized and do some aspects of it (e.g. type and duration) provide better results than others?

3. What are the main limitations and methodological shortcomings of current research in this area?

2.2 Inclusion/Exclusion criteria

Although the aim of this review was to be as inclusive as possible with the current relevant literature, we nevertheless recognize the importance of setting boundaries about which papers to include. This review was carried out during the period June 2010 - May 2011, therefore papers published beyond this date are not included in this review. The search was limited to English language publications about human subjects only. Studies and review articles that met the following criteria were selected:

2.2.1 Inclusion Criteria

The individual studies and reviews that were included in the review met the criteria below:

- Individual studies that measure the efficacy of exercise in improving BPSD. We used Caspersen et al's. (1985) classic definition of exercise as planned,

structured, and repetitive activity for the purpose of improving health (paragraph 1.4.1).

- Review articles that examine intervention studies assessing the efficacy of exercise in improving BPSD.

- Papers should have been published in peer-review journals using relevant keywords appearing in the title or abstract.

2.2.2 Exclusion Criteria

Studies were excluded because they:

- examined the efficacy of exercise on cognitive impairment only.

- had a primarily pharmacological focus.

- were single case reports, observational studies or qualitative studies.

- Individual studies that reported combined interventions (i.e. combining exercise with another psychosocial intervention) were excluded as these are unable to establish the absolute effect of exercise. This criteria was not possible to apply to reviews as they covered a mix of interventions, which would have meant excluding all reviews.

2.3 Database search

Medline, Embase, PsychInfo and PubMed were searched using a combination of keywords:

1. physical activity and dementia/Alzheimer's disease
2. exercise and dementia/Alzheimer's disease
3. non-pharmacological interventions and dementia
4. exercise, sleep disturbance and dementia/Alzheimer's disease
5. exercise, apathy and dementia/Alzheimer's disease
6. exercise, aggression and dementia/Alzheimer's disease
7. exercise, wandering/repetitive behaviours and dementia/Alzheimer's disease
8. exercise, depression/mood and dementia/Alzheimer's disease

Other sources were also searched including reference lists and book chapters. Seven hundred and twenty-three articles were screened through evaluating their titles and abstracts. Articles were excluded because of reasons outlined in the exclusion criteria. The majority of excluded papers were studies of pharmacological interventions. Other initial exclusions encompassed studies that were unrelated to dementia or were not BPSD specific. For example papers about physical exercise interventions for cognitive symptoms of dementia were excluded. Unfortunately, specific details on numbers of papers excluded for each particular reason were not recorded. Sixteen studies fitted the inclusion criteria. Of these, 10 were review articles and 6 were additional papers not included in these reviews. No publications were included twice. The search process is described in Figure 2.1 as a Prisma diagram (Liberati et al., 2009).

Each paper included in the reviews was examined to assess their inclusiveness. **Table 2.1** describes the reviews and **Table 2.2** describes the individual articles explored.

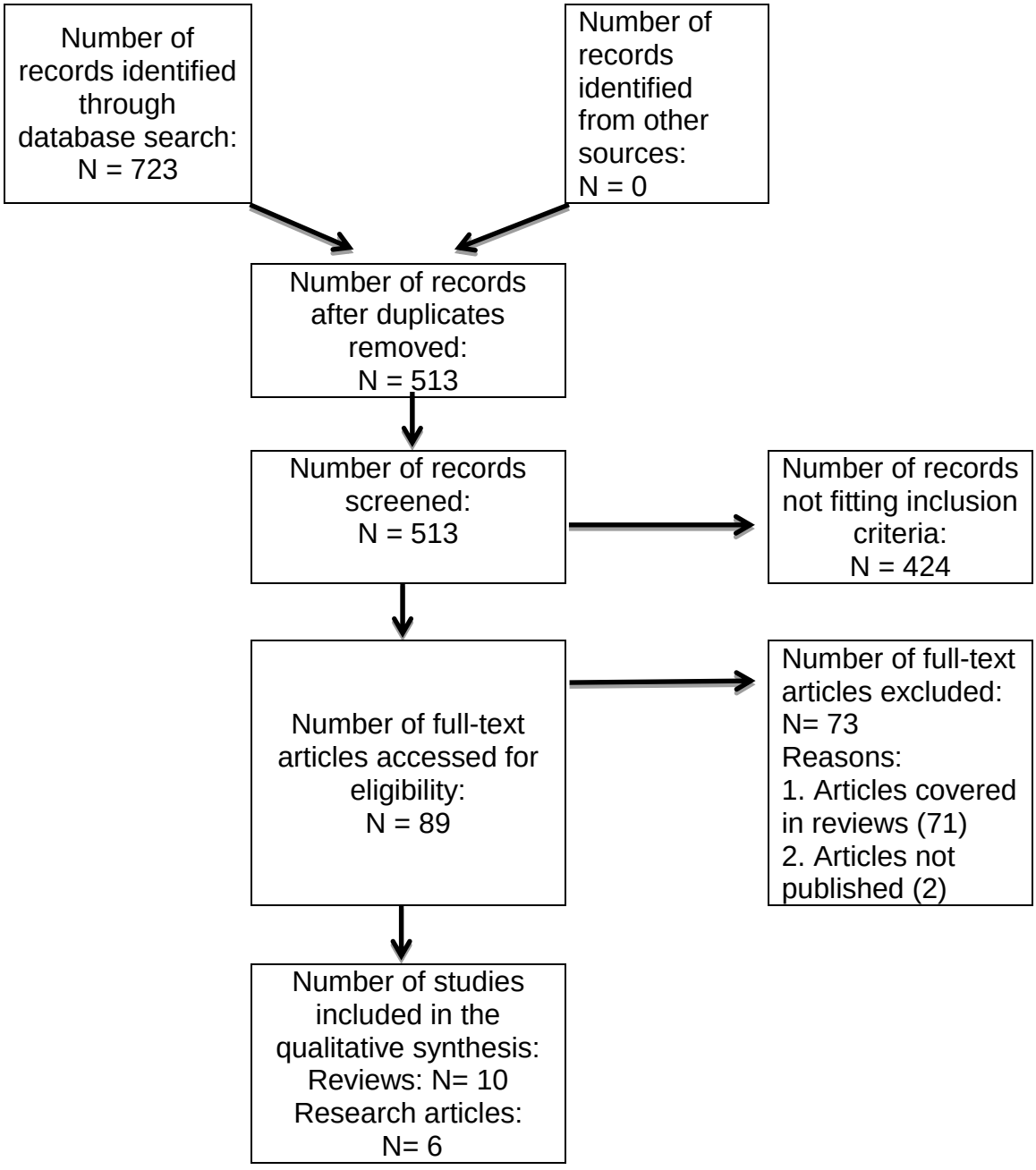


Figure 2.1 PRISMA flowchart describing the search process of finding articles examining the efficacy of exercise on BPSD (Thuné-Boyle et al., 2012)

Table 2.1 Summary of reviews included

Reviews	No. of trials	BPSD outcomes assessed	Types of exercise explored	Effect of exercise
Deschenes & McCurry (2009)	0	Sleep	any type of exercising	Concluded that no controlled trials examining the effect of exercise on sleep have been conducted thus far.
Eggermont & Scherder (2006)	27	Mood and sleep.	Various; walking, sport activities, aerobics, strength, flexibility and sit stand repetitions.	Sustained walking benefits depression and agitation. Exercise beneficial to the quality of sleep.
Forbes et al. (2009)	4	Behaviour and depression.	aerobic, strength, balance training, walking, hand movement	No conclusions possible.
Heyn et al. (2004)	9	Behaviour.	Functional, endurance, recreational, mobility (walking), isotonic and aerobic (incl. strength and flexibility) exercises.	Exercise training improved behaviours. Not able to establish which type of training exercise were the most beneficial.
McCurry et al. (2000)	0	Sleep	any type of exercising	No studies fitting the inclusion criteria found.
Overshott et al. (2004)	2	Agitation, apathy, depression, sleep.	daytime physical activities and exercises	Exercise reduces agitation. Exercise was not discussed in relation to depression, sleep or apathy.
Robinson et al. (2006)	1	Wandering	physical exercise	No robust evidence to recommend the use of exercise to reduce or prevent wandering in people with dementia.
Shub et al. (2009)	3	Sleep	aerobics, endurance activities, strength training, balance, flexibility training	Exercise improved sleep. Should walk for 30 minutes a day in natural light.
(Siders et al., 2004)	9	Wandering	walking, outdoor activities	Taking methodological limitations into account, there appears to be some evidence that structural activities reduces wandering during the day and night.
Vital et al. (2010)	4	Depression	strength and flexibility exercises, walking, balance training	Two studies presented reductions in depression while the other two did not.

Table 2.2 Additional papers not included in the reviews displayed in **Table 2.1**

Author, year & country	Design	Recruitment	Participants and sample size	Exercise intervention	Follow-up time scale	Outcome variable(s) & measurement	Findings
Aman & Thomas (2009) USA	Prospective between group design.	A special needs unit of two nursing homes.	50 residents with dementia (SLUMS < 20); 40 = Exercise group; 10 = control group (those who refused exercise).	30 minutes of exercise three days a week; 15 min aerobics and 15 min resistance.	3 weeks	Depression; Cornell Scale of Depression, agitation; the Pittsburgh Agitation Scale; Cohen/Mansfield Agitation Inventory	Improvements in agitation after three weeks.
Edwards et al. (2008) USA	Repeated measures design pilot study.	Two nursing homes.	36 residents with dementia	Mainly chair based exercise but some walking, 3 times a week for 30 minutes over 12 weeks.	3 and 12 weeks	Affect (anxiety, depression and anger); the Philadelphia Geriatric Center Apparent Affect Rating Scale.	Immediate short term effect on reducing anxiety only. Long-term effect on reducing both anxiety and depression.
Hokkanen et al. (2003) Finland	RCT pilot	Dementia nursing home.	Four people with dementia	16 sessions of dance and rhythmic movement lasting 30-45 min, once a week.	16 weeks	Depression and apathy; The Neuropsychiatric Inventory (NPI).	No reduction in depression or apathy.
Regan et al. (2005) UK	Between group design	Through the community mental health team, the Alzheimer's Society, via memory clinics,	224 participants with Alzheimer's disease (MMSE >20)	Any; participants were divided into absent, moderate or vigorous exercise groups.	N/A	Depression; the Cornell Scale for Depression in Dementia.	Lack of exercise was an independent predictor of depression (association, not causation) $p<0.001$.

Author, year & country	Design	Recruitment	Participants and sample size	Exercise intervention	Follow-up time scale	Outcome variable(s) & measurement	Findings
		through care homes, day hospitals and inpatients units.					
Steinberg et al. (2009) USA	RCT	Recruited from the John Hopkins Comprehensive Alzheimer Program, the department of psychiatry, Baltimore	27 home dwelling patients with Alzheimer's (MMSE>10): 14=intervention 13=control.	Daily programme of aerobic, balance and flexibility, and strength training, shown to patients and carers, to be done at home. Control = home safety assessment.	6 and 12 weeks	Depression and apathy. Neuropsychiatric Inventory, the Cornell Scale for Depression in Dementia.	A trend towards worse levels of depression in the exercise group.
Volicer et al. (2006) USA	Repeated measures design	Two dementia special care units at different locations.	90 veterans with dementia provided with long-term care (MMSE 0-19)	Continuous meaningful activities, e.g. moving from the table to a circle, moving chairs, marching to music, going from one area to another.	12 weeks	Agitation, sleep disturbance, use of psychotropic medications. Not clear what measures were used.	Decreased agitation, improved sleep and a reduced use of psychotropic medication.

2.4 Exercise as treatment for BPSD

The benefits of exercise for healthy older adults are well documented and are linked to improved physical and psychological outcomes including the prevention of heart disease, stroke, diabetes, falls, depression, cognitive decline and dementia (Elward and Larson, 1992; Mather et al., 2002). Exercise may enhance sleep and contribute to an increased quality of life via promotion of relaxation, and maintenance of daytime wakefulness (Montgomery and Dennis, 2002). Currently, the literature contains several reviews (Table 2.3) examining the efficacy of exercise in dementia (Deschenes and McCurry, 2009; Eggermont and Scherder, 2006; Forbes et al., 2008; Heyn et al., 2004; McCurry et al., 2000). These reviews examine different outcomes, different modalities of exercise, different aspects of behavioural and psychological symptoms and use different inclusion criteria. Consequently, heterogeneity in the reviews makes it difficult to draw definitive conclusions about the role of exercise in managing BPSD, and difficult to do a meta-analysis.

Heyn et al (2004) carried out meta-analysis of exercise in dementia and reported data on 30 trials of exercise. The authors reported on trials that included strength, cardiovascular or flexibility regimes; and analysed for functional, cognitive or behavioural outcomes. A significant positive effect of exercise on behavioural outcomes was reported (Effect Size = 0.54; 95% Confidence Interval = 0.36-.72). However these trials do not provide a full picture of the effectiveness of exercise on BPSD for a number of reasons. There was considerable heterogeneity in terms of

the interventions, and exercise was often combined with other behavioural interventions. Thus, it is difficult to isolate the impact that exercise has had on behavioural outcomes. Some regimes were quite complex and require a high degree of physical fitness that would preclude many older adults with complex physical problems and moderate or profound dementia from performing them. Moreover, they were potentially unsustainable without the support of trained therapists. Finally, the relatively high cost of delivery and specialist input required may prevent the interventions being used more widely. Most trials included in the analysis were relatively small, with only two of the eight studies that reported effects on behaviours having samples in excess of 100 participants.

Table 2.3 Overall summary of the efficacy of exercise in BPSD

Symptom	Effects of exercise
Anxiety	An immediate short term effect of chair based exercise and some walking on anxiety was found, which was maintained at 12 weeks (Edwards et al., 2008).
Depression	Forbes et al. (2009) was not able to make any conclusions about the efficacy of exercise on depression as few studies fitted their very robust inclusion criteria. The findings of other studies are contradictory. There is no improvement in depressed mood after doing 30 minutes of aerobic exercise three times a week for three weeks (Aman and Thomas, 2009). However, sustained walking benefits depression (Eggermont and Scherder, 2006) but only in the long term (Edwards et al., 2008), with fewer depressive symptoms after three months (Logsdon et al., 2005). Comprehensive exercise as well as walking for 16 weeks reduces depressed mood where the effect of comprehensive exercise was superior to walking (Williams and

Symptom	Effects of exercise
	Tappen, 2008).
Apathy	One pilot study with a small sample size found no effect of daily aerobics, flexibility and strength exercises on apathy after three months (Steinberg et al., 2009).
General behaviour	Exercise training improved behaviours (Heyn et al., 2004) but the type of behaviour is not specified and it is not clear which type of training exercise were the most beneficial. Large effect size studies had more frequent exercise sessions per week while medium effect size studies delivered the longest exercise training.
Repetitive behaviour	No studies available.
Aggression Agitation	Improvements in agitation were demonstrated after three weeks of aerobic exercise (Aman and Thomas, 2009). Sustained walking benefits agitation (Eggermont and Scherder, 2006; Overshott et al., 2004) and meaningful exercise decreases agitation (Volicer et al., 2006). Chair based exercise had no effect on anger in the short or long term (Edwards et al., 2008).
Wandering	Some limited evidence shows that exercise (walking and structural activities) reduces wandering during the day and night (Siders et al., 2004).
Sleep disruptions	Some evidence that exercise (e.g. walking) improve sleep (Shub et al., 2009; Volicer et al., 2006) although (Deschenes and McCurry, 2009) concluded that no robust controlled trials examining the effect of exercise on sleep have been conducted thus far.

2.4.1 Type of exercise

The reviews of studies described varied approaches to the concept of exercise. For example, Shub et al. (2009) included studies using exercise protocols ranging from

walking to more comprehensive programmes such as aerobics, endurance activates, strength training, balance and flexibility training, and concluded that walking is the most feasible and effective activity. Heyn et al. (2004) included studies examining walking, cycling, chair based exercise, flexibility and weight training but did not compare effectiveness between different modalities. Siders et al. (2004) only mentions dancing as exercise and argues that exercise had been poorly operationalized in studies. Forbes et al. (2008) reviewed studies examining aerobics, walking, 'meaningful' exercise and flexibility but could not carry out an analysis to determine a dose-response between the type, frequency, and intensity of physical activity due to the small number of trials included in the review. Vital et al. (2010) included studies examining walking, aerobics, strength and flexibility training but also concluded that there is no consensus on what is the most effective modality. The papers included in Eggermont and Scherder's (2006) review evaluated seated exercise, walking, aerobics, music training, sit to stand repetitions, and strengthening and flexibility exercises where the effect of walking was superior to the other modalities. Some reviews failed to mention how exercise had been conceptualised in the studies they reviewed (Deschenes and McCurry, 2009; McCurry et al., 2000; Robinson et al., 2006).

Exercise was also conceptualised in different ways in the individual papers included in this review. Some studies evaluated chair based exercises and walking (Edwards et al., 2008) while others explored aerobics (Aman and Thomas, 2009; Steinberg et al., 2009), dance and rhythmic movement (Hokkanen et al., 2003) or

‘meaningful’ activities such as marching to music, moving from a table to a circle and walking from one area to another (Volicer et al., 2006).

Most of the reviews and individual papers included in this review either did not address or are inconclusive about identifying the most effective type of exercise as therapy for BPSD. Eggermont and Scherder’s (2006) recognise that walking is more efficacious than other forms of exercise and Shub et al. (2009) identify walking as the most feasible form of exercise.

2.4.2 Frequency and duration of exercise

Heyn et al. (2004) coded studies with regards to the intensity, frequency and length of the intervention but were unable to demonstrate a significant finding for these training characteristics. Eggermont and Scherder (2006) provided clear details of the frequency and duration of the exercise interventions when available. They found that higher frequency of exercise (daily or several times a week) was related to better outcome (sleep) irrespective of duration. Siders et al. (2004) also describe the frequency and duration of studies but do not discuss these in any detail while Forbes et al. (2008) were unable to examine the effect of frequency and intensity of exercise due to the small number of trials. Shub et al. (2009) concluded that: “*Patients with dementia and carers should be instructed to walk for exercise daily for 30 minutes, preferably outside in natural light”*. Others made no mention of frequency or duration of exercise (Robinson et al., 2006).

Of the individual papers, when reported, duration of exercise varied from a daily programme of exercise (Steinberg et al., 2009) to 30 minutes, three times a week

(Aman and Thomas, 2009; Edwards et al., 2008) and 30-45 minutes once a week (e.g. Hokkanen et al., 2003). This limited evidence indicates that exercise should be carried out daily or several times a week for it to be effective.

Heyn et al. (2004) reported that the mean duration of exercise interventions that reached a large effect size was 14.5 weeks and a medium effect size was 23.4 weeks. However, these effect sizes applied to mixed outcomes including cardiovascular, functional and behavioural aspects. Consequently, we could not draw a conclusion about the most effective duration period for our intervention.

2.4.3 Place of exercise

The studies included in the reviews by Eggermont and Schreder (2006) and Siders et al. (2004) were conducted in care homes, although one study included in Siders et al. (2004) was conducted outside. Other reviews (Deschenes and McCurry, 2009; Heyn et al., 2004; McCurry et al., 2000; Overshott et al., 2004; Robinson et al., 2006; Shub et al., 2009) provided little information about the place of exercise as did Forbes et al. (2009) due to not being able to assess difference between these.

Of the individual studies, most took place within care homes (e.g. Aman and Thomas, 2009; Edwards et al., 2008; Hokkanen et al., 2003; Volicer et al., 2006). Steinberg et al. (2009) however, carried out their intervention outside the care home setting where participants exercised within their own home.

2.4.4 Design

Some of the review papers included some form of quality criteria to the designs of the studies included (Eggermont and Scherder, 2006; Robinson et al., 2006) and/or only included papers using RCTs with a non-intervention control group (e.g. Forbes et al., 2009; Heyn et al., 2004). In the review by Forbes et al. (2009) studies had follow-up times ranging from seven weeks to three months but the effect of exercise at follow-up was not examined due to lack of trials. Deschenes and McCurry (2009) concluded that no controlled trial had been conducted to examine the effect of exercise on sleep. Heyn et al. (2004) and Robinson et al. (2006) also point out the absence of blinding procedures and the lack of long-term follow-ups in studies while Siders et al. (2004) highlights a lack of RCT designs and a lack of control group included in studies. Other reviews (e.g. Overshott et al. 2004; Shub et al. 2009) only mentions the importance of conducting RCT studies but fail to critically examine the methodology of papers under review.

Of the individual papers, only two studies (Hokkanen et al. 2003; Steinberg et al. 2009) used a randomised controlled trial design. However, both of these were pilot studies. The others used either a repeated measures design (Edwards et al., 2008; Volicer et al., 2006) or a between group design (Aman and Thomas, 2009; Regan et al., 2005). Of those using a between group design, the control group consisted of those who refused to exercise (Aman and Thomas, 2009) and those who simply did not exercise (Regan et al., 2005). In these studies the groups would almost invariably be different at the start and consequently any differences observed are likely to be due to the pre-existing differences. In Steinberg et al.'s (2009) RCT

study, the control group were given a home safety assessment only. Follow-up times also varied from three weeks (Aman and Thomas, 2009) to 16 weeks (Hokkanen et al., 2003).

2.4.5 Sample size

The meta-analysis by Heyn et al. (2004) excluded research papers using less than five participants and mentions the problem of small sample size in current studies using an RCT design. Eggermont and Scherder (2006), Forbes et al. (2009), Siders et al. (2004) and Vital et al. (2010) also provided clear details of sample size and made similar comments with regards small sample size and low power of studies.

The sample size in the individual studies was small overall, with only two studies, which were not RCTs, having 90 participants or more (Regan et al., 2005; Volicer et al., 2006). Steinberg et al. (2009) is the largest RCT with 27 participants. The remainder had samples ranging from four to 50 (e.g. Aman and Thomas, 2009; Hokkanen et al., 2003).

2.4.6 Cognitive disability and diagnosis

Eggermont and Scherder (2006) only included studies where participants had an MMSE (Mini-Mental State Examination) score of 24 or less and although they describe the diagnosis of participants within each study, these were not discussed further. Heyn et al. (2004) included papers where participants had MMSE scores of less than 26 or a pre-existing diagnosis of dementia. Seventy-five percent of the

studies reported the MMSE score. The type of dementia diagnosis affecting the participants was described but not discussed further. Siders et al. (2004) report that cognitive disability and type of dementia was rarely described. Indeed, Forbes et al. (2009) also highlight the lack of homogeneity in terms of diagnosis and severity of disease in current studies. Some reviews (e.g. Vital et al., 2010) only included patients with Alzheimer's disease while others (e.g. Overshott et al., 2004; Shub et al., 2009) did not discuss diagnosis or cognitive status.

Many of the individual studies ignored the potential importance of diagnosis type (e.g. Edwards et al., 2008; Hokkanen et al., 2003; Volicer et al., 2006) although most reported the MMSE or SLUM (Saint Louis University Mental Status) scores used as an inclusion criterion and describe the diagnosis of their participants (e.g. Aman and Thomas, Edwards et al., 2008; 2009; Regan et al., 2005; Steinberg et al., 2009). However, two studies did have a homogenous sample (only people with Alzheimer's disease; Regan et al., 2005; Steinberg et al., 2009).

2.4.7 Limitations of the literature review

The major limitation of this literature review is that it completely relied on previously published research that was identified using the critical interpretive approach, the search methodology described in paragraph 2.3 and the appropriateness of these studies given the inclusion/exclusion criteria. This review was carried out within very limited time frames and its conduct and the trial design phase overlapped. Therefore, a few aspects of the trial design were not primarily informed by these findings, but by decisions taken at Advisory and Steering Committee meetings.

Single studies that investigated combined interventions were excluded from the review, however the reviews included did incorporate combined interventions. For example an RCT by McCurry and colleagues (2005) was not included on the review because the intervention included both walking and a sleep hygiene programme. The review was restricted to English papers only. This review was sent for publication in May 2011, consequently it did not include papers that were published beyond this date. As a result relevant reviews such as the one by Tadros et al (2013), which explores the effectiveness of Tai Chi on BPSD were not included.

2.5 Summary

There are plausible mechanisms for reduction of BPSD using exercise as therapy (Cooney et al., 2013). However, exercise programmes for people with dementia have been poorly conceptualised and it is unclear which aspects of exercise (e.g. type and duration) provide better results than others. We need to understand further what behavioural and psychological symptoms responds best to what type of exercise/intervention, how exercise may work, for whom and under what circumstances. At the conclusion of the review there appeared to be some indication that walking is a feasible exercise that can help reduce depression (Edwards et al., 2008; Eggermont and Scherder, 2006; Williams and Tappen, 2008), aggression and agitation (Overshott et al., 2004) wandering (Siders et al., 2004) and sleep disturbances (Shub et al., 2009; Volicer et al., 2006). However, evidence that exercise has a role in improving apathy and repetitive behaviours appeared to be completely lacking. The beneficial effect of duration and frequency

of exercise was also unclear although some studies suggested that walking for at least 30 minutes, daily or several times a week may enhance outcome (Eggermont and Scherder, 2006; Heyn et al., 2004; Shub et al., 2009). Indeed, studies examining the effect of daily exercise had more favourable outcomes. However, the methodological shortcomings of current work in this area are substantial and future studies need to focus on conducting robust longitudinal trials of well-defined exercise interventions appropriate for people with dementia. The EVIDEM-E trial was designed to measure and clarify the effect of such a well-defined exercise intervention.

3 EVIDEM-E TRIAL DESIGN AND METHODS

3.1 EVIDEM

EVIDEM-E was one out of five components of the EVIDEM program. EVIDEM stands for “Evidence-based Interventions in Dementia: Changing practice in dementia care in the community: developing and testing interventions from early recognition to end of life”. EVIDEM was a £2 million program of research funded by the National Institute for Health Research (NIHR) under grant code RP-PG-0606-1005. It was a consortium of academic and NHS professionals who conducted five research projects, from 2007-2013, that explored the trajectory of dementia process, from diagnosis to end-of-life care (Table 3.1). EVIDEM-E (exercise) was one of those five projects, which aimed to determine the effectiveness of physical exercise delivered through a program of incremental walking for treating behavioural and psychological symptoms of dementia compared with treatment as usual.

The program was hosted by Central & North West London NHS Foundation Trust (CNWL). It commenced in 2007 and reached its conclusion in 2013.

Table 3.1 Description of the other EVIDEM projects

Study title	Aims	Design	Findings
EVIDEM-ED: A cluster-randomised controlled trial to improve early diagnosis and clinical management of dementia in primary care	To test a customised educational intervention developed for general practice, promoting both earlier diagnosis of dementia and concordance with management guidelines.	The intervention was tested in an unblinded cluster randomised controlled trial (**RCT**) with a pre- and post-intervention design, with two arms: usual care compared with the educational intervention.	Case detection rates were unaffected by the intervention. Carers' recall of advice given suggested that a large minority had not received the information recommended by the National Institute for Health and Clinical Excellence (NICE) dementia guidelines.
EVIDEM-C: Promoting continence and managing incontinence with people with dementia living at home	To investigate (1) the incidence of the problems for people with dementia living in their own homes; (2) the published evidence for management; (3) the experience; and (4) the strategies and issues faced by people with dementia, their carers and the professionals trying to support them, as well as the feasibility of testing different designs of continence pads and tools to aid primary care nurses in tailoring their advice, management and support.	This **qualitative study** had four interlinked phases: 1. Reviewed the evidence about prevalence and effective interventions. 2. Explored the experiences and strategies used by people with dementia and their carers to manage incontinence, and the impact and consequences of that incontinence. 3. Tested the feasibility of an identified intervention. 4. Developed educational resources.	This study suggested that there are strategies and responses that primary care professionals and others can utilise to encourage greater openness, thereby lessening the taboo of incontinence within the stigma of dementia. It remains to be seen if these approaches, combined with more emphasis of effective containment of excreta, will influence decisions about relocation of people with dementia to care homes.

Study title	Aims	Design	Findings
EVIDEM-EoL: Quality of care at the end of life	1. To characterise dementia residents living in care homes and describe their respective pathways to death, including a survival analysis to identify indicators of the end of life. 2. To describe the care and support needs of this population, and of their carers. 3. To establish how care home staff and NHS primary care practitioners define, assess and provide end-of-life care for this population. 4. To describe how different contexts and models of care in care home environments influence experiences of end-of-life care. 5. To identify the treatments and interventions received and services and resources used, leading up to death.	This study used a prospective, **mixed-methods design** including case notes analysis, interviews, mapping of service use and economic evaluation. This study tracked care received by 133 dementia residents over 18 months in six residential care homes, including medication review and economic evaluation.	Just over 20% of the resident cohort died. There were no significant differences between those who died and those still alive in terms of sex, age, care home, duration of prior residence or a formal diagnosis of dementia. Sedative load was not significant but inappropriate prescribing was. Phase 2 used a co-design approach [Appreciative Inquiry (AI)] with three of the six care homes that built on existing relationships and expertise and, when appropriate, end-of-life care tools. The intervention was evaluated in terms of its ability to address the different types of uncertainty. AI did not increase resource use and there was a reduction in hospital costs.
EVIDEM-MCA: Implementing the Mental Capacity Act 2005 (MCA)	To identify the implementation issues arising from the introduction of the MCA in the services working with people with dementia and their carers over a 5-year period, in community settings (including care homes) To explore and make recommendations about continued professional development programmes about the MCA, and their links to adult	**Qualitative design**: The study was designed as four phases to reflect the trajectory of the dementia syndrome: (1) pre diagnosis; (2) post diagnosis; (3) living with dementia after diagnosis; and (4) towards the end of life. Tailored, semi-structured topic guides were	Baseline interviews indicated limited awareness, knowledge and understanding of the MCA but by follow-up these had grown. The need for training to be a continuous process informed by supervision, rather than one-off events was identified. An 'information merry-go-round' for people seeking advice and information was found. Some 'well' older people had made financial plans but appeared reluctant to think about HSC preferences and

Study title	Aims	Design	Findings
	safeguarding training and practice.	developed to explore the research questions at each phase.	choices. Principles of the MCA, such as 'best interests' decision-making, were useful for carers to apply when deciding for their relatives. Few professionals are aware of offences under the MCA and lack confidence in distinguishing criminal acts (ill treatment and wilful neglect) from poor care.

3.2 Evolution of the trial design

Study design was the first component of the EVIDEM-E project since the original grant proposal was very general and unspecified. The development of the protocol was the first task of the project team. This allowed the candidate to play an unusually large role in trial design. The design was developed through interactions between the study team and the steering group, which was comprised of: consultant psychiatrist, physiotherapist, occupational therapist, exercise therapist, assistant clinical psychologists, voluntary sector representatives and two carers.

The EVIDEM-E study was designed as a pragmatic, randomised, controlled, single-blind, parallel-group trial (Schulz et al., 2010). The parallel group design is commonly used when comparing two treatments (Turner, 2013). Participants were randomly allocated to either intervention or control group and remained in their allocated group throughout the trial. Cluster randomisation was discussed when recruitment from care homes was considered (Campbell et al., 2000). Clustered randomisation of care homes would have controlled for contamination effects. Contamination happens when behaviour of a participant in a specific arm of the trial may be influenced by another participant in the opposite arm of the same trial (Torgerson, 2001). The same members of staff might support participants on either arm of the trial; therefore contamination across participants could have increased. However, considering the small expected number of recruitments from care homes, it was decided to randomise participants individually.

Randomised controlled trials (RCT) are considered as “The most scientifically rigorous method of hypothesis testing available in epidemiology” (Last, 2001). During the last 50 years the effect of an intervention has been tested though RCTs rather than in observational studies because RCTs provide the most clear and unbiased evaluation of effect. Randomisation is one of the most powerful elements of RCT design as it removes selection bias and enables distribution all variables which might have an effect on outcomes equally between intervention/control groups. The process of randomisation was completely removed from the study team and was assigned to external, independent researchers. Randomisation enables distribution of potential confounders equally and avoids selection by perceived likelihood of favourable / unfavourable outcome. Blinding is another fundamental element of RCTs that minimises information bias during outcome assessments. Unfortunately, an intervention like exercise cannot be received blindly by participants who are bound to know their arm allocation. Hence, this study was single-blind with the researcher being blind to participants’ allocation. The data analysis was also conducted blindly by the researcher.

EVIDEM-E was a pragmatic trial with explanatory elements. Patsopoulos (2011) maintains that there is a continuum between pragmatic (effectiveness) and explanatory (efficacy) trials and these concepts are not dichotomous. Efficacy trials determine the outcome of an intervention under ideal circumstances. Effectiveness trials measure the degree of effect under “real world” clinical settings. EVIDEM-E employed limited exclusion criteria, included a large sample size and utilized a simple intervention which was delivered in real life routine conditions that were not

optimal. However, the intervention was delivered by a single exercise therapist, and there were formal follow-up meetings with participants. These two elements are characteristic of explanatory trials. The design effects on study's internal and external validity are further discussed on Chapter 6.

Individuals with a diagnosis of dementia, which were confirmed with ICD-10 criteria using the DCR- 10, were recruited to the study together with their carer. In order to be eligible, participants had to have at least one behavioural & psychological symptom in one of the sub-scales (paragraph 1.2.3.1, pp50) of the Neuropsychiatric Inventory (NPI) (except hallucinations or delusions occurring in isolation); and score at least 2 for severity ('causes distress') and 2 for frequency ('often- about once a week') in the NPI rating sub-scale. There is no plausible mechanism by which the intervention (exercise) might affect psychotic symptoms (paragraph 1.4.2.6, pp80) therefore the domains of delusions and hallucinations were excluded from the inclusion criteria. Suitability for inclusion into the trial was assessed, based on availability of an identified carer and the ability of the patient-carer dyad to perform exercise regime safely.

Community-dwelling individuals including those living in residential and care facilities were being recruited through the EVIDEM programme, Central and North West London NHS Foundation Trust, West London Mental Health NHS Trust, East London NHS Foundation Trust, Surrey and Borders Partnership NHS Foundation Trust and North Thames Dementias and Neurodegenerative Diseases Research Network (DeNDRoN).

Risk assessment was performed to assess the suitability of participant dyads for the intervention at baseline. Assessment included measurement for risk of falls using the Falls Risk Assessment Tool (FRAT) (Nandy et al., 2004) and the Timed Unsupported Steady Standing (TUSS) scale (Studenski et al., 1994). These measures were chosen because they are validated and widely used in the population and they were not likely to be burdensome to participants.

FRAT is a widely used tool validated for application in primary care and community populations. It includes recording history of any fall in the previous year, four or more prescribed medications, diagnosis of stroke or Parkinson's disease, reported problems with balance, inability to rise from a chair without using arms. Potential participants with three or more risk factors were not included in the study.

TUSS is test of balance that is widely used by physiotherapists and occupational therapists when assessing falls' risk in aging population living in the community. During the tests the participant is asked to stand without holding onto a support (e.g., a table or chair) with their hands by their sides for 60 seconds. Participants who could not stand unaided for 1 minute were not included in the study.

After confirming eligibility and obtaining consent from carers and people with dementia that had the capacity to consent, and assent from the carers of participants that lacked such capacity, initial baseline assessments were carried out at participants' homes. Eligible dyads were then randomized into one of two arms: the treatment arm which included receipt of the intervention in addition to treatment as usual (TAU) or the control arm which received TAU only. Both the treatment and

control arms were re-assessed for all outcomes at week 12 (primary end point). Interim re-assessment happened at 6 weeks after initiation of exercise. Further telephone contact occurred at 26 weeks to assess adverse events (including mortality) change in domiciliary status and adherence to the exercise regime.

Treatment as usual (TAU) for BPSD could encompass any of the following:

- *Pharmacological Interventions*
  - Antipsychotic drugs
  - Anti-anxiety drugs
  - Mood stabilizers
  - Antidepressants
  - Sedative hypnotics
  - Cholinesterase inhibitors
- *Psychological Therapies and Approaches*
  - Behavior-oriented approaches
  - Cognition-oriented approaches (reality orientation, skills (or memory) training)
  - Emotion-oriented approaches (supportive psychotherapy, validation therapy, sensory integration)

- Stimulation-oriented approaches (activities and recreational therapies, art therapies)

3.2.1 Stopping rules and discontinuation

If there were a significant statistical difference ($p<0.05$) between the number of reported AE/SAE by the intervention and control groups the Trial Steering Committee (TSC) and Principal Investigator (PI) would consider discontinuation of the trial. The TSC had the authority to stop the trial.

3.2.1.1 Safety variables and endpoints

Safety variables included falls risk assessments and functional abilities. Safety endpoints were falls and significant adverse events (AEs) spontaneously reported during the study and discontinuations due to AEs.

3.2.2 Intervention

Physical exercise was delivered as an individually tailored regime of walking designed to become progressively intensive. This was facilitated by a qualified exercise therapist and delivered to participants in the treatment arm of the trial at their homes.

3.2.3 Type of exercise

The steering committee and study management team discussed different modes of exercising such as: strength, cardiovascular or flexibility regimes. Ultimately, a simple walking regime was decided upon, as it met the criteria for exercise yet

seemed more likely to be acceptable, applicable to a wider population and sustainable in a community setting (Piercy et al., 2008). Walking does not require specific training or use of equipment, can be done almost anywhere and at any time at no extra financial cost. Our literature review findings also favoured walking to other types of exercise. Regular walking can improve physical health (Eyler et al., 2003) and several BPSD elements such as depression (Robertson et al., 2012), anxiety (Merom et al., 2008) and sleep (Shub et al., 2009), consequently it may have a positive effect on BPSD.

3.2.4 Intensity and duration of exercise

The exercise therapist facilitated physical exercise in the participant-carer dyad with the expectation that the participant-carer dyad performed the exercise regime regularly (5 days per week) and independently of the therapist. The Department of Health (2011, 2004) advises that older adults should carry out at least 30 minutes of moderate intensity walking on 5 days a week, in order to obtain health benefits. Eggermont & Scherder (2006) also suggest that exercise programmes should include walking of at least 30 minutes duration in order to benefit mood and agitation. Considering the frailty and complex physical conditions of our target population walking frequency was established as 20-30 minutes of walking, 5 days a week at a moderate intensity.

In terms of intervention length, the decision for it to last for 3 months was taken pragmatically as a balance between attrition and duration. Subsequent research

has reported that 50% of people who start an exercise program will dropout within 6 months (Linke et al., 2011).

The intensity was measured through Rating of Perceived Exertion scale (RPE)(Heath, 1998), in which the dyads were trained by the exercise therapist. The RPE is a Likert type scale that is used to measure the intensity of exercising by assessing body's physical signs such as heart rate, breathing rate and perspiration/sweating. There are a number of RPE scales but the most commonly used by trainers is the 15 point scale, which runs from 6 (rest) to 20 (exhaustion). Participants were instructed and supported to gradually increase their exertion to moderate level i.e. score 12-13 in the Borg scale (Figure 3.1).

Figure 3.1 Rating of Perceived Exertion (Heath, 1998)

3.2.5 Dyadic exercising

It was decided to involve a dyad (person with dementia and their carer) in the intervention for several reasons. Pragmatically, we could have not been able to support every participant 5 days a week, 20-30 minutes a day, because of lack of resources. We did discuss group exercising as an optional intervention but this alternative would have affected the ability of the exercise therapist to tailor the intervention to each participant. The duration, intensity and frequency of the intervention were tailored to each dyad's abilities and physical condition. Tailoring interventions to individuals' needs and abilities maximises compliance with the intervention (Castro et al., 2002; Connell and Janevic, 2009). Another crucial reason was that we sought to withdraw the social support from the exercise therapist, which may be considered as a confounder, and explore the effect of just walking during weeks 6-12. The intervention was structured so that the therapist adopted a phased withdrawal approach utilising both face-to-face contacts and telephone support contacts (Figure 3.2). Most importantly, according to the Reduced Stress-Threshold Model of BPSD: a person's abilities need to match the environmental demands and a discordance between the two can result in BPSD. Therefore, our exercise therapist had to make sure that the level of exercise was appropriate and would not exceed individuals' skills and abilities, otherwise we would have instigated deterioration rather than improvement of negative mood and challenging behaviours.

It was decided to involve a dyad (person with dementia and their carer) in the intervention for several reasons. The essential principle of Kitwood's (1997) person-

centred approach is to promote personhood and it is the carer's responsibility to ensure this. Likewise, the Reduced Stress-Threshold model hypothesizes that stress levels can improve by providing support to compensate for impaired abilities, and carers are the best suited persons who can provide this kind of support. Walking with a carer could control for factors that could lead to increased stress levels such as fear of falling or getting lost and improve the perception of self-efficacy.

Pragmatically, we could have not been able to support every participant 5 days a week, 20-30 minutes a day, because of lack of resources and the costs attached. We did discuss group exercising as an optional intervention but this alternative would have affected the ability of the exercise therapist to tailor the intervention to each participant. Another crucial reason was that we sought to withdraw the social support from the exercise therapist, which may be considered as a confounder, and explore the effect of just walking during weeks 6-12. The intervention was structured so that the therapist adopted a phased withdrawal approach utilising both face-to-face contacts and telephone support contacts (Figure 3.2).

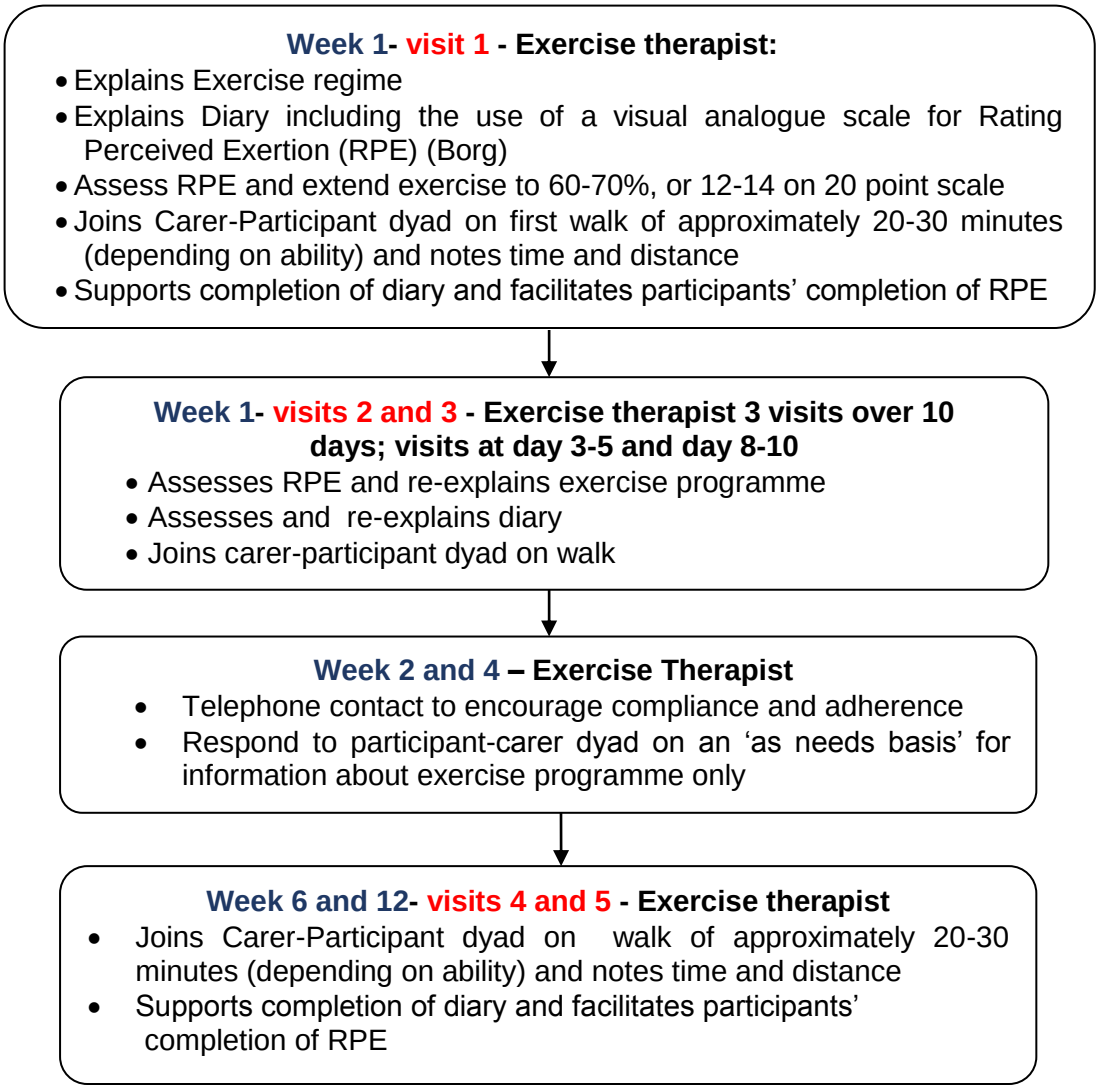


Figure 3.2 Intervention schedule

Particular consideration was given by the Steering Group and study management to the use of monitoring equipment by the participants to record their activities e.g. Global Positioning System receivers and pedometers. The following issues were identified:

- Measurement accuracy and information bias (participants would be likely to forget wearing their equipment or they would continue to wear equipment during non−activity time) (Cyarto et al., 2004)

- Practicality and intrusion (wearing equipment for 12 weeks on daily basis can be intrusive and this could have affected participation in the study and could give rise to differential attrition)

- Methodological problems (introducing a self-administered assessment of exercise within the control group could constitute an intervention in its own right (Cyarto et al., 2004). There is potential for this to promote increased levels of exercise within the control group and thus reduce the detectable effect size).

Therefore, it was agreed to evaluate participants' level of exercise through measurements of the participants' self-reported Rate of Perceived Exertion (exercise group only). A proxy measure of fitness was also utilised to assess for compliance with intervention. Heart rate at rest was assessed at the beginning, middle and end of the trial for all participants. We expected that should participants adhere to the prescribed exercise regime, their fitness would improve and consequently so would their heart rate at rest. However we recognised that detecting such changes in cardiovascular health were ambitious.

3.3 Trial protocol

3.3.1 Sample

Patients with a clinician's diagnosis of dementia with at least one significant BSPD symptom defined by the Neuropsychiatric Inventory (NPI) (excluding the domains of delusions and hallucinations) were eligible for the trial. The diagnosis of dementia was confirmed in accordance with the ICD-10 Diagnostic Criteria for Research (DCR-10). All types of dementia subtypes were included in the trial as they are all characterized by overlapping BPSD symptoms.

We recruited participants with dementia with an identified carer. The carer could be either a family member or a professional e.g. a care home worker. We ensured the carers' level of physical health and their ability to support the participant with dementia in the trial by assessing risk of falls through FRAT and TUSS, and by writing to their GP (Appendix 1.2).

3.3.2 Recruitment base

This study was conducted in several inner city, urban and semi-rural locations in and around London. Participants were recruited either directly from a research register of people with dementia (managed by North Thames DeNDRoN) whom had expressed a general interest in research, or by self-referral; or indirectly via primary clinical services or specialist mental health services (e.g., memory assessment and community mental health).

Participant recruitment was both retrospective and prospective: individuals with dementia known to secondary care professionals were identified and suspected new cases were further investigated to confirm diagnosis. Regular reminders about the study were sent to participating secondary care teams within the network catchment area. A central register of all referrals was maintained.

3.3.3 Recruitment process

3.3.3.1 The Clinical Research Network: Dementias and Neurodegeneration

The Clinical Research Network: Dementias and Neurodegeneration (DeNDRoN) is part of the National Institute for Health Research (NIHR) and supports the set up and delivery of clinical research in the NHS in dementias. The Clinical Research Network: Dementias and Neurodegeneration has established a research register called DemReg, of patients diagnosed with dementia and carers willing to take part in research studies. Its aim is to link patients and carers, who are interested in dementia research, to teams leading research studies (Iliffe et al., 2011).

Recruitment from DemReg was initiated by an assigned field worker from North Thames DeNDRoN who inspected the registry for people that were eligible to participate in our study, and sent the following information to the person with dementia and the carer:

-a covering letter signed by North Thames DeNDRoN clinical lead

-a participant information sheet

-a response letter and a freepost envelope

3.3.3.2 Memory Clinics, CMHTs and Admiral Nurses Teams

Memory Clinics, Community Mental Health and Admiral Nurses Teams were asked to inspect their patient lists. Lists of people with dementia identified by clinics were checked by their lead clinician. Practitioners were then asked for their opinion about the capacity of the person with dementia to give informed consent, using the Mental Capacity Act (Department of Health, 2005) and the MRC ethics guide (MRC, 2007) as the framework for their judgement. When there were no doubts about capacity, the following information was posted to the person with dementia and the carer:

-a covering letter signed by the lead clinician

-a participant information sheet

-a response letter and a freepost envelope

For those judged as lacking capacity to consent, a consultee was identified and consulted about involvement in the trial. In the event when a consultee could not be identified, the person with dementia was excluded from participation in the trial.

The content of the invitation letter included all study details, and informed the patients of their opportunity to be allocated to one of two groups (exercise intervention; usual care) once they were screened for eligibility and had given their consent to take part in the study. Participants were directed to return letters on a

self-addressed pre-paid envelope to the research team or contact the research team by phone or email. See Appendix 1 for the invitation letter.

Once a response (letter, phone-call or email) was received an initial telephone screen was undertaken to confirm: their interest, the presence of carer, and the likelihood of at least one BPSD symptom. Then an initial interview was arranged at a time and venue convenient to the participants (participants' homes). Potential participants received a written and verbal explanation of the trial. If the participant met inclusion and exclusion criteria we sought consent from both participant and carer, using the consent protocol (see Appendix 1.3, 1.4 and 1.6). Once consent was obtained in accordance with accepted guidelines (Brodaty et al., 1999), participants proceeded to the baseline interview/assessment and then randomisation (Figure 3.3). In the case of individuals who were not capable of giving informed consent, the assent of the participant with agreement of carer was attained (see Appendix 1.5).

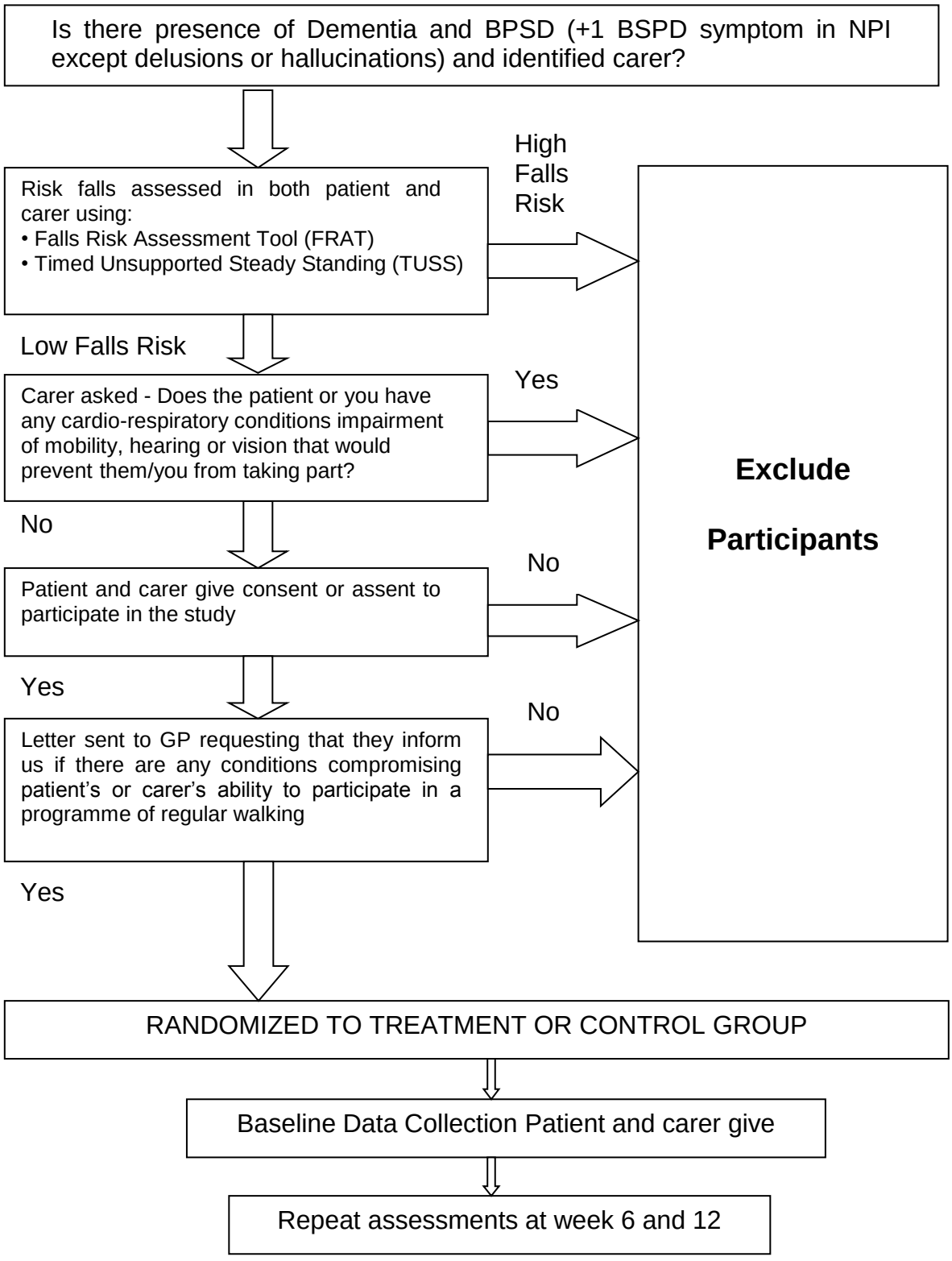


Figure 3.3 Recruitment Process

People with dementia and their carers were given two weeks to respond to the initial contact from DeNDRoN or their clinician. A second mail-out was posted to non-responders once this time has elapsed. Non-response to the second mail-out was considered to be a refusal to participate.

3.3.3.3 Inclusion criteria

The inclusion criteria were as follows:

- Diagnosis of :

a. Dementia in primary or secondary care OR

b. Suspected dementia confirmed by the researcher to ensure the ICD-10 criteria was met;

- Presence of a carer (professional, friend or family member;
- NPI score in any domain (except only hallucination or delusion) of more than or equal to two in severity and more than or equal to two in frequency;
- Consent of participant, or in the case of an individual who was not capable of giving informed consent, the assent of the participant with agreement of carer;
- Consent of carer.

3.3.3.4 Exclusion criteria

Potential participants were excluded if they met any of the following criteria:

- Cardio-respiratory condition, neurological or musculo-skeletal condition of a degree that prevented safe participation in the modified exercise regimen. This decision was taken by participant's GP.

- Three or more falls in the previous year ("frequent fallers") assessed by FRAT and high falls risk defined by TUSS.

- Uncontrolled medical problems, which the GP considered would exclude participants from undertaking the exercise programme. For example, pneumonia, poorly controlled angina, acute rheumatoid arthritis, unstable or acute heart failure.

- Sensory impairment to an extent that it prevented facilitated exercise.

- Patient or carer dissent to engage in the exercise programme.

3.3.3.5 Informed consent

The process for obtaining participant informed consent was in accordance with the Research Ethics Committee (REC) guidance and Good Clinical Practice (GCP). The decision regarding participation in the study was entirely voluntary. All participants that had the capacity to consent and their carers provided written informed consent before they underwent any interventions (including history taking)

related to the study. The consenting process for participants who did not have the capacity to consent are described in the following section (3.3.3.6).

People with dementia and their carers were given a minimum of 24 hours to consider whether they liked to be involved in the trial. The participants were encouraged to ask any questions that could help them make a decision on their potential involvement in the trial. The research worker (the PhD candidate) emphasized that consent regarding study participation could be withdrawn at any time without penalty or affect to the quality or quantity of dyad's future medical care, or loss of benefits to which they were otherwise entitled.

The Informed Consent Forms were signed and dated by both the patient and carer before they entered the trial. One copy of the Informed Consent Form was kept by the participant, one was kept by the research worker (the candidate) (placed in the Trial Master File), and a third was retained in the participant's general practice records.

Where a participant who appeared to be eligible and signed a consent form was subsequently found not to be eligible (e.g. the GP considered they fulfilled one of the exclusion criteria) they were not considered to have entered the study.

The research worker undertook to inform the dyads of any new relevant information about the effect of exercise on BPSD that became available during the course of the trial, and discussed with them whether they wished to continue with the trial.

3.3.3.6 Inclusion of participants unable to consent

The majority of people with dementia are unable to give informed consent themselves (Warner J, McCarney R, Griffin M et al., 2008). In the past the experiences of people with dementia have not been explored and they have often been excluded from participating in research due to ethical concerns. Since involvement in research tends to improve outcomes and may provide access to novel more effective treatments earlier than the rest of the population, such exclusion can itself be considered unethical (McCarney et al., 2007).

We anticipated that any participant who lacked capacity to consent, but who had an Advanced Directive concerning their involvement in research, would be involved according to the information outlined in their Advanced Directive. When clinicians were considering an individual's potential participation in the study they were asked whether the individual had an Advanced Directive and whether this contained any information about research participation. No participant had an Advanced Directive about research participation.

The clinician who recruited the person with dementia to the trial was asked for their opinion about the capacity of the person with dementia to give consent, using the Mental Capacity Act (MCA: Department of Health, 2005) and the Medical Research Council ethics guide (MRC, 2007) as the framework for their judgement. The framework included ability to: understand and retain the information regarding study participation; to use or weigh that information as part of the process of making the

decision and to communicate his/her decision (not necessarily verbally). This process was guided by the five MCA principles:

1. It should be assumed that everyone can make their own decisions unless it is proved otherwise.

2. A person should have all the help and support possible to make and communicate their own decision before anyone concludes that they lack capacity to make their own decision.

3. A person should not be treated as lacking capacity just because they make an unwise decision.

4. Actions or decisions carried out on behalf of someone who lacks capacity must be in their best interests.

5. Actions or decisions carried out on behalf of someone who lacks capacity should limit their rights and freedom of action as little as possible.

Where capacity to consent was absent, a “best interest” decision was made based on advice from clinicians, carers and past behaviour of the person with dementia in accordance with the Mental Capacity Act 2005. In this instance the best interest decision was made by the carer, with the agreement of the participant’s GP, for the person with dementia to participate in the trial. Checking ‘best interests’ included the following MCA guidelines:

- Never make assumptions about the person lacking capacity based solely on their looks, age, appearance, behaviour or condition.
- Consider all the relevant circumstances, including looking at other options.
- Consider postponing the decision if the person may regain the capacity to make it.
- Make sure that the person retains as much control and involvement in the decision-making as possible.

- Think about what the person lacking capacity would have decided for themselves by taking into account what is known of their past and present wishes, feelings, beliefs and values, (particularly if they have been written down). For example, considering a person's views about participating in research before they lost the capacity to consent.
- As far as possible consult with others, such as family, friends and any Deputy or Attorney, and take into account what they think would be in the person's best interests.

It is possible that capacity of participants could have fluctuated during the study. Therefore, the researcher monitored for verbal and non-verbal signs of potential distress in participants' and kept in communication with their carer/consultee to review and reaffirm consent before every stage of data collection. Observation of behaviours, expressed feelings and interactions were also used to assess whether the person with dementia desired to participate in the research (McCormack, 2002).

If informal or formal carers in frequent contact with the person with dementia believed that continued involvement in the trial was a source of distress, their view had precedence over the clinical or researcher perceptions.

3.3.3.7 Compliance and diaries

Compliance was defined as continuation with the exercise programme. This was recorded though diary entries. Participant carers on both study arms were asked to record daily if the dyad walked out as well as length of walks in minutes. Diaries are described in more detail in paragraph 3.5.1.

3.3.3.8 Randomisation

Patient/carer dyads were randomly allocated to receive treatment as usual (TAU) or exercise therapy in addition to treatment as usual (ET). The randomisation ratio for the two groups was 1:1 (ET:TAU). A computer algorithm was used to perform the randomisation centrally by an Independent Randomisation Officer after the initial interview, who then communicated the results to the participant and carer, and to the exercise therapist; but not the research worker or the other Independent Researcher (IR).

3.3.3.9 Concealment and Blinding

In order to maintain blinding, randomisation was performed independently of the research worker (RW) following baseline evaluation. The exercise programme was initiated and supervised by an 'Exercise Therapist' (ETh). Baseline and subsequent evaluations were undertaken by RW. An independent researcher (IR) collected the

primary outcome data (NPI) at weeks 6 and 12 by telephone to minimise the risk of un-blinding.

3.4 Outcome Assessment

Participants were visited in their own homes, by the research worker (RW/the candidate) masked to arm allocation. See Appendix 1.13 for a detailed schedule of assessments. All possible measures were taken to ensure that blinding was not compromised. However, some dyads divulged information about the group they were allocated to. Therefore the efficacy of blinding was assessed at each time point by asking both the IR and RW to indicate which arm they believed each individual dyad was randomised to.

3.4.1 Outcome measures

The research team, the trial steering group and the broader EVIDEM programme board reviewed the available outcome measures and agreed on the following battery:

The Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) is a validated clinical instrument for evaluating BPSD in dementia and is a structured interview that is administered with an informant who is familiar with the patient. This tool can also be used to derive a score which pertains to the carer's distress caused by each behavioural domain. The NPI evaluates the following neuropsychiatric domains: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, dis-inhibition, irritability/lability, apathy, aberrant motor activity, night-time behaviour

disturbances. For each domain a screening question is asked to determine if the behavioural change is present or absent. If the answer is positive the domain is explored at greater depth with the sub-questions. If the sub-questions confirm the screening question, the severity and frequency of the behaviour are determined according to the criteria provided for each domain.

Frequency is scored 1 to 4, and severity is rated 1 to 3. The product (severity x frequency) is calculated for each behavioural change present during the previous month or since the last evaluation. NPI scores range from 0 (no disturbance) to 144 (maximum disturbance).

In carrying out the NPI assessment, the focus rested on eight of the ten domains. The difference between the treatment and control groups in composite scores of agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/ability and aberrant motor behaviour was measured. An impact of physical exercise on hallucinations and delusions was not expected. In studies where NPI was measured in the placebo group a mean reduction of 2.2 was observed (Rolland et al., 2007).

Researchers who carried out the NPI in the study, attended training sessions with the PI, who is an expert user of NPI, in order to enhance inter-rater reliability and increase scoring consistency between assessors. Blind scoring between assessors was compared and training was repeated in two occasions until individual raters were in agreement when scoring blindly on 95% of scores.

DEMQOL-Proxy (Smith et al., 2005) is a 31 item interviewer-administered questionnaire answered by an informant. The measure has been developed by the Section of Mental Health Ageing in cooperation with the London School of Hygiene and Tropical Medicine, the London School of Economics and Nottingham University. The instrument has been validated in the UK and allows assessment of quality of life in moderate and severe dementia. Scores on the DEMQOL-Proxy range from 31 to 134, with higher scores indicating better patient health-related quality of life. DEMQOL-Proxy was chosen in preference to DEMQOL because the latter cannot be applied with participants with moderate and severe dementia allowing assessment in a wider range of population. This instrument is reported to have good acceptability (missing data >5%), internal consistency (Cronbach's alpha ≥ 0.70) and test-retest reliability (Cohen's Kappa = 0.82) (Smith et al., 2005).

The General Health Questionnaire (GHQ-28) (Goldberg, 1972) is a measure of current mental health. The instrument was developed by Goldberg in the 1970s as a 60-item instrument and shorter versions (GHQ-30, GHQ-28 and GHQ-12) were developed later. The GHQ-28 is the most used and popular version, which is divided into four subscales:

- Somatic symptoms (items 1-7)
- Anxiety/insomnia (items 8-14)
- Social dysfunction (items 15-21)
- Severe depression (items 22-28)

All items have a four point Likert scoring (0-1-2-3) that ranges from ‘better than usual’ to ‘much worse than usual’. Caseness in GHQ is identified as the total of the above sub-scales. Thus, the higher the score the more severe the condition. There are no thresholds for individual subscales.

The GHQ-28 was chosen in favour to other measures because it is the most widely-used measure of psychiatric ill health in the UK and has been validated for both clinical and general populations. Internal consistency has been reported in a range of studies using Cronbach’s alpha, with correlations ranging from 0.77 to -0.93. The predictive validity of the GHQ in comparison with other scaling tests of depression is good with specificity coefficients ranging from 74-92 and sensitivity coefficients ranging from 72-92 (Goldberg, 1985). Sensitivity relates to the test's ability to accurately identify a condition while as its specificity refers to the test's ability to exclude a condition correctly.

The Zarit Burden Interview-short version (ZBI) (Bedard et al., 2001) is a commonly used measure that evaluates carers’ burden of caring for older adults with dementia. The original version was published in 1980 (Zarit et al., 1980) and comprised 29 items, later reduced to 22 items version. The short version encompasses 12 items, which are self-reported statements of how carers feel when taking care of someone. All items have a five point Likert scale (0-1-2-3-4), ranging from ‘never’ to ‘nearly always’. Severe burden is represented by high scores. Cut-offs have been developed by arbitrarily dividing the total possible score into roughly equal parts. Bedard et al. (2001) suggest that high burden may be identified by using the top quartile as indicators with an overall score of 17.

The scale was chosen because it has high face validity (α= 0.83), is acceptable to carers and is widely used (Bedard et al., 2001). In a review of 53 articles on caring for someone with dementia published between 1980 and 1997, Bedard *et al* (2001) found that the ZBI, or a measure based on it, was used in 25 (47%) of the studies. The shorter version was used in favour of the longer one to reduce assessment time and carer overload, considering the extensive baseline assessment battery. Bedard *et al.* (2001) report that the short version of the ZBI produced comparable results to the full version (correlations ranging from 0.92-0.97) and reducing the number of items did not affect the properties of the ZBI.

The Client Service Receipt Inventory (CSRI) (Beecham and Knapp, 2001) has been developed in the Centre for the Economics of Mental Health and the Personal Social Services Research Unit. The CSRI is a questionnaire that gathers retrospective information about the interviewee's use of health and social care services, accommodation and living situations, income, employment and benefits as well as socio-demographic information. It also records information about the main carer. The CSRI is a tool commonly used in service and economic evaluation studies. This data was collected retrospectively at baseline, covering the six months prior to the assessment, and at follow up 12 weeks into the trial. The resources used during the exercise intervention were recorded to estimate the costs of the intervention. This outcome will not be reported in this thesis as it is beyond its scope and I (the candidate) was not involved in its analysis.

Participants' general level of fitness was assessed as heart rate at rest and blood pressure readings taken during each time point by the research worker using an Omron (BP562) wrist blood pressure monitor.

3.5 Baseline assessment

In addition to the outcomes outlined above MMSE, socio-demographic data, co-morbidities and prescribed medicine were sought at recruitment (see Appendix 1.13). Confirmation of clinical diagnosis of dementia was ascertained during screening using the ICD-10 criteria.

Baseline demographic data that was collected for the dementia participants consisted of: age, gender, occupancy, ethnicity, marital status, level of education, dementia sub-type, length of diagnosis, medical problems and FRAT score. Carers' demographic data included: age, gender, relationship to patient, GHQ, ZBI. The measures described above were collected at baseline, 6 and 12 weeks follow-up.

Mini-mental State Examination was performed with all participants with dementia. This outcome was only measured at baseline.

3.5.1 Diaries

All participant-carer dyads were provided with diaries to record the level of their exercise and any difficulties they encountered when walking (See Appendix 1.11 and 1.12). Diaries for the intervention group differed slightly from the control group. The dyads in the intervention group were also asked to complete a visual analogue scale called Rating of Perceived Exertion (RPE) (Heath, 1998). Both groups were

also asked to enter information in the diaries about what they enjoyed or did not enjoy regarding their walks, as well as reasons for not exercising.

3.5.2 Follow-up assessments

Table 3.2 depicts the assessment schedule for both the intervention and control groups.

Table 3.2 Administration of outcome measures

Day	Administrator	Assessment Schedule			
		Exercise Dyad group		Treatment as usual group	
		Measure	Subject	*Measure*	Subject
0	*Researcher*	Demographics ICD-10 MMSE NPI DEMQOL GHQ ZBI CSRI Medication Vital Signs (BP&HR)	Participant+Carer Participant Participant Carer Carer Participant+Carer Carer Participant+Carer Participant Participant+Carer	Demographics ICD-10 MMSE NPI DEMQOL GHQ ZBI CSRI Medication Vital Signs (BP&HR)	Participant+Carer Participant Participant Participant Carer Carer Participant+Carer Participant+Carer Participant Participant+Carer
0	*Independent Researcher 2*	RANDOMISATION and SEND DIARIES TO ALL			
1-2	*Exercise therapist*	RPE Timed walk Diary	 Participant+Carer 		
3-4	*Exercise therapist*	RPE Timed walk Diary	Participant+Carer Participant+Carer 		
6-8	*Exercise therapist*	RPE Timed walk Diary	 Participant+Carer 		
40-46 **Week 6**	*Independent Researcher 1 (telephone contact)*	NPI Remind Completion of Diaries	Carer Participant+Carer 	NPI Remind Completion of Diaries	Carer Participant+ Carer
40-46 **Week 6**	*Researcher*	DEMQOL GHQ ZBI	Carer Participant+Carer Carer	DEMQOL GHQ ZBI	Carer Participant+Carer Carer

Day	Administrator	Assessment Schedule			
		Exercise Dyad group		Treatment as usual group	
		Measure	Subject	*Measure*	Subject
		Medication Adverse events Vital Signs (BP&HR)	Participant Participant+Carer Participant+Carer	Medication Adverse events Vital Signs (BP&HR)	Participant Participant+Carer Participant+Carer
40-46	*Exercise therapist*	RPE Timed walk Diary	Participant+Carer		
80-88	*Independent Researcher 1 (telephone contact)*	NPI Remind Completion of Diaries	Participant Participant+Carer	NPI Remind Completion of Diaries	Carer Participant+Carer
80-88 **Week 12**	*Researcher*	DEMQOL GHQ ZBI CSRI Medication Adverse events Vital Signs (BP&HR)	Carer Participant+Carer Carer Participant Participant Participant+Carer Participant+Carer	DEMQOL GHQ ZBI CSRI Medication Adverse events Vital Signs (BP&HR)	Carer Participant+Carer Carer Participant Participant Participant+Carer Participant+Carer
80-88	*Exercise therapist*	RPE Timed walk Diary	Participant+Carer		
90-98	*Researcher*	Collection of Diaries	Participant+Carer	Collection of Diaries	Participant+Carer
182-196 **Week 26**	*Researcher*	Telephone contact Change in domicile? Still exercising? Mortality assessment	Carer	Telephone contact Change in domicile? Still exercising? Mortality assessment	Carer

3.6 Statistical Methods

3.6.1 Sample size and power calculations

Improvement of BPSD measured by the NPI was used as the main outcome measure for the purpose of the power calculations Assuming that 80% of patients in the control group were likely to have scored positively for BPSD as measured by the NPI at the 12 week follow-up; and based on an anticipated between-group (control minus intervention) absolute risk difference of 30% in the proportion of people with BPSD, it was calculated that a sample size of n=116 would provide 90% power to detect this difference with a 5% (2-sided) significance level. To allow for an anticipated attrition rate of 20%, the target sample was set at n=146 (calculated by http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html)

Table 3.3 Power Calculation

Intervention	Difference	N (including compensation for 20% attrition)
0.4	0.4	70 (88)
0.5	0.3	116 (145)
0.6	0.2	238 (298)

3.6.2 Data entry

To minimize the risk of errors of data entry, a double entry method was used. The Epidata program (Lauritsen, 2008) provided an opportunity for automated checks for consistency of data entry. Double entry of data provided in paper form was

undertaken using automated consistency and logical checks on Epidata Entry (Version 3.1). The results of each questionnaire for each time period, and the screening and demographic data was entered onto an Epidata master file. The content of the master file was checked for accuracy by double entry by a different individual. These files were then exported to SPSS (Version 21) (IBM Corp, 2012) data files and were combined to provide a comprehensive database of variables (Norusis, 2010). Table 3.4 describes the advantages and disadvantages of using different database systems to enter data.

Table 3.4 Description of database systems

Database Systems	Easy to design	Validation and checks	Minimizes error/data corruption	No privacy issues	Suitable for large projects
Spreadsheet (e.g. Excel)	V	X	X	V	X
Commercial database programs (e.g. Access)	X	X	V	V	X
Web-based data entry (e.g. Opinio[5])	V	X	X	X	X
EpiData	V	V	V	V	V

[5] Opinio is a web-based survey tool developed and supported by University College London

Data was stored encrypted and password-protected on local drive with weekly backup. The central database was maintained at CNWL NHS Foundation trust headquarters.

3.6.3 Data protection

The study was fully compliant with the provisions of the Data Protection Act (UK Parliament, 1998). All records were kept in a locked filing cabinet at the study centre. Confidentiality of electronic records was ensured by password protection.

3.6.4 Data analysis

Categorical data was analysed using Chi-squared tests. Means and standard deviations or proportions were calculated (by group) for age, sex, years of education, the presence of significant medical or psychiatric history, diagnosis, duration of dementia, and MMSE score at baseline.

At 26 weeks mortality rate and domicile status were compared between groups using Chi-squared tests.

Primary analysis was by intention-to-treat and based on available data without imputation of missing values. The primary outcome was the absolute number of participants below the threshold (reduction of three points or more in the NPI score) at endpoint.

1. ANCOVA was used to analyse the differences in mean NPI scores between the control and intervention groups at end point (12 weeks), adjusting for baseline NPI scores.

2. Participants were categorised into two groups: Those who had a clinically significant reduction of three points or more in the NPI score, and those who had not. We analysed the difference in the proportions of those who had a clinically significant reduction in NPI score (by three points or more), between the control and intervention groups at end point (12 weeks).

3. Per-protocol analysis was also conducted. Sensitivity analyses were conducted to determine the possible effects of withdrawals. Compliance with the intervention was explored and analysed. All analyses were completed by the candidate blind to allocation status using the statistics package SPSS, version 21 (IBM Corp, 2012).

3.6.5 Adverse events and risk management

3.6.5.1 Definitions

An adverse event (AE) is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the trial.

An AE includes a / an:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after intervention even though it may have been present prior to the start of the trial.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the trial that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and/or convenience admissions).

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received exercise intervention or usual treatment that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation for non-elective procedures

4. Sudden or rapidly progressive major disablement

5. An event that caused the participant to seek non-routine medical treatment.

Important medical events that did not result in death, be life-threatening, or require hospitalisation could be considered a serious adverse event when, based upon appropriate medical judgment, they could jeopardize the patient or participant and could require medical or surgical intervention to prevent one of the outcomes listed in this definition. All adverse events were assessed for seriousness, expectedness and causality.

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

3.6.5.2 Reporting of adverse events

All treatment related serious adverse events were recorded and reported to the Trial Steering Committee (TSC) and Research Ethics Committee (REC) as part of the annual reports. Unexpected serious adverse events were reported within the timeframes to the REC as stated below.

During the trial conduct monitoring of adverse events was carried out. Participants were asked to contact the trial site immediately in the event of any serious adverse event. Adverse Events were brought to the attention of the study team by either:

- *Telephone call to the study team*. Participants were encouraged to call the study team if they experienced any adverse effects during the study.

- *Notification by GP*. Participant's doctors were encouraged to contact the study team of any AEs they were made aware of.

- *Notification by carer*. The participant's carer was encouraged to contact the study team, either by returning an AE postcard or by telephoning the study team, if they observed any AEs in the participant or themselves.

On notification of an AE at the study centre, the Principal Investigator called the subject and carer for further information. The Principal Investigator determined seriousness and causality in conjunction with any treating medical practitioners.

All adverse events were recorded and closely monitored until resolution, stabilisation, or it had been demonstrated that the study treatment was not the cause.

3.6.5.3 Risk management

To ensure the safety of the researchers the GP was asked if there was a history of violence with any participants to be interviewed. In case of participants recruited from residential or nursing homes, staff were approached and asked for their opinion of any relevant history of violence in the individual being approached for participation. Where participants were recruited from secondary care, similar information was obtained from the secondary care team or Community Mental Health Team (CMHT). Falls risk were minimised by assessment prior to randomisation.

The risk issues identified by the project team were:

- Inadvertent disclosure of dementia
- Carer suffering from undiagnosed dementia
- Falls – (excluded high falls risk; exercise therapist monitored; adverse event reporting)
- Cardiovascular events (excluded high risk, exercise therapist monitored; adverse event reporting)
- Worsening of BPSD (exercise therapist monitored; adverse event reporting)
- Accidents – exercise therapist assessed road sense and undertook location risk assessment for exercise location (e.g. traffic density, kerb height, risk of mugging/assault), ability of carer to manage the person with dementia safely in the streets.

3.6.5.4 Trial intervention related SAEs

Any serious adverse event that was deemed directly or possibly related to or suspected to be related to the trial intervention was reported to the TSC and ethics committee. The event was reported immediately of knowledge of its occurrence to the Principal Investigator. The Principal Investigator would:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment.
- Take appropriate medical action, which could include halting the trial and inform the sponsor of such action.

- If the event was deemed related to the trial treatment, inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.

- Within a further 8 days send any follow-up information and reports to the REC.

- Make any amendments as required to the trial protocol and inform the REC as required.

3.6.5.5 Removal of participants from interventions, assessments or the trial

Participants could withdraw from the trial at their own request or be withdrawn at the discretion of the Investigator. The participants were made aware that this would not affect their future care. Those who withdrew from the trial or follow-up were not replaced.

Participants who could not be contacted were considered as lost to follow up. Participants were accepted as lost to follow-up when 2 phone calls, letters or visits to the participant and carer were fruitless.

3.6.5.6 End of trial notifications

After the trial a summary of the results was sent to all participants (Appendix 2.8).

3.7 Ethical and regulatory aspects

This trial was granted ethical approval by the Outer North East London Research Ethics Committee, REC reference number: 09/H0701/67, and local Research and Development Offices.

The participant's GP had clinical responsibility for the participant throughout the trial. Study personnel informed the GP of any adverse events and any significant clinical problems that were brought to the investigators' attention.

All study records will be securely stored for 5 years after the completion of the study.

Every effort was made to maintain confidentiality of data supplied by participants. Participants were free to withdraw from the study at any time and were reassured that doing so would not affect their medical care.

3.7.1 Records

3.7.1.1 Case report forms

Each participant was assigned a unique Participant Trial Number, allocated at randomisation, for use on Case Report Forms (CRFs), other trial documents and the electronic database. CRFs were treated as confidential documents and were held securely in accordance with regulations. A separate Trial Recruitment Log (TRL) was set up to record confidential participant information including, name, date

of birth, address, and Participant Trial Number. This permitted identification of all participants enrolled in the trial, in case additional follow-up was required.

All paper forms were filled in using pen. Errors were lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

3.7.1.2 Source documents

Source documents were filed at the investigator's site and included consent forms, questionnaires and diaries. Only trial staff as listed on the Delegation Log had access to trial documentation other than the regulatory requirements listed below. The Delegation Log included the names and signatures of all team members, their specific trial duties and dates of their involvement in the trial. The Delegation Log was updated throughout the trial period.

3.7.1.3 Direct access to source data / documents

The CRF and all source documents were available at all times for review by the Principal Investigator, and for inspection by the sponsor [Central and North West London NHS Foundation Trust] and relevant regulatory authorities, including R&D departments.

3.7.2 Quality Assurance & Audit

3.7.2.1 Research staff training

The researcher conducting the recruitment and outcome interviews underwent training in administering the relevant questionnaires, in Good Clinical Practice (GCP) and in participant risk assessment.

3.7.2.2 Indemnity arrangements

This project was indemnified through Central North West London NHS Foundation Trust. This covered participants in the event of negligent or non-negligent harm. Standard NHS indemnities applied.

3.8 User and Public Involvement/ Trial steering committee

User representatives on the TSC were recruited through the Alzheimer Society and Age UK and were involved in the development, implementation and interpretation of the study. This involvement included: advice on trial and intervention design, advice on recruiting patients, invitation letters, the design of information leaflets and research instruments, piloting assessments, helping to assess progress, contributing to the evaluation of the project, the interpretation of findings and the dissemination of results. User representatives were invited to trial steering committee meetings and also to provide assistance to the study.

The Trial Steering Committee (TSC) provided a critical overview of the trial, and met quarterly. The TSC also acted as the Data Monitoring Committee. The TSC

included the Principal Investigator, the project lead, researchers, independent representatives of relevant voluntary organisations, individuals with expertise in exercise promotion and falls prevention, a statistician, and nominees of the funding body. The TSC membership criteria were that non-study personnel could not exceed study-personnel. Because no medicinal products were being tested and the risks of the kind of exercise that was being promoted were low, a separate data management and ethics committee was not convened, but responsibility for overview of the risks of the trial rested with the TSC.

3.9 Methods for Disseminating and Implementing Research

The detailed study methodology was published on BMC Trials (Cerga-Pashoja et al., 2010). Appendix 1.15 shows the dissemination strategy. The support of the National Institute for Health Research (NIHR) has been credited in all publications that have arisen from this project in accordance with the acknowledgment and disclaimer agreed between NIHR and the EVIDEM Consortium.

4 RECRUITMENT CHALLENGES

One of the focal points of the EVIDEM-E study design was to make participation accessible and to keep involvement burden at minimum by means of limiting exclusion criteria; ensuring intervention was easy and imposed low risk to participants; limiting input required from professionals and teams who would identify potential candidates; simplifying documentation and study procedures; and by tailoring the intervention to each participating dyad. The study was hosted by Central and North West London (CNWL) NHS Foundation Trust, which is one of the largest providers of healthcare in the UK and provides care for about 2,000 people with dementia. The study had received strong support from Memory Clinics, Community Mental Health and Admiral Nurses Teams during pre-recruitment phase. On these bases we had predicted to recruit 146 participants in 17 months [January 2010-May 2011] (Figure 4.1).

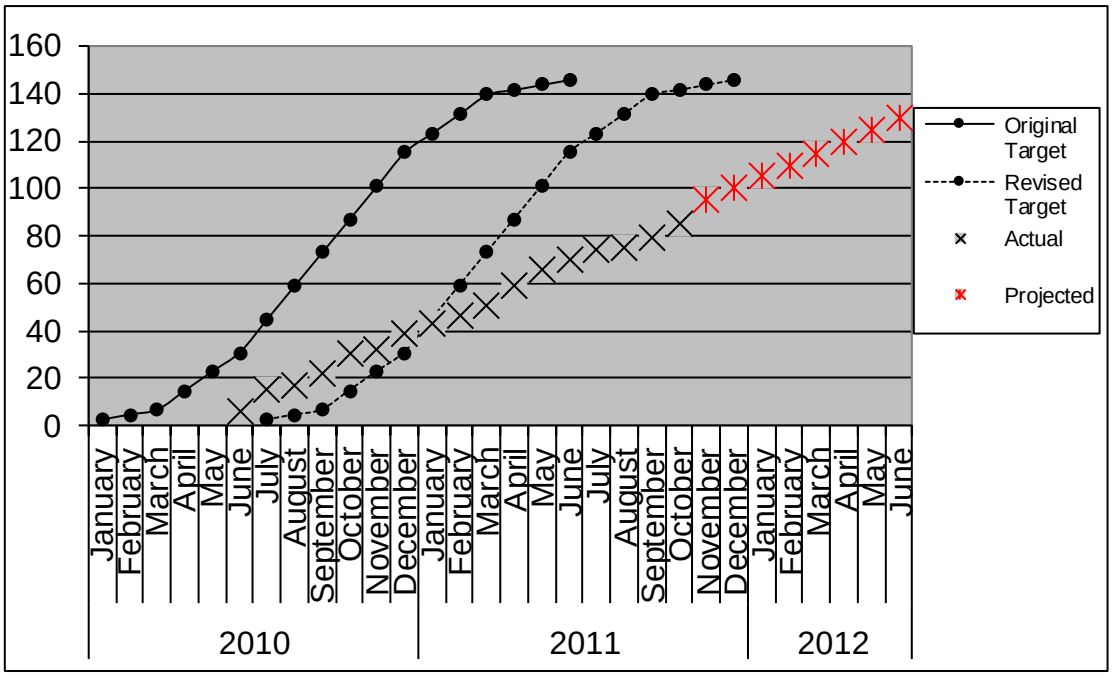


Figure 4.1 Predicted and actual accrual rates

During the first 6 months of the study the research team actively contacted 20 teams that provide care for people with dementia in CNWL. The research team spent 130 hours of direct contact with clinicians from these teams, where they were briefed about: study aims and objectives, inclusion/exclusion criteria, identification of potential candidates and referral procedures. Clinicians were given study leaflets, identification flowchart (Appendix 1.14) and information sheets. During the first 6 months of recruitment the research team prepared and sent out 300 invitation packs to clinical teams. During the same period of time the clinical teams distributed only 25 of those packs to their patients, and just 4 patients (with their carers) were recruited within the first 6 months as a result. This initial recruitment rate was at high contrast with the study's predicted recruitment target, for the same period, of 30 dyads.

Recruitment to the trial improved when alternative mechanisms were tried, especially expanding recruitment/identification sites including recruitment from a registry of patients and carers (DemReg) held by the North Thames Dementias and Neurodegenerative Diseases Research Network's (NT- DeNDRoN). The DemReg is a register for people with memory problems and their carers, who are willing to take part in research studies of dementia and have given prior consent to be contacted by researchers working on the field. Initially we invited potential participants from DemReg though a mail-out. We sent study information sheets and reply slips to 88 people with dementia or their carers. Just 3 participants were recruited to the trial as the result of the mail out (Figure 4.2).

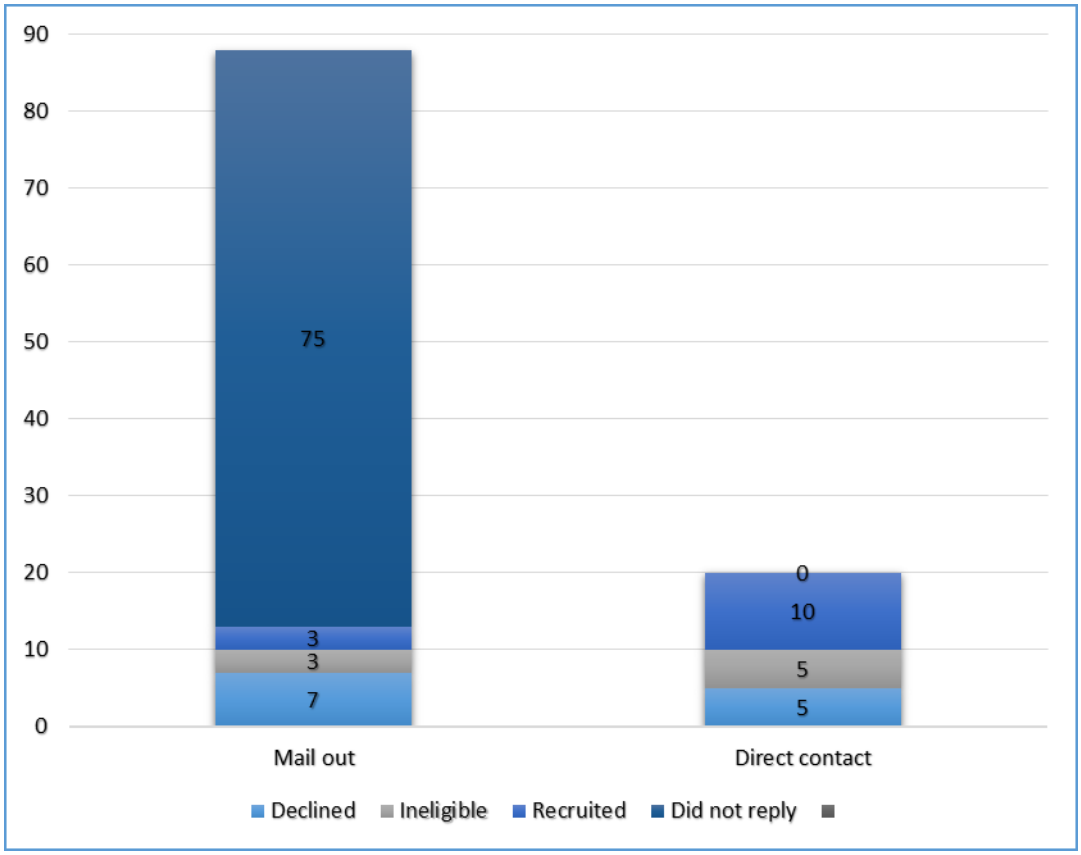


Figure 4.2 Recruitment frequencies from DemReg mail out and direct contact

Direct contact with potential participants, however, had a quick and positive effect on increasing recruitment accruals. DemReg members, who had already given their consent to be contacted by the researcher, were called on the phone and study objectives and participations information was explained. Consequently, half of the persons contacted directly, during a period of two weeks, were recruited into the study.

Surprised by the incongruity between clinicians' verbal support and their limited promotion of the study, we invited clinicians (team managers, nurses, occupational therapists, physiotherapists and psychologists) to a focus group on their perceptions

of research, impediments to their role as recruiters and potential solutions to the study's recruitment difficulties.

The group described how clinicians are increasingly challenged by patients 'informed about the latest research'. The group indicated they often had to provide counter evidence in response to 'headline', and sometimes "sensationalised" research conclusions. Together with patients' limited understanding of varying quality in research and the importance of clinical judgment for each individual, this could have (in the group's view) an adverse impact on the patient/clinician relationship. When recruiting to research, the group felt responsible as the source of the research invitation, assuming a degree of accountability for the research project's value and conduct (See Table 4.1, quotation1a). This responsibility was experienced as unreasonable, as they often had no part in the study's design and administration, and so there was a risk that recruiting might be perceived as potentially unrewarding or worse, detrimental to patients. While the group perceived the value of research, they also identified several concerns about recruiting their patients to EVIDEM-E (See Table 4.1, quotes 1b-d). Understandably, recruitment was regarded as a low priority in consultations and all too easily 'slipped off the radar' (See Table 4.1, quote 1e). However, the group did suggest ways to enhance recruitment to EVIDEM-E (Table 4.1, quotes 1f-h). All three suggestions aimed to enhance the participants' experience opposed to theirs as recruiters, and the first suggestion involved increasing clinician workload.

Table 4.1 Findings from the focus group on recruitment to the trial

a.	Clinician accountability for research "*What if they agree due to your relationship with them, when you've said this thing is going to be great…?"*
b.	Overburdening 'vulnerable' individuals with voluminous Participant Information Sheets/Invitation "*I was just wondering if you could take it (information pack) out and talk them (participants) through, rather than this big pack arriving. I'd be thinking 'waw' I thought I was just going out on a walk…"*
c.	Anxiety over the patients' feelings after researcher withdrawal *'"From our perspective they have participated in research……but they got nothing to say: thank you very much. I think that kind of puts people off."*
d.	Concern that participants would be dissatisfied when allocated to a control group *"I'm thinking about when putting someone forward, they've agreed to go forward with it, only for them not to be put in the category where they actually get the intervention. I think this maybe holds people [professionals] back from encouraging people [clients].* *"We have to tell the client what is it they get out of this. ……...what if they go on the control group and get nothing?*
e.	Low priority in individual clinical context *"A lot of people just want practical advice and support….if someone is, let's say, incontinent. What can I do, what can I put in place? It's the practical solution to a problem that they have. And even if we say that we bring experience, knowledge and information that doesn't really matter because there is something that is going on at that time that needs to be sorted."* *"I don't see it as likely that patients that will be offered some sort of treatment will ask: 'why are you saying this is the best treatment?' and ask for a justification. Many of our patients would be grateful because what they are looking for is an outcome, they are not interested how we get there. They just want positive outcome."*
f.	Continuation of treatment – themselves to be trained to deliver the EVIDEM-E intervention "*I think it would be really useful if we could do it (exercise intervention) ourselves and have a go. With proper training and under you observing it, I*

	don't see a reason why we couldn't." *"Would it be possible, not as part of the trial, simply a form of walking with somebody who has got some sort of behavioural problems, and we can try it out after being trained by your exercise therapist."*
g.	Feedback provided face to face to participants *"You need to talk to people. The feedback is very important, whether it (the study) has success or not. At the end they (participants) should be given some feedback."*
h.	Provision of carer respite *"There is a lot going on for carers at that particular time. And I think that whilst in their heart of hearts they might want to be involved and participate, but if the services are not going in to enable them to have a good night sleep, or maybe incontinence worry is a primary concern….. A lot of times carers will actually say: I want a break. I want someone to physically do it (walking) for me. I've been up all night, they've been going to the toilet, they are restless, agitated, they ask repetitive questions. And it will be really nice that while the therapist takes them out the carer can put their feet up for 10, 15, 20 minutes. That's the expectation of the carer, that someone will do that. That'll be the motivation."*
i.	Tangible Rewards *"what's in it for us?"*

5 RESULTS

5.1 Introduction

This section begins with a description of the flow of participants through each stage of the trial. The characteristics of the sample recruited are presented and compared for both the intervention and control group. Results and associated statistical analysis for primary and secondary outcomes are presented. Per-protocol analysis and compliance with the intervention have also been addressed and findings from the analysis are described.

Finally, blinding efficacy for the researchers and qualitative data findings are presented towards the end of the chapter.

5.2 Recruitment

The results of this study are reported in accordance with the CONSORT statement on reporting randomized controlled trials (Schulz et al., 2010). The flow diagram below (Figure 5.1) gives an outline of the recruitment and attrition process during the trial.

One hundred and thirty-one participant dyads were randomized to either receive the exercise regime in addition to treatment as usual (treatment), or to receive treatment as usual only (control). Eighty nine percent of dyads completed the trial, with seven and eight dyads lost from the control group and the intervention groups respectively.

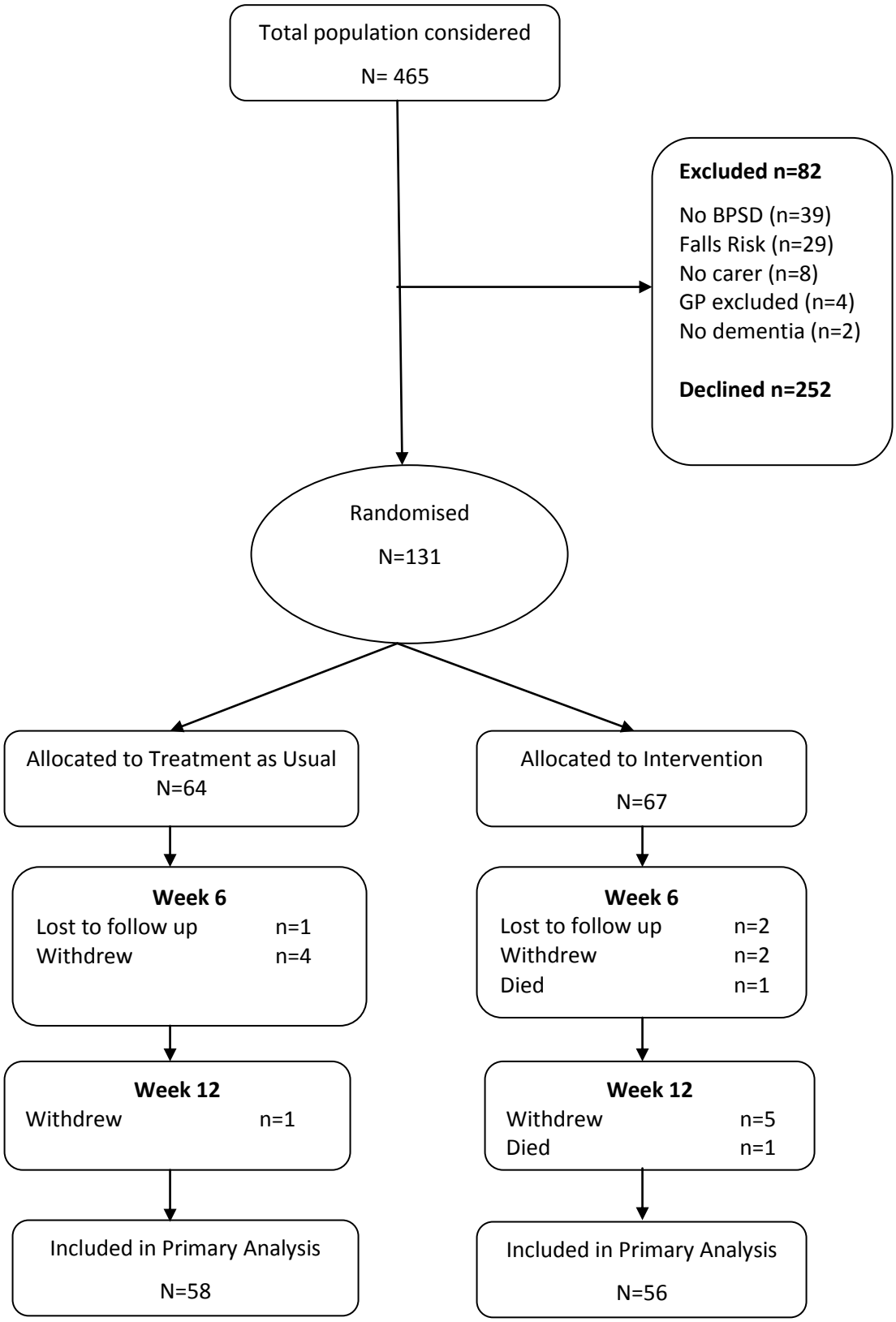


Figure 5.1 Flow diagram of recruitment and attrition

5.2.1 Exclusions

Four-hundred and sixty-five dyads were approached during the study. Two-hundred and twenty-five individuals declined participation in the study. Eighty-two individuals were not recruited for the reasons outlined below.

The most common reason for exclusion was because potential participants did not meet the criteria for BPSD. The rest were identified as being at risk of falls, had no carer that could support them during the trial, were excluded by their GP, and two individuals were not diagnosed with dementia. Comparison of excluded sample with recruited participants was not possible because of lack of baseline data for those excluded.

Characteristics of participants that discontinued the trial are presented on Table 5.1. There were no statistically significant differences between participants that discontinued the trial and those that carried on (Table 5.5) for: gender ($\chi 2$=1.01, DF=1, p=0.38[6]), age (t=3.19, DF=21.5, p=0.69), MMSE (t=-0.54, DF=21, p=0.59) and NPI (t=1, DF=22, p=0.31).

[6] Fisher's exact test

Table 5.1 Description of participants that discontinued the trial

Participants that discontinued the trial	Control	Intervention
Gender	M 0 F 6 (100%)	M 4 (36%) F 7 (64%)
Age (mean, sd, range)	75.5, 6.7, 64-84	79.7, 6.7, 64-89
MMSE (mean, sd, range)	12.33, 10.9, 10-28	18.91, 5.3, 10-25
NPI (mean, sd, range)	26.67, 11.1, 11-36	26.73, 19.14, 7-68

Main reasons for attrition were loss to follow up and deterioration of physical health. More details are presented in Table 5.2.

Table 5.2 Reasons for attrition

Reasons for trial discontinuation	Control	Intervention
Died	0	2
Lost to follow up	1	2
Withdrawn by research team (at risk of falls)[7]	0	1
Physical health deterioration	1	2
Carer could not commit	2	1
No reason given	2	3
Total (frequencies and %)	**6 9%**	**11 16 %**

Attrition was relatively low given the age of participants and the severity of the dementia (Forbes et al., 2015). The Chi-square statistic is 1,4377, the p-value is 0.230, therefore this result is not significant at $p<0.05$.

[7] Participant contributed to data collection at all time points.

5.2.2 Declines

Twenty-two percent of the persons approached did not respond (DNR). The main reasons for declining study participation were carer unavailability (46%) and person with dementia and/or carer being too unwell to take part (36%) (Figure 5.2).

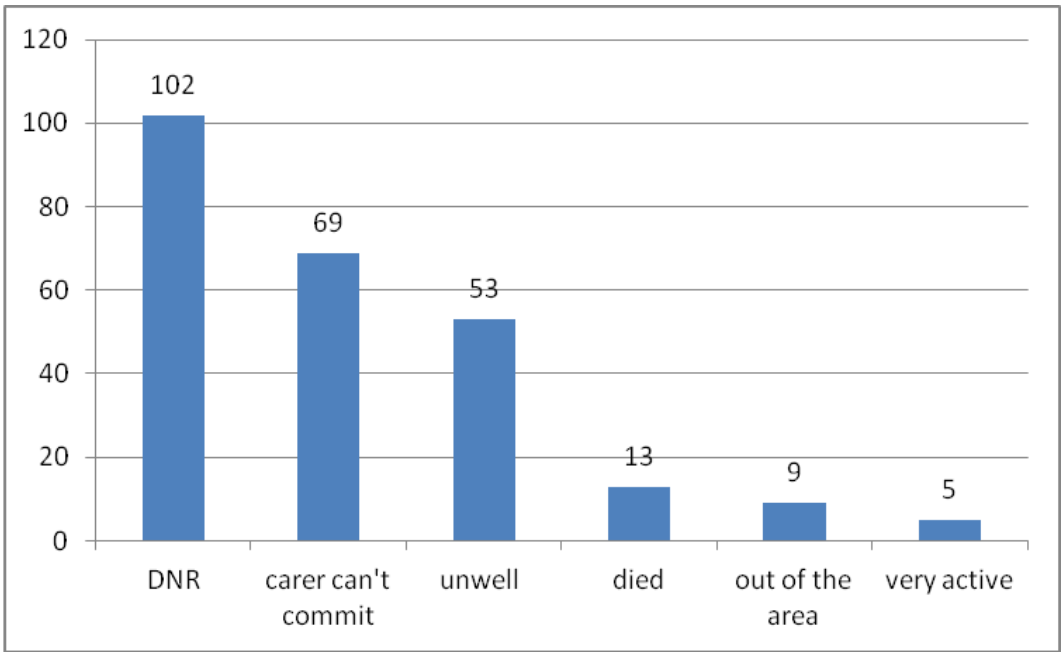


Figure 5.2 Reasons for declining participation in the trial

5.3 Characteristics of study sample

5.3.1 Demographic data of sample

Descriptive statistics for the baseline demographic and the outcome data are presented for each group in Table 5.5, Table 5.6 and Table 5.7.

Baseline characteristics of carers and patients in the two randomised groups were compared using summary statistics. Numbers and proportions are presented for binary and categorical variables while means and standard deviations are

presented for continuous variables. No statistical inference was used (i.e. there was no significance testing or use of confidence intervals) for baseline comparisons.

5.3.2 Gender

The overall sample (people with dementia and carers) was predominantly female (163: 99). This was as the result of a higher prevalence of female carers (89:42). The sample of the participants with dementia was more balanced with 57 males and 74 females. The Alzheimer's Society (2007) reports that the male to female gender ratio of dementia in UK population is 1.4 to 1, at age 65–69 years. This ratio falls to 0.2 to 1 (five women for every man affected) for those aged 95 and over. Our sample's male: female ratio was 0.77 to 1, which considering sample's wide age spectrum (58-99 years old) was representative of the population.

5.3.3 Age

The age of participants with dementia ranged from 58 to 99 years old with a mean and mode of 78. Men and women did not differ and had a mean of 78 and 79 years old respectively.

Participants with dementia were typically older than the carer participants (78.85±7.1 Vs. 63±16.2). Carers' ages varied from 22 to 89 years old, with a mean age of 63.

5.3.4 Education

The majority of our sample of patients and carers was educated to secondary

school level (n=85, 65.9%). They were followed by those who attended University and post-graduate courses (n=25, 20.3%). Eleven participants (8.9%) had accomplished primary school education and two people had not attended any form of formal education.

5.3.5 Living arrangements

Most of the participants with dementia were living in the community (89%, 116/131) and were being cared for, most commonly, by partners or adult age children. The remainder (11%, 15/131) of participants with dementia were residents of care homes. A recent survey of the Alzheimer Society (Lakey et al., 2012) reports that 69% of people with dementia live in the community and 31% live in a care or nursing home. Our sample is slightly under representative of the proportion of people in care or nursing homes. This may be explained by the dyadic character of the intervention and the time commitment, which rendered participation in care home settings very challenging.

5.4 Description of Disease Characteristics of the Analysed Sample at Baseline

5.4.1 Dementia subtype and severity

Alzheimer's disease was the most prevalent type of dementia (n=82, 62.6%), followed by unspecified dementia in 20 cases (15.3%), vascular dementia (n=10, 7.6%), mixed dementia (n=7, 5.3%), Lewy-body (n=5, 3.8%), frontotemporal dementia (n=4, 3.1%) and one person was diagnosed with Parkinson's.

Our sample included a range of dementia severities assessed by baseline MMSE. MMSE was classified as mild for scores ranging from 21-24, moderate for scores 10-20, and as severe for scores lower than 10 (Folstein et al., 1975). Thus, 52 people (40.3%) presented with mild symptoms, 42 (32%) moderate symptoms and 35 (27.1%) participants suffered from severe dementia.

5.4.2 Time when diagnosed with dementia

Most participants were diagnosed with dementia within the previous two years (n=73, 56%). Just above 33% (n=42) were diagnosed three to five years before study participation, and 10 participants (8%) were diagnosed more than 5 years prior to participation.

5.4.3 BPSD

Behavioural and psychological symptoms of dementia measured by the NPI (30.6, sd 17.7; range 4-80) were comparable to those reported in similar populations (Cummings et al., 1994; Lebert et al., 2004).

The NPI total score indicates the summation of various behaviors, and can be regarded only as a rough guide to the extent of the BPSD. Gauthier et al. (2010) argue that the total NPI score may not reflect a change in BPSD symptoms despite a reduction in individual domain scores, as “the domain effect is not sufficient to impact significantly on the total NPI score”. NPI clusters, on the other hand are considered to provide information that is more clinically relevant (Gauthier et al., 2010), and evaluating the effect of a treatment intervention on each cluster of NPI

symptoms may be more likely to give an accurate representation of its efficacy. The NPI items were grouped into four sub-syndromes (Aalten et al., 2007, 2008; Robert et al., 2005), Table 5.3).

Table 5.3 Clustering of NPI categories

Category	Symptoms
Hyperactivity	Agitation/aggression
	Irritability
	Euphoria
	Disinhibition
	Aberrant motor behaviour
Affective	Dysphoria/Depressed mood
	Anxiety
	Night time behaviour
	Appetite
Apathy	Apathy
	Night time behaviour
	Appetite
	Aberrant motor behaviour
Psychosis	Delusions
	Hallucinations

NPI cluster scores at baseline were comparable between the control and the intervention groups (Table 5.4, Figure 5.3, Figure 5.4, Figure 5.5, Figure 5.6).

Table 5.4 NPI cluster scores for the intervention and the control group

NPI Clusters	Group Allocation	N	Mean	Std. Deviation
Hyperactivity	Control	64	10.81	7.932
	Intervention	67	11.88	10.756
Affect	Control	64	13.73	8.354
	Intervention	67	11.51	8.466
Apathy	Control	64	14.13	9.511
	Intervention	67	12.39	8.440
Psychosis	Control	64	5.05	4.858
	Intervention	67	6.36	6.333

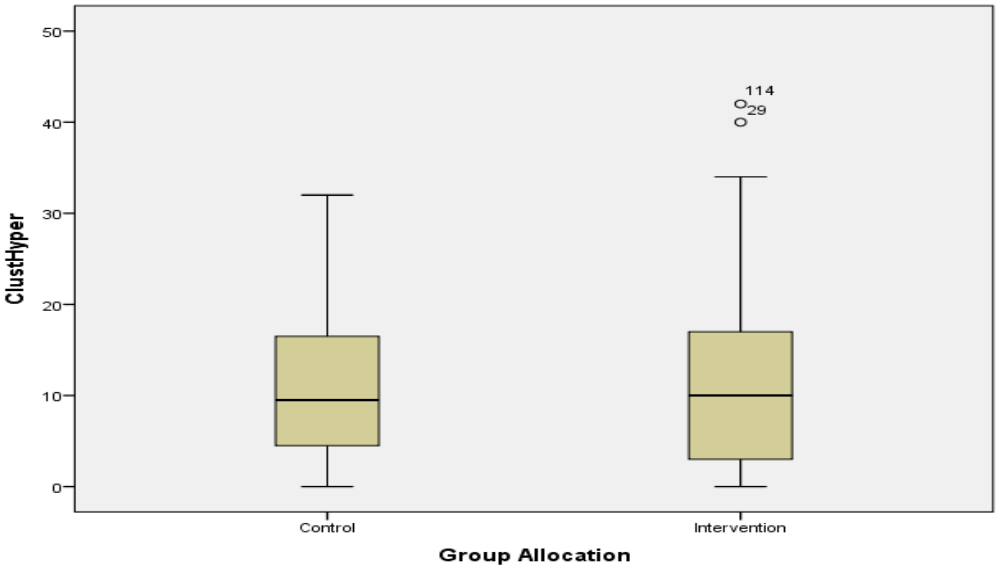


Figure 5.3 Hyperactivity cluster scores for the control and intervention arms.[8]

[8] The central band is the median score, the box represents the inter-quartile range and the lines represent the 2.5% and 97.5% percentiles. Outliers are shown as small circles outside the whiskers.

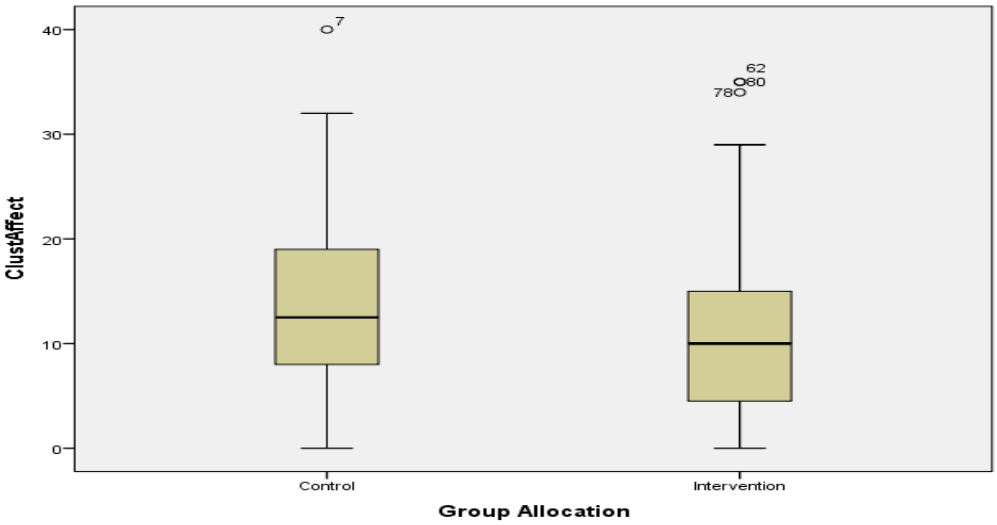


Figure 5.4 Affect cluster scores for the control and intervention arms

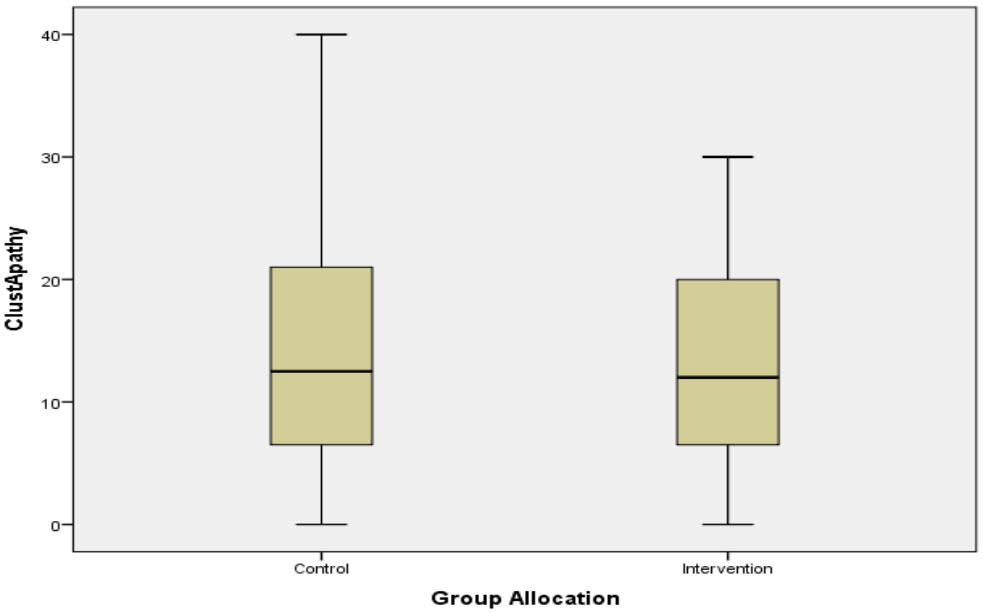


Figure 5.5 Apathy cluster scores for the control and intervention arms

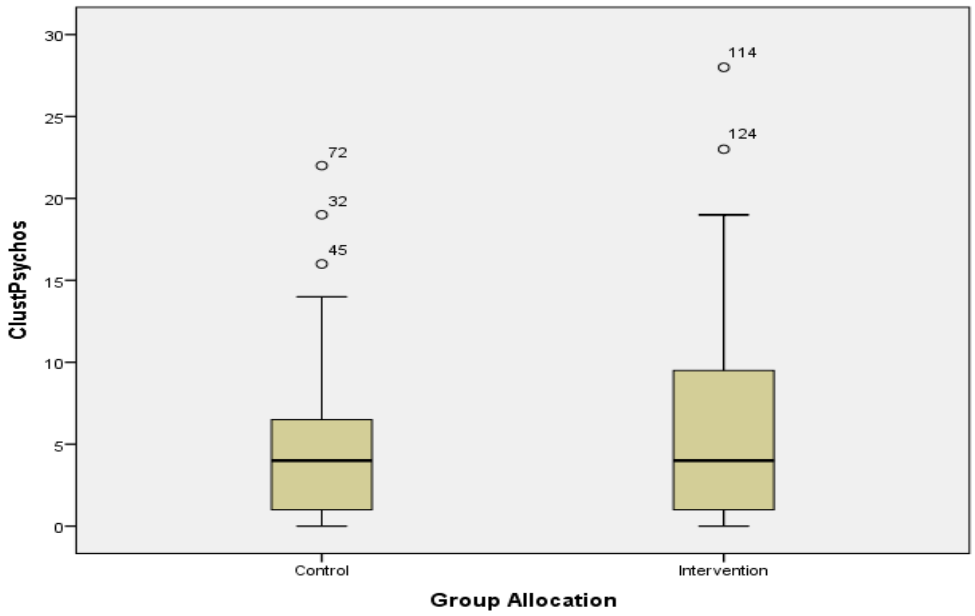


Figure 5.6 Psychosis cluster scores for the control and intervention arms

5.4.4 Quality of life

Quality of life for people with dementia at baseline as measured by the Demqol-Proxy was relatively good (101.3 ± 13.9). The scores for Demqol-Proxy can range from 31 to 124, with higher score indicating better quality of life (Banerjee et al., 2006). Smith et al. (2005) reported findings and validation data for Demqol-Proxy on 99 carers of people with mild to severe dementia. They reported a mean of 92.4 and range 55.8–118.83.

5.4.5 Carers' psychological wellbeing

Thirty-six carers (27%) reached validated threshold for 'caseness' relating to psychological wellbeing (GHQ) (Goldberg et al., 1997). Range scores are presented in detail in Table 5.7.

5.4.6 Carer burden

Twenty-five carers (19%) reached validated threshold for ‘caseness’ for carer burden (ZBI) (Schreiner et al., 2006). Range scores are presented in detail in Table 5.7.

5.4.7 Physiological measures

Heart rate and blood pressure readings were within the normal range in our sample (Table 5.6, Table 5.7)

5.4.8 Psychotropics and antipsychotics intake

Most of the patients with dementia (85/131 or 64.9% overall) were not prescribed any type of psychotropic drugs; 41/131 (31%) patients were taking one psychotropic medication; and just 5/131 (3.8%) people were taking two types of psychotropic drug (

Figure 5.7). Antipsychotics’ intake was also low with 12 patients (6 in each intervention arm), or 9% of the sample being prescribed antipsychotics.

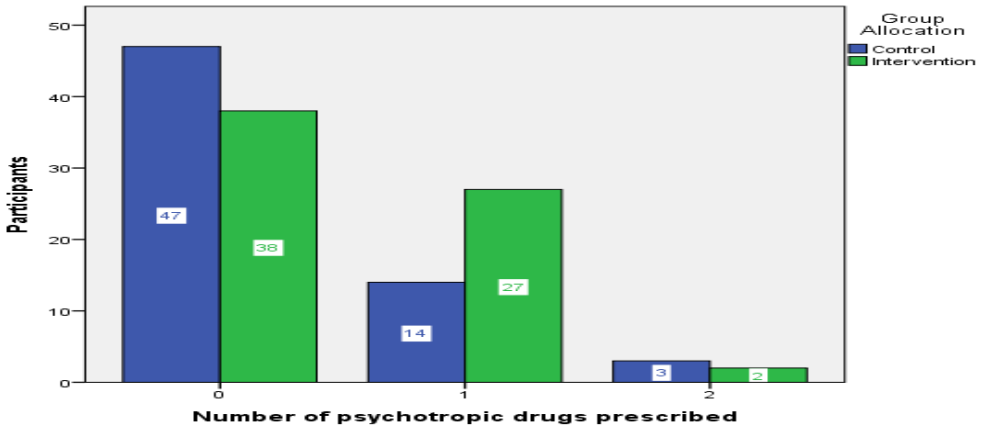
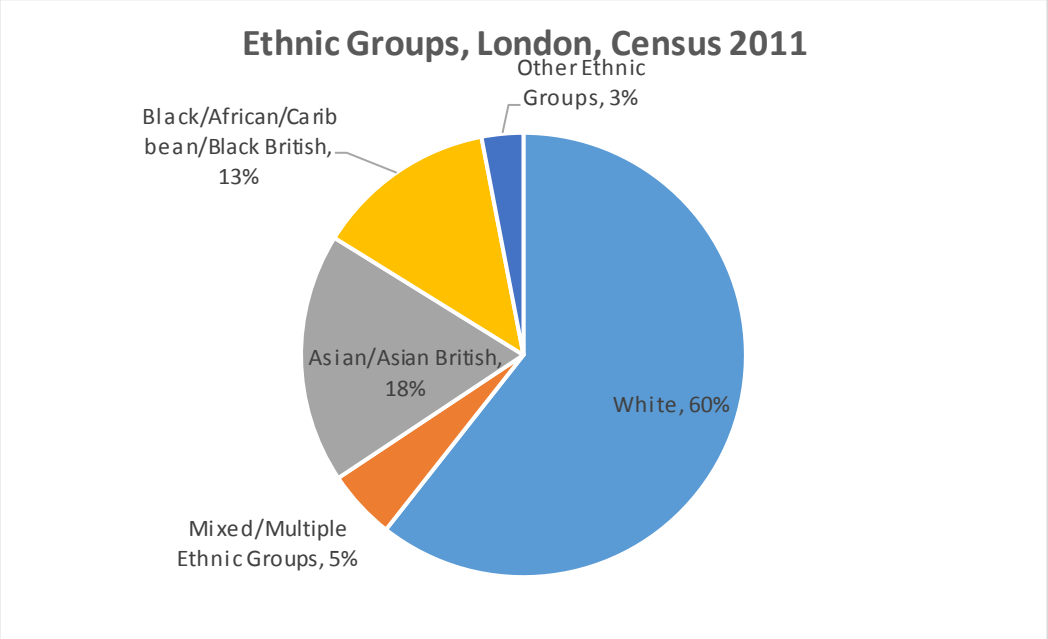


Figure 5.7 Psychotropics' intake for the intervention and control group participants

5.4.9 Ethnicity

Our sample was predominantly white but with representation from all major ethnic groups residing in London urban areas. Figure 5.8 depicts pie-charts of ethnicity groups' data in London according to Census 2011 and ethnicity groups of EVIDEM-E sample. Although the ethnic diversity of the study population did not match that of the local population we were able to recruit participants from different ethnic backgrounds.



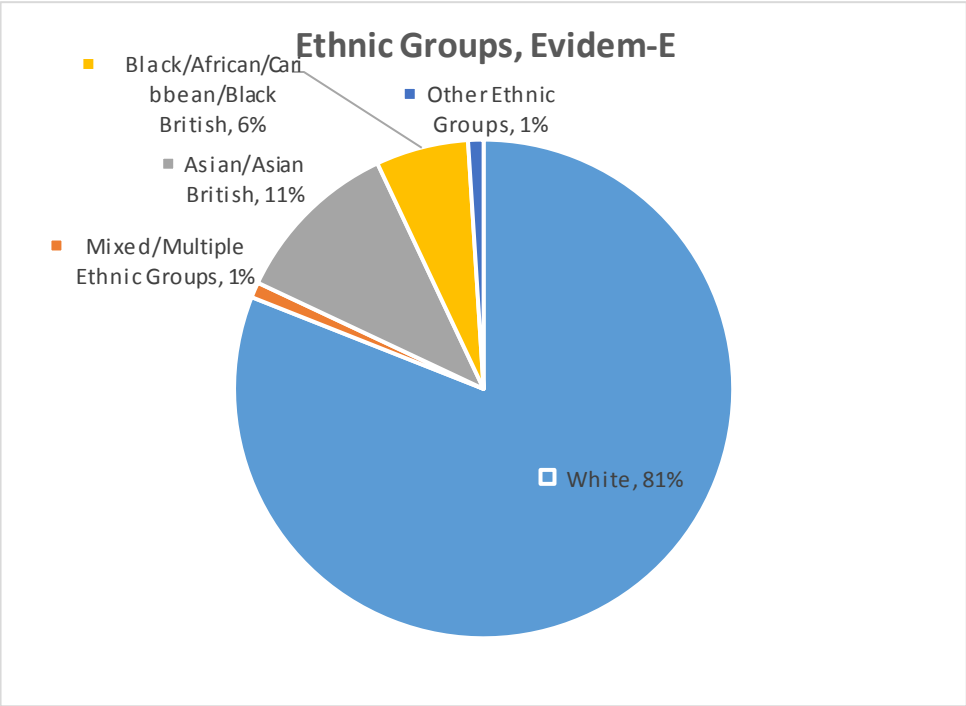


Figure 5.8 Ethnic group data from Census 2011 and the EVIDEM-E sample

5.4.10 Marital status

The majority of our sample were married (89, 68.5%), 33 (25.4%) were widowed, 4 (3.1%) single, 2 (1.5%) divorced and 2 co-habiting.

5.4.11 Effectiveness of randomisation

Socio-demographic characteristics, health parameters and carers' descriptors were compared between the control and intervention groups (Table 5.5). There were no significant differences between groups in all parameters indicating effective randomisation.

Table 5.5 Demographic characteristics

Control Group N 64		**Intervention Group N 67**	
Age (mean; sd; range)	78; 7.4; 58-99	**Age (mean; sd; range)**	79; 6.8; 64-97
Gender	M 25 (39.1%) F 39 (60.9%)	**Gender**	M 32 (47.8%) F 35 (52.2%)
Ethnicity	White 50 (78.1%) Asian 9 (14.1%) Black 3 (4.7%) Other 2 (3.1%)	**Ethnicity**	White 56 (83.6%) Asian 5 (7.5%) Black 5 (7.5%) Other 1 (1.5%)
Marital Status	Married 45 (71.4%) Widowed 15 (23.8%) Single 1 (1.6%) Divorced 2 (3.2%)	**Marital Status**	Married 46 (68.6%) Widowed 18 (26.9%) Single 3 (4.5%) Divorced 0
FRAT score	0 12 (18.8%) 1 16 (25%) 2 36 (56.3%)	**FRAT score**	0 14 (20.9%) 1 26 (38.8%) 2 27 (40.3%)
Accommodation	Home 57 (89.1%) Care home 7 (10.9%)	**Accommodation**	Home 59 (88.1%) Care home 8 (1.9%)
Years of Education (mean; sd; range)	*11.92; 5.9; 0-36*	**Years of Education (mean, sd, range)**	*12.1; 4.1; 6-23*

Table 5.6 Characteristics of participants, by study arm

Control Group N 64		Intervention Group N 67	
MMSE (mean, sd, range)	14.9; 8.7; 0-29	**MMSE (mean, sd, range)**	16.3; 7.4; 0-30
Dementia Severity	Mild 26 (40.6%) Moderate 19 (27.7%) Marked 19 (27.7%)	**Dementia Severity**	Mild 26 (40%) Moderate 23(35.4%) Marked 16 (24.6%) Unknown[9] 2 (1.3%)
Dementia Subtype	Alzheimer's 38 (64.4%) Unspecified 6 (10.2%) Vascular 6 (10.2%) Mixed 3 (5.1%) Lewy body 3 (5.1%) Frontotemporal 1 (1.7%) Other 2 (3.3%) Unknown 9 (3.2%)	**Dementia Subtype**	Alzheimer's 44 (67.7%) Unspecified 7 (10.8%) Vascular 4 (6.2%) Mixed 4 (6.2%) Lewy body 2 (3.1%) Frontotemporal 3 (4.6%) Other 1 (1.4%) Unknown 2 (1.3%)
Years since Diagnosis	≤2 years 38 (62.3%) 3-5 years 18 (29.5%) 6-9 years 5 (8.2%) Unknown 3 (1.9%)	**Years since Diagnosis**	≤2 years 35 (54.7%) 3-5 years 24 (37.5%) 6-9 years 5 (7.8%) Unknown 3 (2%)
Physical Conditions	None 22 (34.9%) One 23 (36.5%) Two 9 (14.3%) Three 7 (11.1%) Four 1 (1.6%) Five 1 (1.6%) Unknown 1 (1.6%)	**Physical Conditions**	None 28 (41.8%) One 26 (38.8%) Two 6 (9%) Three 5 (7.5%) Four 2 (3%) Five 0
Antipsyc. intake	6 (9.4%)	**Antipsyc. intake**	6 (9%)
NPI (mean, sd, range)	30.6; 16.8; 4-80	**NPI (mean, sd, range)**	30.6; 16.8; 4-80
Demqol-Proxy (mean, sd, range)	97.3; 14.1; 59-117	**Demqol-Proxy (mean, sd, range)**	99.8; 13.1; 58-122
Heart Rate	68	**Heart Rate**	66
Blood Pressure	127/70	**Blood Pressure**	129/70

[9] This information was not available from the informants.

Table 5.7 Carers' characteristics by study arm

Control Group N 64		**Intervention Group N 67**	
Age mean, sd, range	*60. 9;17; 22-88*	**Age mean, sd, range**	*65.4; 14.9; 27-89*
Gender	M 25 (39.1%) F 39 (60.9%)	**Gender**	M 17 (25.4%) F 50 (74.6%)
FRAT score[10]	0 46 (71.9%) 1 13 (20.3%) 2 5 (7.8%)	**FRAT score**	0 40 (59.7%) 1 21 (31.3%) 2 6 (9%)
Relationship	partner 35 (54.7%) child 21(32.8%) relative 5 (7.8%) paid 3 (4.7%) friend 0	**Relationship**	partner 42 (62.7%) child 17(25.4%) relative 2 (3%) paid 5 (7.5%) friend 1(1.5%)
GHQ	cases 17 (27%) non-cases 46 (73%)	**GHQ**	cases 19 (28.4%) non-cases 48(71.6%)
ZBI	cases 10 (16.1%) non-cases 52 (83.9%)	**ZBI**	cases 15 (23.1%) non-cases 50 (76.9%)
NPI (mean,sd, range)	11.9; 8.1; 0-39	**NPI (mean, sd, range)**	11.8; 8.9; 0-38
Heart Rate	70	**Heart Rate**	69
Blood Pressure	127/73	**Blood Pressure**	122/71

[10] Falls risk assessment was carried out for both people with dementia and their carers as part of the risk assessment.

5.4.12 Missing data

Missing data was examined for all main study variables by randomised group through logistic regression. Data was missing at random from both the intervention and control groups without being affected by group allocation and gender of participants (β=1.57, p=0.42); gender of carers (β=1.7, p=0.35); age of participants (β=1.6, p=0.40); age of carers (β=0.88, p=0.85); dementia subtype (β=1.69, p=0.36), dementia severity (β=1.49, p=0.47); education (β=1.94, p=0.30); ethnicity (β=1.39, p=0.56), marital status (β=1.37, p=0.57); relationship to carer (β=1.65, p=0.38) or co-morbidity (β=1.29, p=0.65).

5.4.13 Tests of Normality

Normality of data is a prerequisite for utilising parametric statistical tests. Distribution of the primary outcome data, the NPI, was assessed through the Kolmogorov-Smirnov test. The p-value was 0.004 therefore we rejected the alternative hypothesis and concluded that the data came from a non-normal distribution (Table 5.8, Figure 5.9).

Table 5.8 Test of normality for NPI scores at week 12

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Week12NPI	.104	116	.004	.908	116	.000

The Q-Q plot (Figure 5.9) provides a visual comparison of the quantiles from our data sample to the theoretical quantiles. The points in the Q-Q plot depart from the straight line and form a bow shape that indicates right-skewed data, which could not have come from a normal distribution.

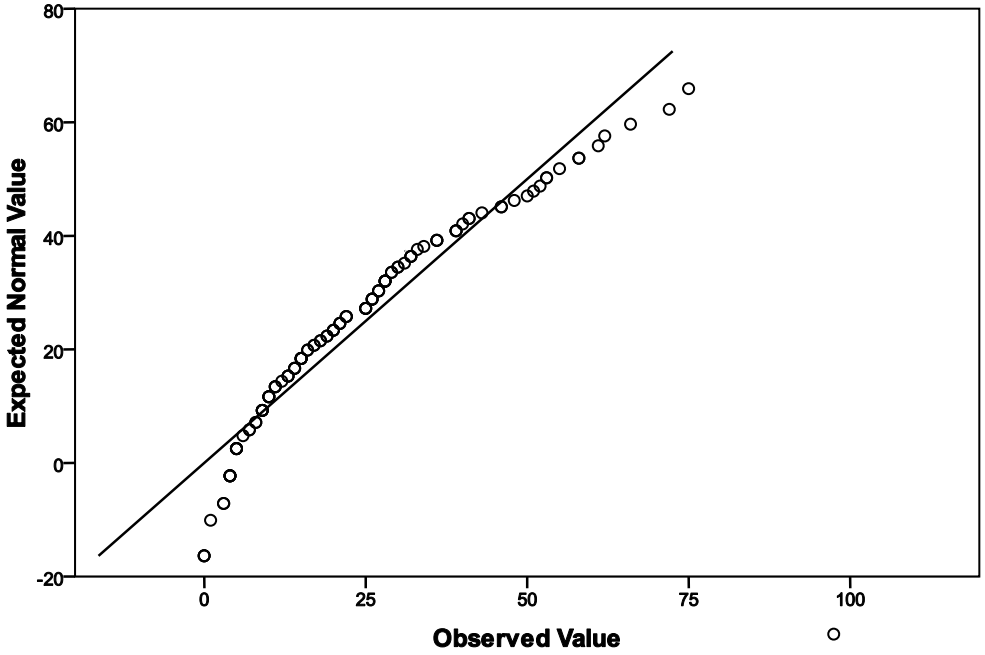


Figure 5.9 Normal Q-Q Plot of NPI values at week 12

NPI data was log transformed using natural logs (all values were added 0.5 initially because 0-vales cannot be logged). The log transformation, however, did not normalise the data (p=0.003) (Table 5.9, Figure 5.10), thus, non-parametric analysis was used to analyse NPI at week 12.

Table 5.9 Test of Normality for the NPI log transformed data

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
NPILOG (12 weeks)	.107	113	.003	.966	113	.006

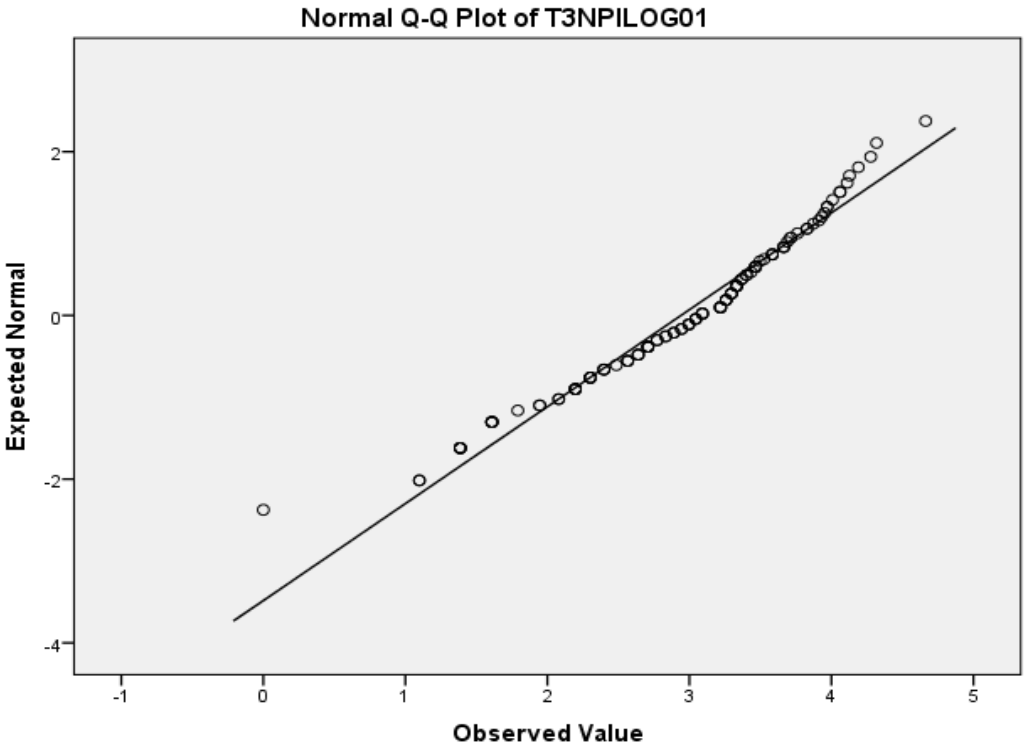


Figure 5.10 Normal Q-Q Plot of NPI log transformed values at week 12

The points in the Q-Q plot (Figure 5.10) represent quantiles of the log-transformed data compared to theoretical quantiles. The inverted bell shape indicates left-skewed data that is not normally distributed.

5.5 Analysis of Primary Outcomes-Intention to treat analysis

Intention-to-treat (ITT) analysis provides unbiased comparisons among the treatment and control groups because it avoids biases introduced by non-random attrition (Detry and Lewis, 2014). ITT analysis requires that all participants are analysed as members of the treatment group to which they were randomized regardless of their compliance with, or whether they received, the intervention.

5.5.1 ANOVA analysis

Participants were categorised into two groups: Those who had a clinically significant reduction in BPSD (NPI score) of three points or more, and those who had not. Binary logistic regression was used to analyse the difference in the proportions of those who had a clinically significant reduction in NPI score between the control and intervention groups at 12 weeks. There was no significant difference in the proportions of participants reaching a clinically significant reduction of three or more points in NPI score at week 12 compared to baseline, between the control and intervention groups (OR=1.41, p=0.36, 95% CI [0.67, 3.01], Table 5.10).

Table 5.10 BPSD improvement at week 12

NPI	Control	Intervention	Odds Ratio (OR)	95% CIs	P-value
Change (≥3)	33/57 (57.9%)	39/59 (66.1%)	1.41	0.67-3.01	0.36

5.5.2 Mann-Whitney U test

In addition, change in NPI total score (8 domains) between groups at 12 weeks was tested by Mann-Whitney U test, which indicated no significant difference between intervention groups (Z=-1.077, p= 0.28) [Figure 5.11, Table 5.11].

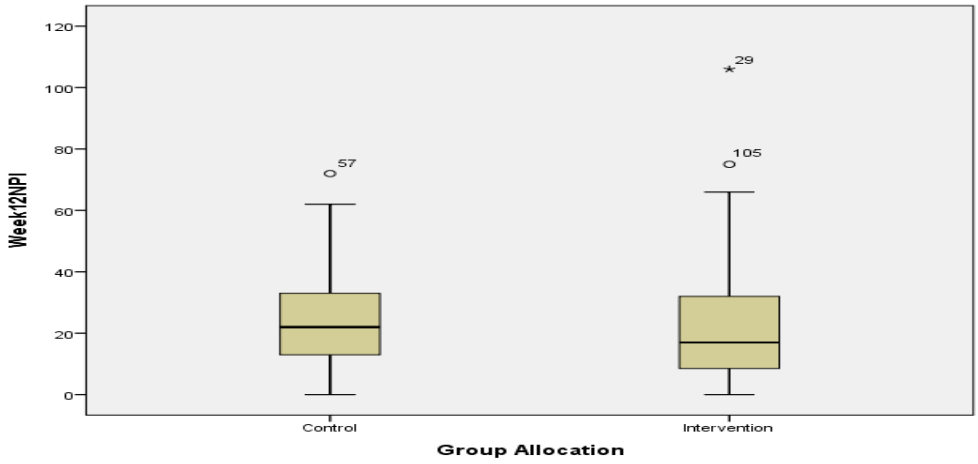


Figure 5.11 NPI scores at week 12: means, medians and interquantile range

Table 5.11 Descriptive for NPI values at week 12

Group Allocation	Mean	Median	Range
Control	25.65	22	0-72
Intervention	23.93	17	0-106

5.5.3 ANCOVA analysis

In order to test week 12 NPI score adjusted by baseline score (ANCOVA), residuals were inspected to check the assumption of normality. A residual plot

allows visual assessment of the distance of each observation from the fitted line. The relationship between residuals and predictive values in Figure 5.12 and Figure 5.13 look reasonable enough to carry out a linear regression.

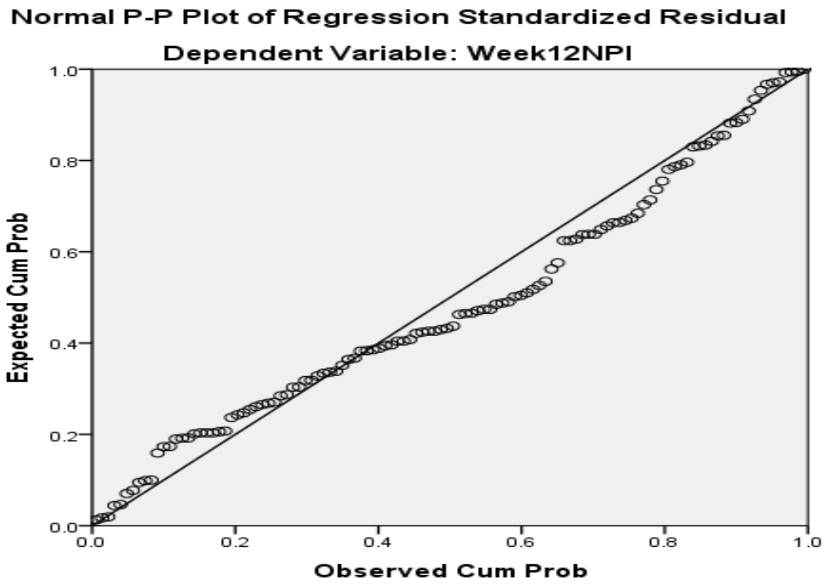


Figure 5.12 Normal P-P plot of regression standardized residuals of NPI values at week 12

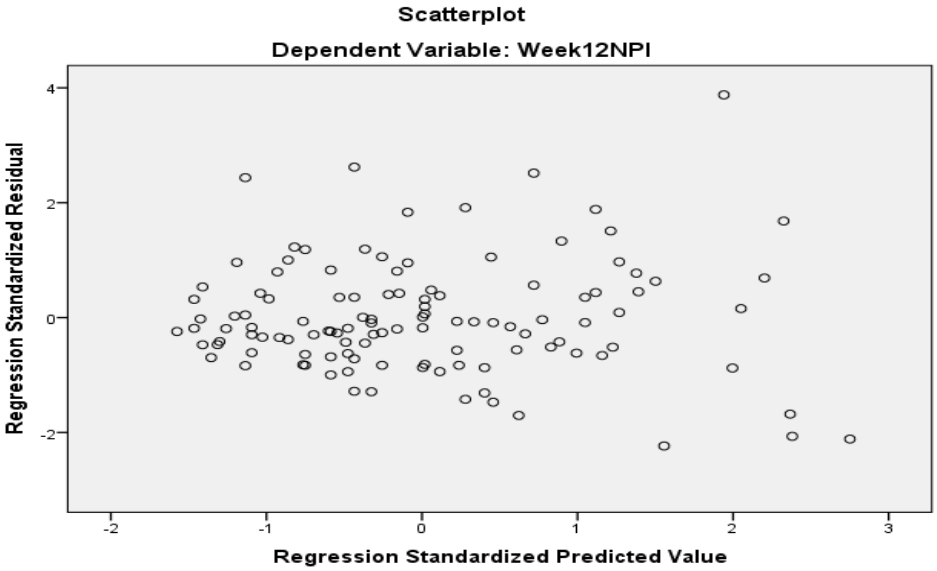


Figure 5.13 Scatterplot of regression standardized residuals of NPI values at week 12

There was no significant difference in NPI score at 12 weeks (β=-0.41, p=0.6, 95% CI [-7.37, 4.32]), where β represents the difference in mean NPI scores (intervention minus control groups at week 12) adjusted for baseline NPI scores.

5.5.4 6-week follow up analysis

NPI was also examined at 6 weeks to measure interim changes. There were no significant differences in BPSD symptoms at 6 weeks between the intervention and control groups in:

- Clinical reduction of BPSD (reduction of NPI score of 3 or more points) (β=-0.81, p=0.76, 95% CI [-6.08, 4.45]) Table 5.14 (ANOVA).
- Differences in NPI scores tested by Mann-Whitney U test (Z=-0.59, p= 0.56).
- Differences in NPI scores adjusted by baseline score (ANCOVA), (β=-0.81, p=0.76, CI [-6.08, 4.4.45]).

5.5.5 NPI cluster analysis

There were no significant differences at weeks 6 and 12, between groups, for all cluster categories (Table 5.12, Table 5.13).

Table 5.12 Between-group analysis for NPI clusters at week 12[11]

Cluster Categories	Allocation	Mean±sd 12 weeks	Adjusted difference in means	95% CIs	p-value
Hyperactivity	Intervention	10.86 ±1.03	-0.82	-4.03,1.15	0.27
	Control	9.68 ±1.27			
Affective	Intervention	9.86 ±1.08	-0.03	-3.38, 2.42	0.74
	Control	8.63 ±1.13			
Apathy	Intervention	11.6 ±1.13	-0.03	-3.38, 2.45	0.75
	Control	10.2 ±1.23			
Psychosis	Intervention	4.51 ±0.68	-0.05	-2.32, 1.26	0.56
	Control	4.58 ±0.83			

Table 5.13 Between-group analysis for NPI clusters at week 6[12]

Cluster Categories	Allocation	Mean±sd 6 weeks	Adjusted difference in means	95% CIs	p-value
Hyperactivity	Intervention	10.1±9.2	-1.59	-4.7, 0.5	0.11
	Control	11.8±8.9			
Affective	Intervention	9.9±8.9	-0.19	-2.5, 3.03	0.85
	Control	11.8±8.3			
Apathy	Intervention	9.9±8.8	-0.88	-3.8, 1.5	0.38
	Control	11.8±8.3			
Psychosis	Intervention	5.9±6.9	0.9	-0.9, 2.6	0.37
	Control	4.5±5.2			

[11] Adjusted for baseline corresponding measures.
[12] Adjusted for baseline corresponding measures.

5.6 Analysis of Secondary Outcomes

Carer's burden as measured by the Zarit Burden Inventory (ZBI) doubled by week 12 for the control group participants, but decreased from 23% to 17% for those in the intervention group; (OR=0.18, p=0.01, CI [0.05, 0.69], Figure 5.14).

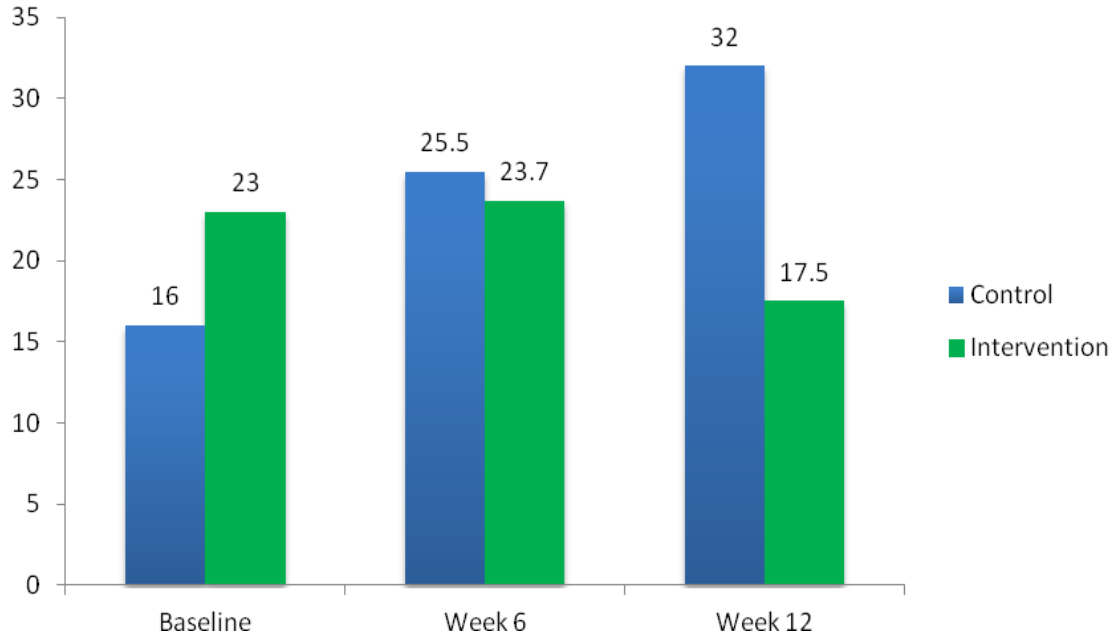


Figure 5.14 ZBI cases

There were no statistically significant differences between the groups at week 12 on: Carers' mental health (GHQ), carers' distress (NPI) and quality of life of participants with dementia (Demqol-proxy) (Table 5.14).

Table 5.14 Secondary outcome analysis – Categorical data

Outcome	Week	Control Frequency (%)	Intervention Frequency (%)	OR	95% CI	p-value
NPI[13]	6	32/56 (57.1%)	39/62 (62.9%)	1.27	0.61 : 2.66	0.52
	12	33/57(57.9%)	39/59 (66.1%)	1.41	0.67 : 3.01	0.36
GHQ[14]	baseline	46/63 (73%)	48/67(71.6%)			
	6	24/57 (42.1%)	16/62 (25.8%)	0.42	0.18 : 1.00	0.05
	12	24/56 (43%)	17/55 (31%)	0.59	0.24 : 1.43	0.19
ZBI[14]	baseline	52/62 (83.9%)	50/65 (76.9%)			
	6	14/55 (25.5%)	14/59 (23.7%)	0.48	0.14 : 1.67	0.25
	12	18/56 (32%)	10/57 (17.5%)	0.18	0.05 : 0.69	0.01

[13] Odds Ratio of an improvement (reduction) of composite NPI score of 3 or more points between baseline and weeks 6 and 12

[14] Scoring at or above the validated threshold for 'caseness' at weeks 6 and 12

Table 5.15 Secondary outcome analysis – Continuous data

Outcome	Week	Control[1] Mean ± SD	Intervention Mean ± SD	β	95% CI	p
NPI[2]	6	26.6 ± 17.5	25.7 ± 20.5	-0.81	-6.08 : 4.45	0.76
	12	25.6 ± 16.6	23.9 ± 20.6	-1.53	-7.37 : 4.32	0.60
Demqol	6	101.1 ± 14.9	103.6 ± 11.9	1.27	-2.33 : 4.86	0.49
	12	101 ± 13.5	104 ± 10	2.62	-0.78 : 6.02	0.09
NPI Carer distress	6	11.07 ± 7.2	11.5 ± 8.5	-0.06	-2.25 : 2.14	0.96
	12	9.98 ± 5.9	10.9 ± 9.3	1.14	-1.31 : 3.58	0.76
ZBI	6	18.58±8.76	17.71±9.1	-1.19	-3.05 : 0.65	0.20
	12	19.45±8.51	17.07±9.82	-2.81	-4.89 : -0.73	**0.009**

5.6.1 Standardized effect size

Cohen's effect size value (d = .091) suggests a very small effect size. It means there is a large overlap between the NPI means (week 12) for the control and intervention groups. We only have a 9% chance of finding an effect if one exists.

[1] The denominator of week 6 and week 12 data varies as result of participant availability.
[2] Analysis of Covariance (ANCOVA) of the adjusted difference in means (Intervention - Control) at weeks 6 and 12

5.7 Compliance with the intervention

Diaries were returned by 90 (69%) participant dyads; 52 (77.6%) from the intervention group and 38 (59.4%) from the control group. Overall, there were no significant differences between dyads who returned diaries and those who did not for all demographic, disease and carer characteristics.

Within the control group there were some statistically significant differences between dyads which returned diaries and those that did not. Dyads which returned diaries had predominantly partner-carers 26/38 (68.4%); (OR=4.09, p=0.009, CI [1.42, 11.79], carers' age was younger than the carers of those that did not return the diaries and their (patients) MMSE score was higher (Table 5.16).

Table 5.16 Characteristics of groups that returned and did not return diaries in the control group

Outcome	Returned diaries Mean ± sd	Did not return diaries Mean ± sd	OR	95% CI	p-value
Carers' Age	53.88±17.3	65.63±15.44	0.34	3.14, 20.4	0.008
MMSE	17.55±8.31	11.04±7.89	0.37	2.37,10.6	0.003

Walking compliance was achieved when each dyad walked five times or more a week. Walking compliance was slightly higher for the intervention group, with 19/38 (50% of the sample that returned diaries) dyads from the control group and 27/52

(51.9% of the sample that returned diaries) dyads from the intervention group reaching the threshold (Table 5.16, Table 5.17). The difference between the two groups regarding walking frequency was not significant (OR=0.93, p=0.86, CI [0.40, 2.14]).

Table 5.17 Frequencies of walking compliance on the control arm (diary respondents only)

Walking Frequency	Compliant	Non-Compliant
Control	19/38 (50%)	19/38 (50%)
Intervention	27/52 (51.9%)	25/52 (48.1%)

There were statistically significant differences at the end of week one in the self-reported walking time (minutes) between the control ($\overline{X}$=27, SD=47.2) and intervention ($\overline{X}$=10.4, SD=13.7) groups (t=2.1, p=0.04, CI [0.68, 32.5]). This differences remained statistically significant during week 6 for the control ($\overline{X}$=29.3, SD39.4) and intervention ($\overline{X}$=16.2, SD=16.9) groups (t=2.2, p=0.05, CI [-0.51, 26.8], but were not statistically significant at week 12 (t=1.03, p=0.31, CI [-5.58, 17.51].

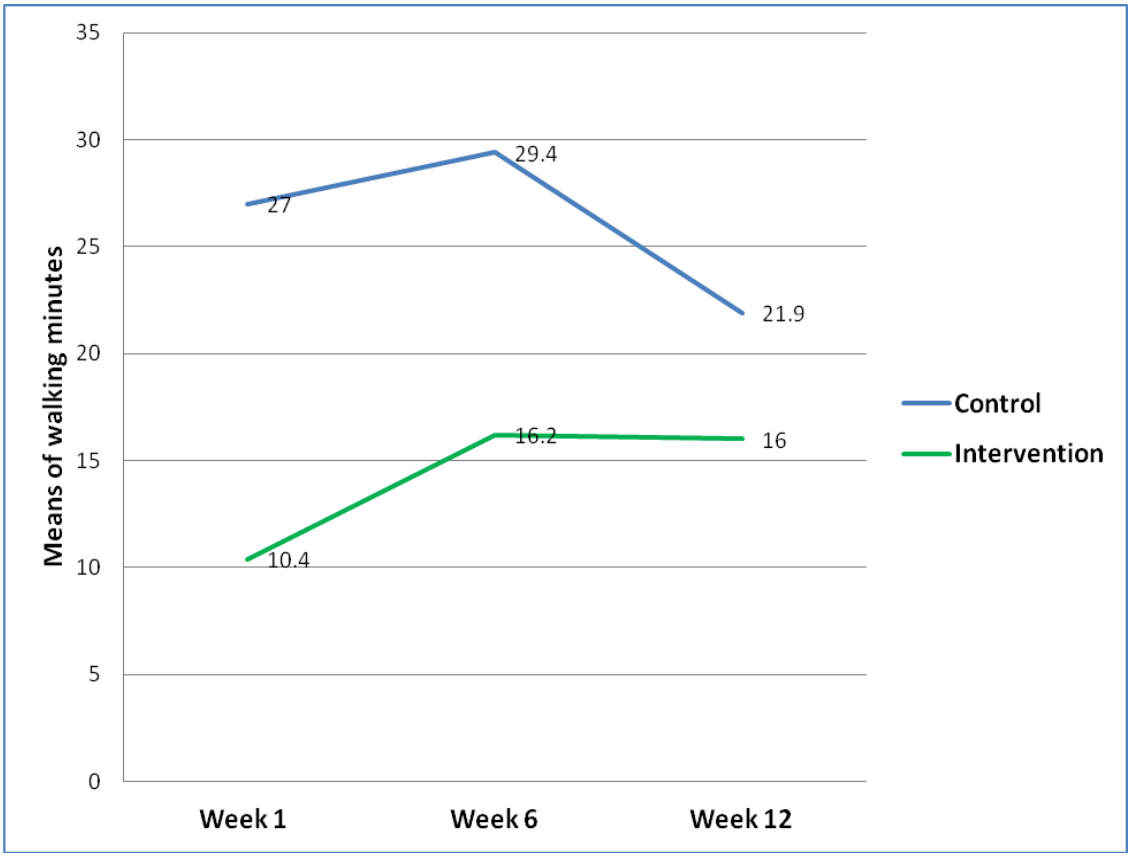


Figure 5.15 Mean walking times for the intervention and control groups

Self-reported walking time (diary) appeared to differ between the groups. The control group increased walking by just over two minutes at week 6 in comparison to week 1, but by week 12 their reported walking time had decreased by almost eight minutes in comparison to week 6. Participants in receipt of the intervention reported increasing their walking time by six minutes at week 6 and retained this change at week 12 (Figure 5.16).

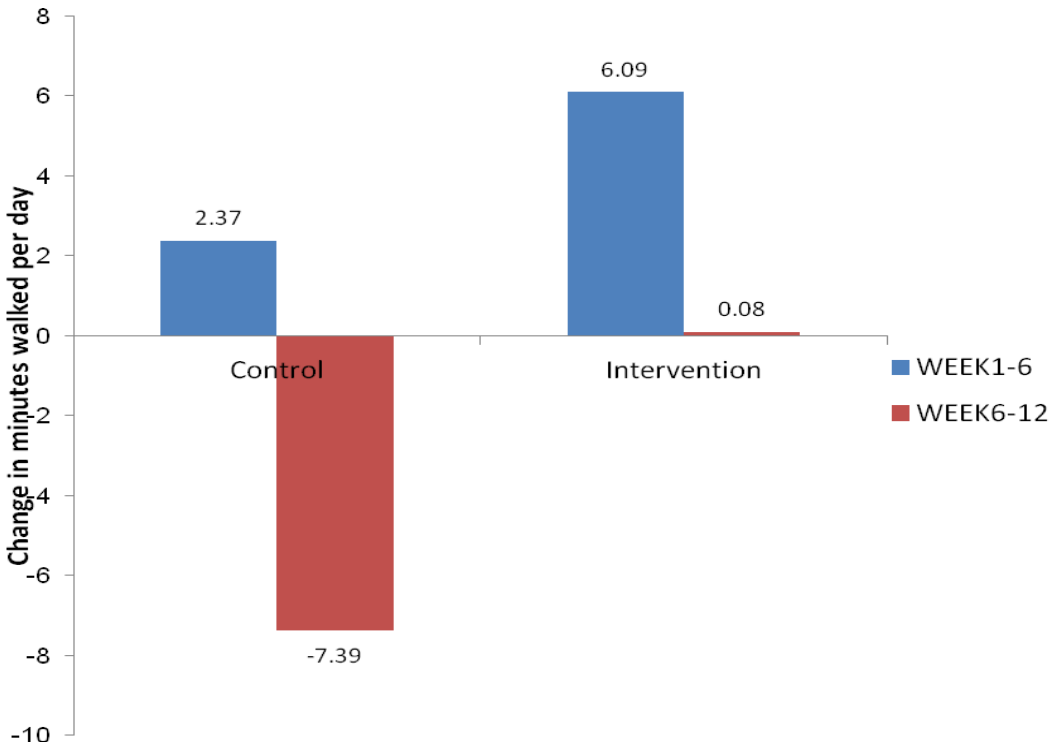


Figure 5.16 Change in walking times

RPE was reported just in the intervention group as it was part of the intervention. Out of the 52 returned diaries on the intervention group only 38 participants reported their RPE, half of which achieved the threshold for compliance (Table 5.18). There were no significant differences between participants that were RPE compliant and those that were not on all demographic, disease and carer characteristics.

Overall compliance with the intervention was considered achieved when participants walked at least 5 times a week and achieved an RPE of 12 or above. This information was obtained by self-reported measures from diary entries. Just

19% (13/67) dyads on the intervention arm were fully compliant with the intervention (Table 5.18, Figure 5.17).

Table 5.18 Frequencies of intervention compliance on the Intervention arm

	Compliant	Non-Compliant
Walking Frequency	27 (51.9%)	25 (48.1%)
RPE	19 (50 %)	19 (50%)
Overall compliance	13 (19.4%)	39 (80.6%)

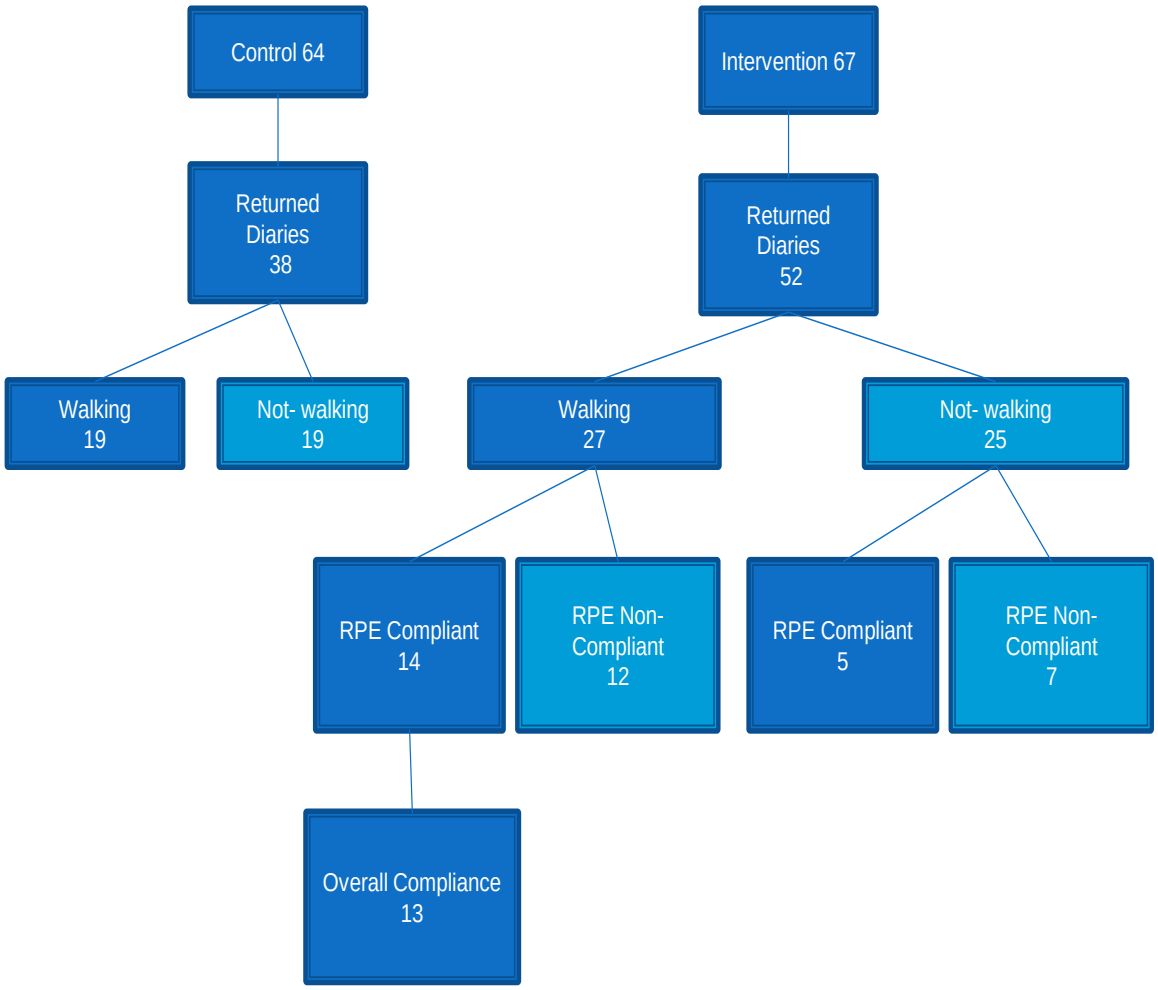


Figure 5.17 Flow diagram of compliance with the intervention

5.8 Per-protocol analysis

Considering the high rate of non-compliance with the intervention, per-protocol analysis was carried out. This analysis was restricted to participants that were compliant with the trial. Compliance was established when participants walked 5 times a week and reached an RPE rate of 12 or above. These elements were analysed individually as well as combined in order to build a better picture of the intervention effectiveness.

5.8.1 Walking Compliance and NPI

The NPI mean score at week 12 was lower for participants in the intervention arm that walked at least five times a week compared to those that did not. The opposite happened with participants in the control arm (Figure 5.18). However, none of these differences were statistically significant.

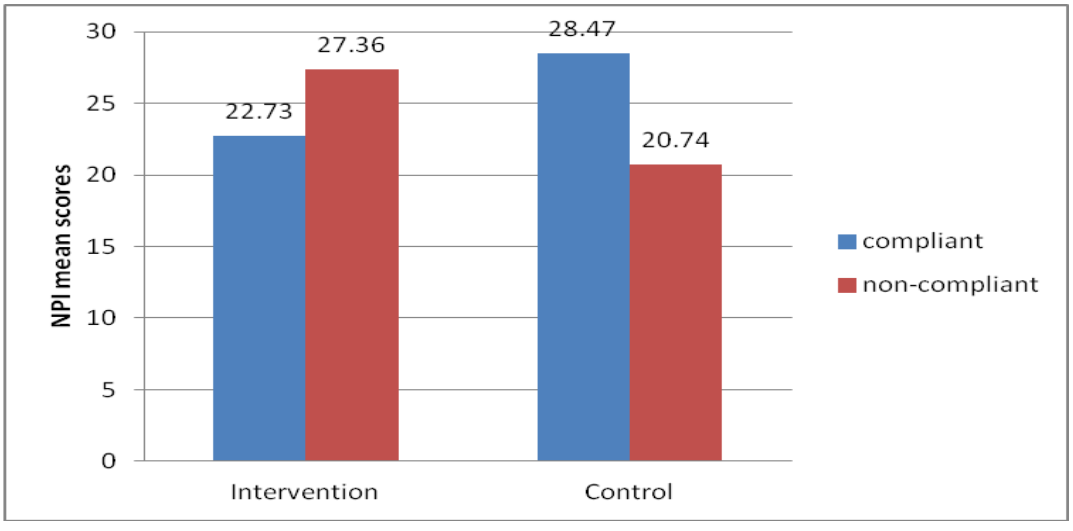


Figure 5.18 NPI mean scores for walking compliant and non-compliant participants

5.8.1.1 ANOVA analysis

Binary logistic regression was used to analyse the difference in the proportions of those who had a clinically significant reduction in NPI score between walking compliant participants in the control and intervention groups at 12 weeks (Table 5.19). A clinically significant reduction in NPI score occurred for 47.1% of participants that were walking compliant in the intervention arm, and for 57.7% of walking-compliant particiapant in the control arm.

Table 5.19 Proportions of walking-compliant participants who reached a significant reduction in NPI at week 12

Group Allocation							
Control				Intervention			
NPI not reduced		NPI reduced		NPI not reduced		NPI reduced	
Count	%	Count	%	Count	%	Count	%
9	52.9%	8	47.1%	11	42.3%	15	57.7%

There was no statistically significant difference in the proportions of participants reaching a clinically significant reduction of three or more points in NPI score at week 12 compared to baseline, between the control and intervention groups (OR=0.65, p=0.49, 95% CI [0.19, 2.43].

5.8.1.2 Mann-Whitney U test

There was no difference in NPI scores at week 12 between participants that were walking compliant in the intervention and control group (Z=-1.48, p= 0.14) (Figure 5.19).

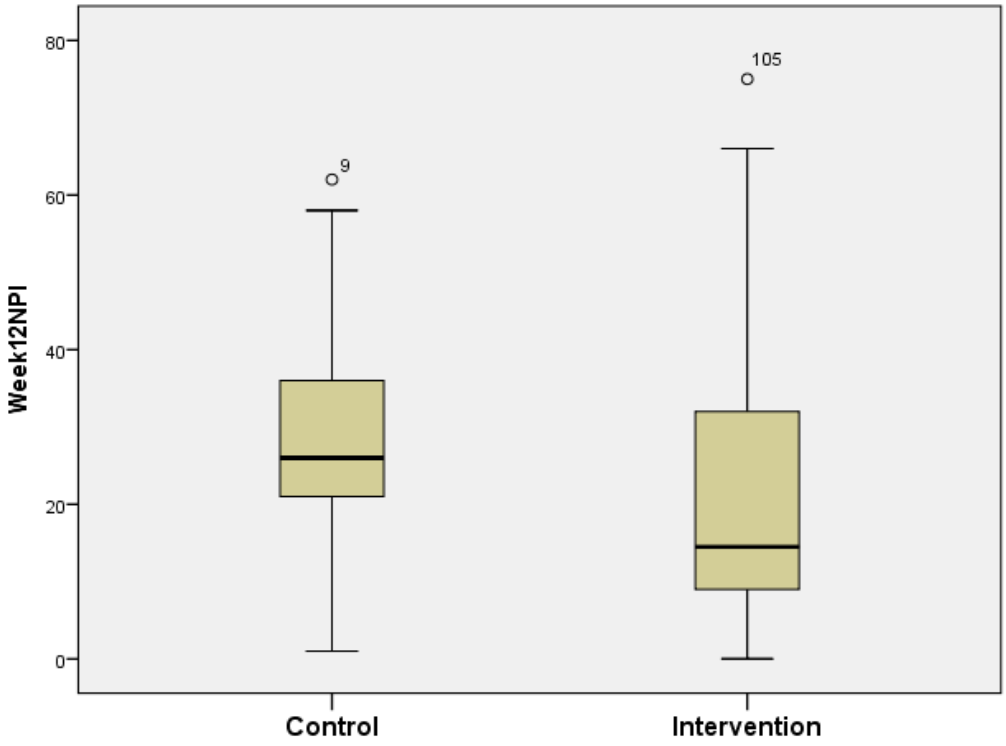


Figure 5.19 Boxplots of NPI scores (week 12) for participants that were walking compliant.

5.8.2 RPE Compliance and NPI – Intervention Group

RPE measurement was part of the intervention and consequently this data is not available for the control group. Between-groups comparisons regarding RPE compliance were therefore impossible.

The NPI score at endpoint was significantly higher for participants on the intervention arm that were RPE compliant compared to participants on the same arm but who did not comply with the RPE β=0.35, p=0.038, 95% CI [0.77, 25.8] (Figure 5.20 & Figure 5.21). This difference was not significant at baseline (β=0.2, p=0.23, 95% CI [-4.49, 18.4]) or at 6-week follow-up (β=0.25, p=0.14, 95% CI [-3.37, 23.6]).

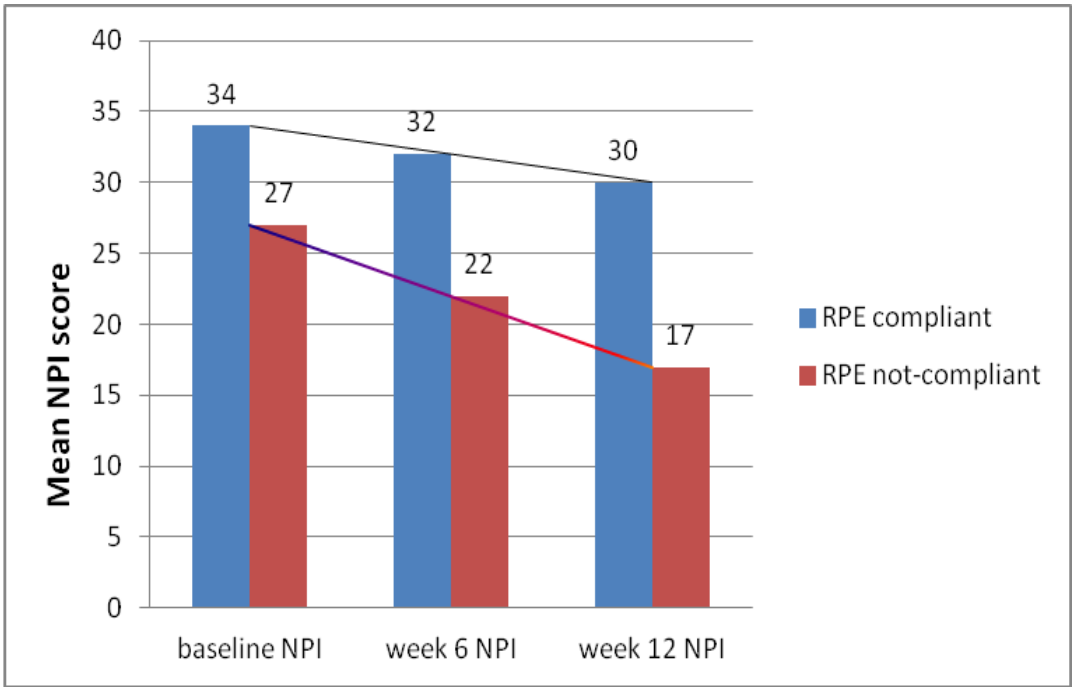


Figure 5.20 NPI mean scores for RPE-compliant and non-compliant participants (intervention arm only)

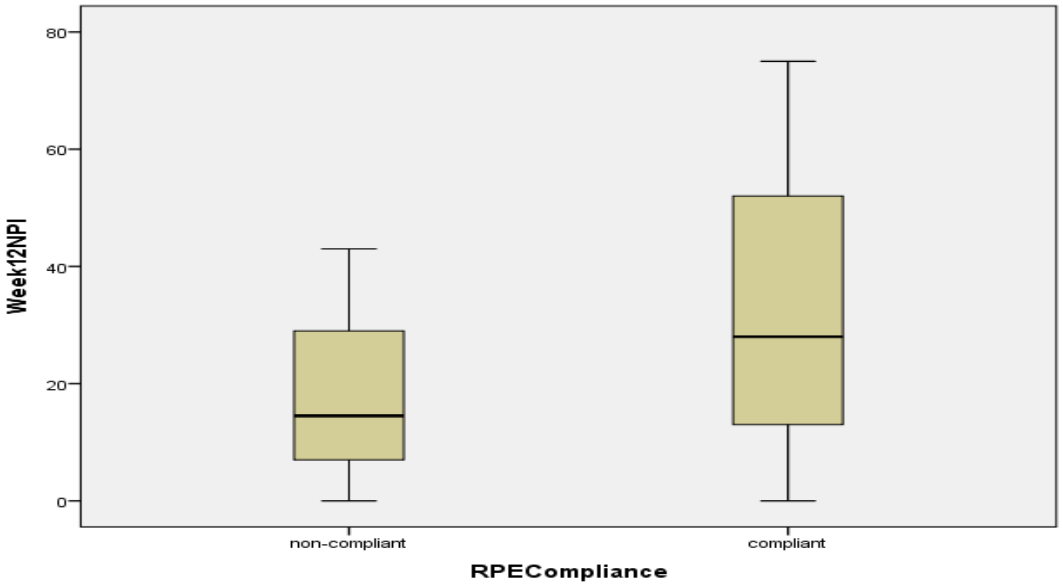


Figure 5.21 Boxplots of NPI scores (week 12) for participants that were RPE compliant and not-compliant (intervention arm only)

There was no statistically significant difference in the proportions of participants reaching a clinically significant reduction of three or more points in NPI score at week 12 compared to baseline, between the RPE-compliant and non-compliant participants OR=1.2 p=0.79, 95% CI [0.31, 4.59] (Figure 5.21).

5.8.3 Effect of compliance within the intervention group

There was no difference in NPI scores at week 12 for participants that were compliant overall and those that were not (β=0.128, p=0.181, 95% CI [-3.62, 18.99]) (Figure 5.22).

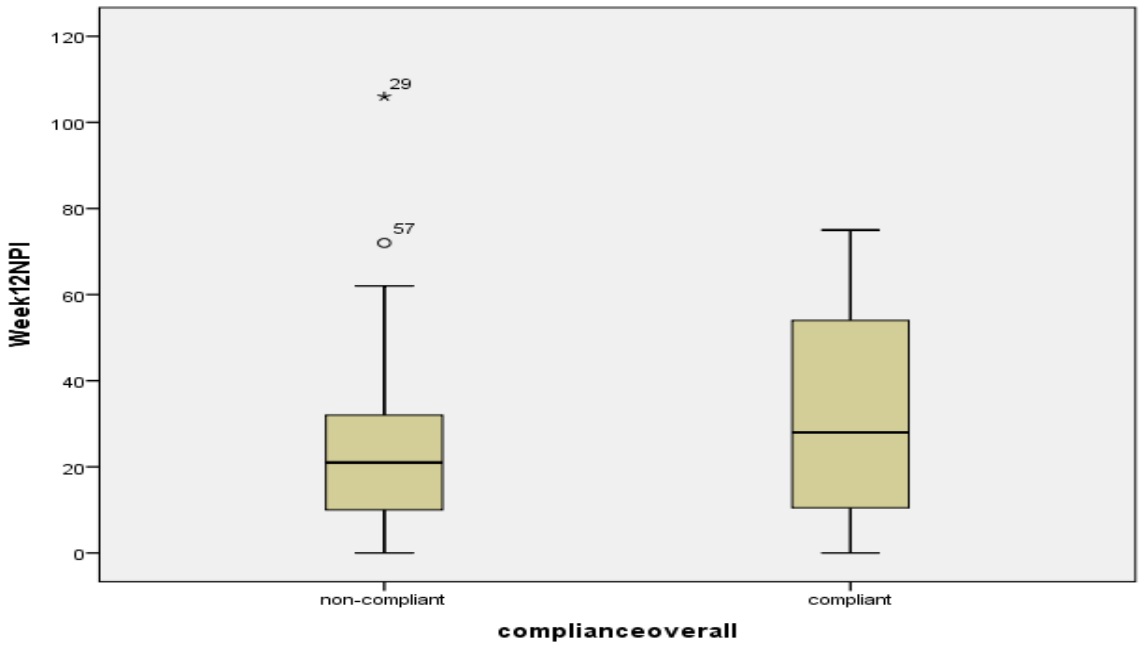


Figure 5.22 Boxplots of NPI scores (week 12) for participants that were compliant and not-compliant with the intervention (RPE + walks) (intervention arm only)
However, The NPI score at 6-weeks was significantly higher for participants on the intervention arm who were compliant compared to participants on the same arm who did not comply overall β=0.27, p=0.032, 95% CI [1.28, 26.88] (

Figure 5.23).

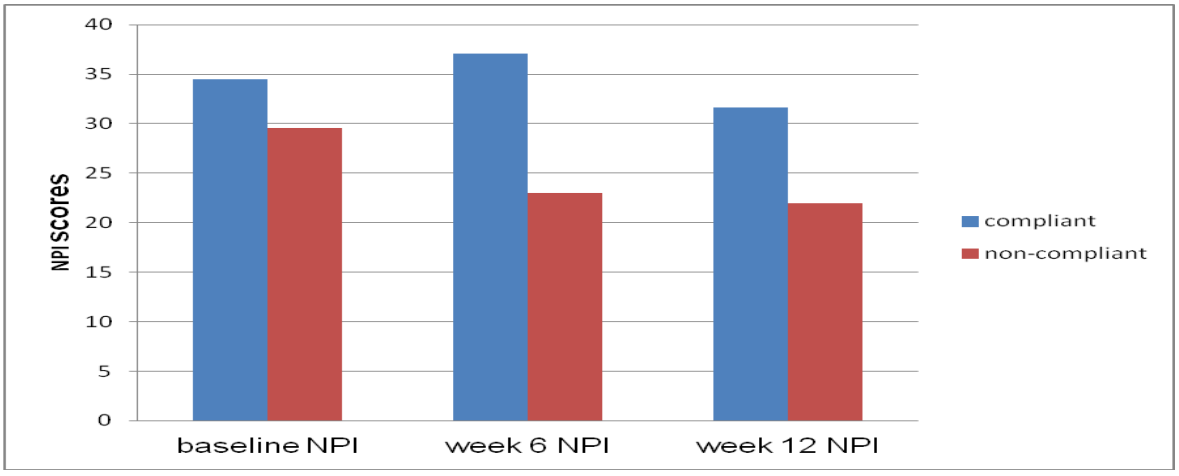


Figure 5.23 NPI mean scores for compliant and non-compliant intervention group participants (RPE + walks) (intervention arm only)

There was no statistically significant difference in the proportions of participants reaching a clinically significant reduction of three or more points in NPI score at

week 12 compared to baseline, between the intervention compliant and non-compliant participants OR=1.75 p=0.36, 95% CI [0.53, 5.83].

5.8.4 Blinding

Table 5.20 indicates de-blinding occasions for researchers that collected study data. Researcher 1 (the candidate) had face to face contact with participants and researcher 2 contacted participants on the phone. Face to face contact led to more de-blinding occurrences compared to telephone contact, and intervention arm participants were more prone to divulging such information compared to participants in the control arm of the trial.

Value of Kappa=1 indicates full agreement between scores. In our analysis Value of Kappa=1 means that the researcher is de-blinded on every occasion. The further the value from 1 the lower the level of de-blinding. The level of agreement is higher for the researcher who had face to face contact with participants than the researcher who contacted participants on the phone (week-6: K=0.46 Vs K=0.002 and week-12: K=0.69 Vs K=-0.25) [Table 5.20].

Table 5.20 De-blinding for researchers

	De- blinded			
	Control	**Intervention**	**Measure of agreement (Kappa)**	**P value**
Week 6 Researcher 1	5/57 (8.8%)	9/62 (14.5%)	0.46	0.03
Week 6 Researcher 2	0/54	6/60 (10%)	0.002	0.89
Week 12 Researcher 1	4/56 (7.8%)	10/57 (17.5%)	0.59	0.13
Week 12 Researcher 2	0/47	3/50 (16%)	-0.25	0.58

5.8.5 Adverse events

Two serious adverse events and six adverse events were reported during the study (Table 5.21). All events were followed up by the research team and were consequently classified as unrelated to the trial. Both serious adverse events were reported as deaths from natural causes and both participants were on the intervention arm.

The adverse events were all falls, which did not happen during trial activity and were not trial related. Overall, two adverse event happened to participants on the control arm of the trial and four to those on the intervention arm. Only one of the adverse events resulted in injury but not hospitalisation. The participant that was injured was in the control arm of the trial.

Table 5.21 Rates of adverse events

Type of adverse event		Control	Intervention	Total
Adverse Events	Falls without injury	4	1	5
	Falls with injury	0	1	1
Serious Adverse Events		0	2	2

5.8.6 Follow-up at week 26

No major changes were reported at 26-week follow up. Four individuals had moved from their family homes to care homes. Three of those individuals were in the control group and one in the intervention group (OR=0.38, p=0.42, CI [0.04, 3.85]).

Further three deaths were reported at week 26, two from the control group and one from the intervention group. This difference was not significant (OR=1.76, p=0.55, CI [0.28, 11.07])

No significant difference was reported in medication intake.

Walking adherence was difficult to directly assess because the candidate was blinded to arm allocation. Therefore, carers were asked if the person with dementia was walking more, less or the same compared to the beginning of the trial. Results are presented in Figure 5.24.

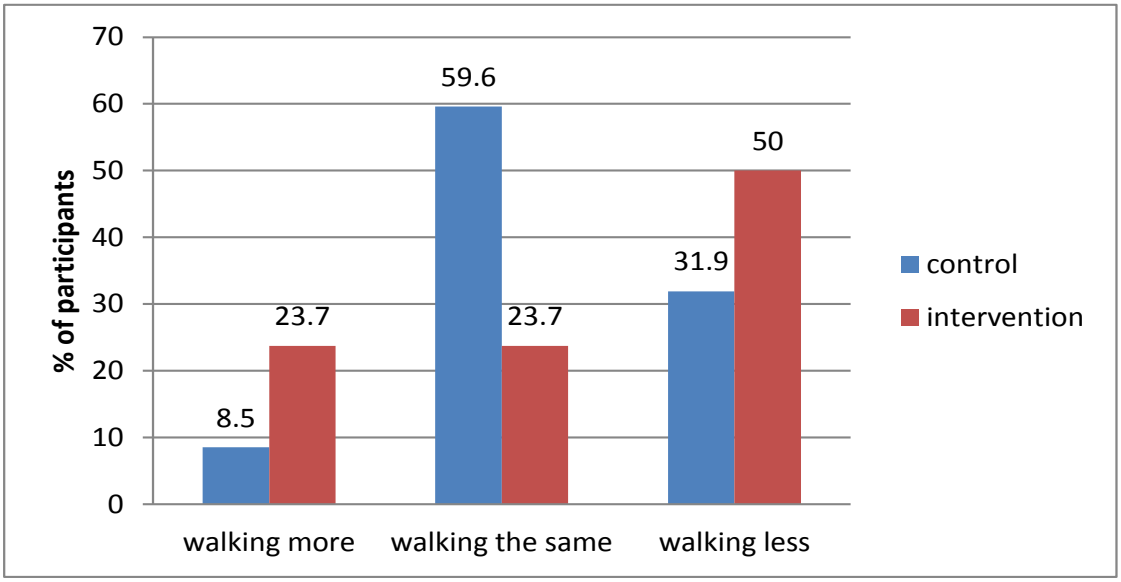


Figure 5.24 Self-reported walking activity at week 26

6 DISCUSSION

6.1 Overview of results

6.1.1 Primary Outcome

It has been reported that exercise can potentially improve a range of factors, which psychological theories of BPSD (Paragraph 1.3.3) consider critical for symptom development and maintenance, including:

- Physical health: through reduction of pain, improvement of constipation, enhancement of balance (Allan et al., 2009; Plooij et al., 2012).
- Mental health: improved depression and anxiety symptoms through possible increase of brain neurotransmitters; increased release of β-endorphins; reduction in muscular tension; by providing positive reinforcement and improving self-efficacy (Conn, 2010; Craft and Perna, 2004; Craft, 2005; Dunn, 2010; Gogulla et al., 2012).
- Cognitive decline: by improving brain neuroplasticity and cognitive networks (Ahlskog et al., 2011; Erickson et al., 2011).
- Sleep problems: through increased light exposure, suppression of melatonin secretion during the day, to help regulate circadian rhythms (Loprinzi and Cardinal, 2011; McCurry et al., 2005).
- Environmental factors: as a result of increased social interactions and sensory stimulation (Hersch and Falzgraf, 2007).

Based on the above (discussed in paragraph 1.4.2, pp 74), we hypothesized that an array of BPSD symptoms would improve as a consequence of these changes. Although the process of EVIDEM-E study design focused on intervention effectiveness rather than theoretical frameworks our hypothesis was underpinned by several theoretical models of BPSD such as:

- Kitwoods's Theory of Personhood: embraces a person-centred, non-pharmacological approach to individuals with dementia (Paragraph 1.1.2) (Kitwood, 1997). Our tailored, programme of walking took into account individual needs and skills, environmental factors, physical and mental health in line with this theory.
- The Environmental Vulnerability model: argues that considering the decreased level of competence of people with dementia their likelihood of being disturbed by the environment increases (Cohen-Mansfield, 2000). In accordance with this approach we tried to increase the level of competence of participants and lower environmental stressors by: conducting the intervention with individuals rather than groups; including carers who could provide unique support; involving an exercise therapist who devised individualised programmes; selecting walking as an activity that is easy to carry out and sustain.
- The Unmet Needs model: Figure 6.1 depicts the way the Unmet Needs model may apply to our exercise intervention for BPSD (Cohen-Mansfield, 2000) (Paragraph 1.3.3, pp 58).

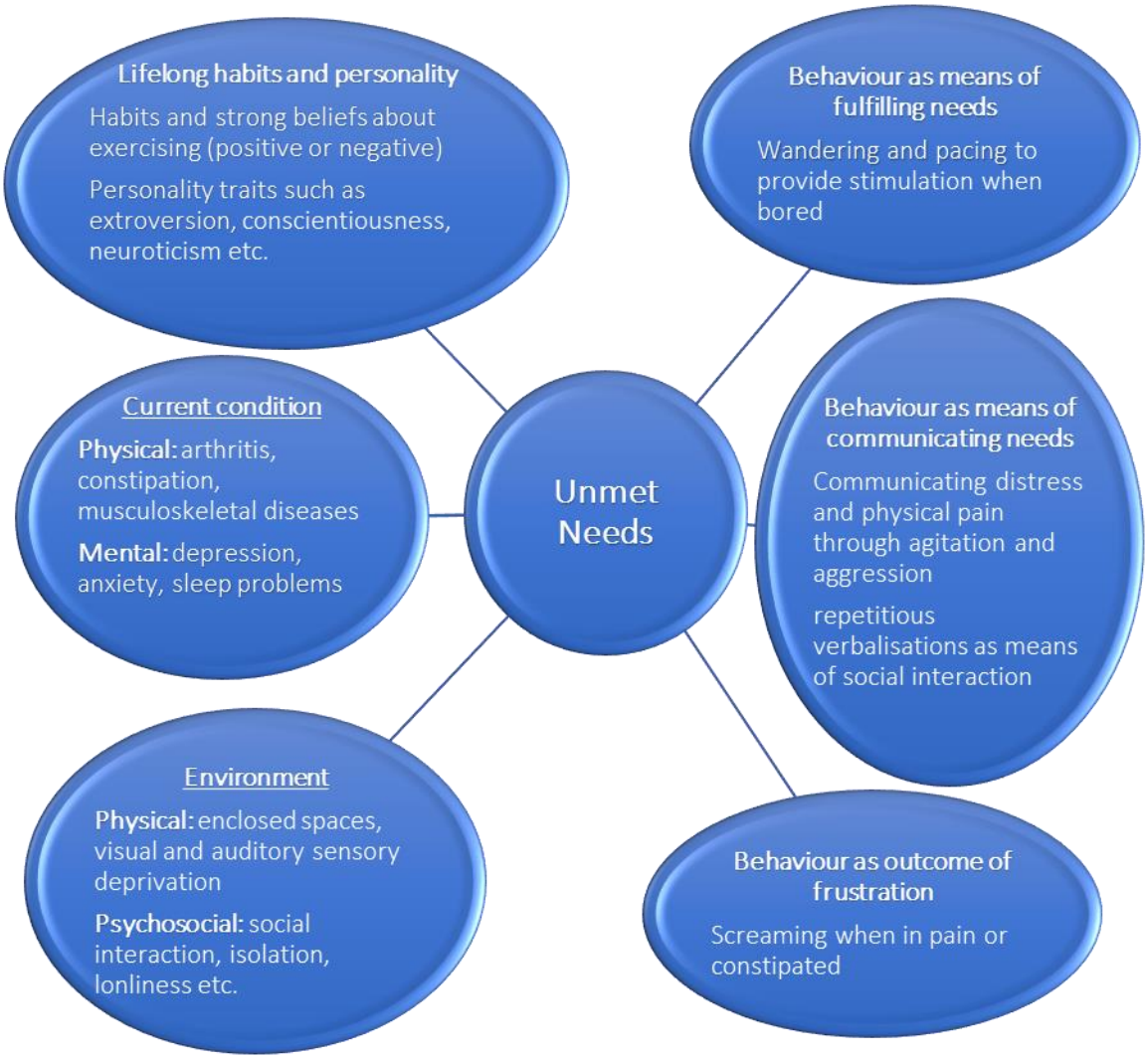


Figure 6.1 Unmet needs model and exercise (based upon Cohen-Mansfield, 2000)

This study shows that the intervention of walking, tailored to participant-carer dyads, designed to become progressively intensive and lasting between 20-30 minutes per day, 5 days a week, does not appear effective in treating behavioural and psychological symptoms of dementia as measured by NPI score after 12 weeks. The intervention group was 41% more likely than the treatment as usual group to experience a clinically important reduction of Neuropsychiatric Inventory score (3 points or more), but this was not a statistically significant difference.

All the aforementioned models of BPSD are very complex and include a range of factors that we could not control for such as: lifelong habits and personality; coping styles and help seeking attitude; quality of relationship with carer; socioeconomic factors. The inability to influence these components obviously limits the effect of what at first sight we considered to be a simple intervention of walking. Perhaps exercise alone is insufficient to have a significant effect on BPSD, in a population (both people with dementia and carers) where unmet needs are substantial (Carers UK, 2008; Lakey et al., 2012).

The possibility remains that the exercise regime we prescribed was not appropriate or of sufficient intensity or duration to impact upon BPSD. It would have been unethical for the therapist to have encouraged more intense exercise within this frail population who are prone to falls. Furthermore, prevailing NICE guidelines were taken into account in the study design, which recommend that older people should exercise 30 minutes a day on 5 or more days a week (NICE, 2008).

A large proportion of the treatment as usual group experienced an improvement in BPSD over the course of the study, which may be a Hawthorne effect (participants improving aspects of their behaviour in response to their awareness of being observed) attributable to the engagement of research staff with participants (McCarney et al., 2007), or a consequence of the natural fluctuation of BPSD (Devanand et al., 1997). An alternative explanation is that bias was introduced due to changes in exercise behaviour in the control group. Participants in the control group, who were expected to carry on with their normal level of physical activity, increased their walking. The main analysis compared the intervention and control

groups under the assumption that the only significant difference between them was the amount and intensity of physical activity, with the intervention group being more active than the control group.

According to the Health Belief Model (Strecher and Rosenstock, 1997) and the Theory of Planned Behaviour (Ajzen, 1991) (described in paragraph 1.3.3, pp58), participants in the control group who believed they could benefit from regular exercise might have increased their exercise during the study period, which in turn may have reduced any detectable effect due to the intervention. The Trans-theoretical model of change may suggest that participants who joined the trial, unlike those who refused participation, were at least at a preparatory (ready to exercise) stage (Prochaska and Velicer, 1997). Additionally, they were given detailed information about the study hypothesis and the rationale for the intervention design through patient and carer information sheets. Therefore, participants on both arms, at the beginning of the trial, may have had a degree of confidence that the walking intervention could be effective for BPSD, and considered it feasible to be carried out. Of course, this could have changed as the participants progressed into the trial, and some individuals probably regressed in regards to their stages of change. Also, time spent in exercise does not necessarily mean both groups exercised in the same way, but unfortunately we have no means of directly comparing the objective exercise intensity of each group. However, improving and sustaining exercise intensity is notoriously difficult; and those in the intervention group - with the support of a therapist - will have been better placed to achieve this.

On the other hand, our between group comparison could have also been affected by non-compliance in the intervention group. Just 19% of the intervention participants were compliant with the intervention. According to theories of behaviour change, intentions to engage in particular activities are determined by the person's attitude towards the behaviour including the perception of feasibility and benefits after pros and cons are weighed (Ajzen, 1991; Strecher and Rosenstock, 1997). Participants in EVIDEM-E were informed that this was a pragmatic trial and that there was no established evidence that dyadic walking could affect BPSD. Therefore, the benefits for complying with the intervention could have been perceived as not very high by some participants in the intervention arm. Moreover, the barriers of complying with the intervention for this particular population are numerous, such as poor physical health and being prone to falls; worsening of BPSD symptoms; and limited time availability for stressed and busy carers. Compared to health promotion interventions where benefits are established and participants can be influenced to change their behaviour through various strategies, clinical trials are clearly at a disadvantage. It would be considered unethical to unduly influence long term behaviour change in pragmatic clinical trials in case the intervention turns out to be non-beneficial or even unsafe for the participants.

According to the Theory of Planned Behaviour (paragraph 1.5) intentions are determined by the person's beliefs regarding important others' support of the behaviour and perceived self-efficacy (Ajzen, 1991). The fact that the exercise therapist withdrew their support mid-intervention (6 weeks into the trial) may have

been not just premature but also may have had a negative impact on the dyad's perception of self-efficacy and consequently their intervention compliance. The Environmental Vulnerability/Reduced Stress Threshold models (Cohen-Mansfield, 2000) would also suggest that the support from the exercise therapist would have increased the level of perceived self-competency and coping abilities of the person with dementia and their carer and thereby lowered their possibility of being distressed by the environment. Withdrawal of the therapist may have unbalanced the 'press-competence' stability established at the beginning of the trial and consequently may have contributed to the level of non-compliance. Withdrawal of support by the exercise therapist may have, therefore, contributed to a reduction of the effect of exercise on BPSD.

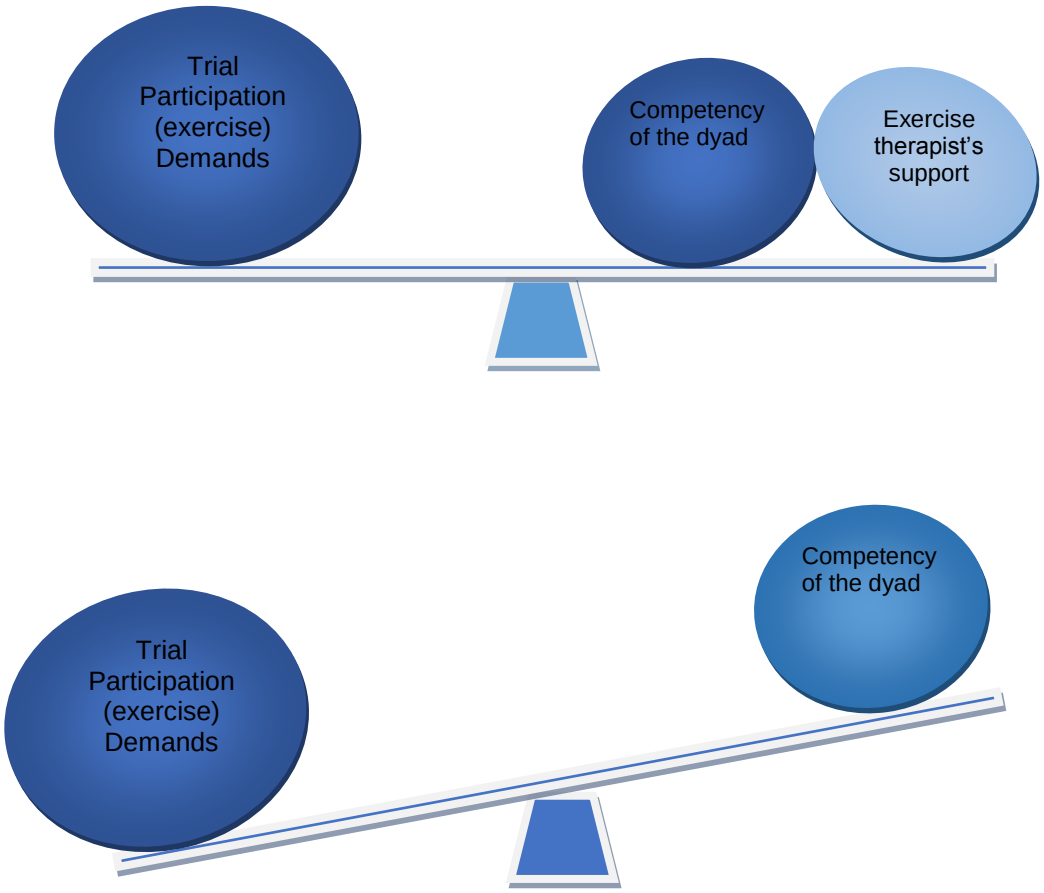


Figure 6.2 Press-competence balance during and after engagement of the exercise therapist

NPI categories were clustered into four groups: hyperactivity, affective, apathy and psychosis. Analysis of these clusters did not reveal any statistically significant differences between arms. This analysis was however carried out post-hoc and the study may have not been sufficiently powered to detect any significant differences for clustered syndromes. Each NPI category was also individually analysed but none of the individual between-group differences reached statistical significance.

6.1.2 Secondary Outcomes

6.1.2.1 Carer's burden

Caregiver's burden as measured by the Zarit Caregiver Burden Inventory decreased significantly in the intervention arm but increased in the control arm. Carers in the intervention group were 82% less likely to become significantly burdened at week 12. This finding might seem surprising considering that BPSD symptoms did not improve, however, subsequent studies have reported similar findings (Yu and Swartwood, 2012; Yu et al., 2013), indicating that there may not be a causal relationship between patients' BPSD symptoms and carers' burden. Yu et al. (2013) who evaluated the impact of aerobic exercise on Alzheimer's symptoms of a community based sample (n=26) reported that although NPI scores remained unchanged over a 6-month period the carers' distress decreased by 40%. However, these studies provided exercise interventions to patients with dementia only, offering 8-10 hours per week respite to carers during intervention periods. Thereby, carers' burden in these studies may have been reduced as a result of respite provisions (Conlin et al., 1992; Flint, 1995). Carers in the intervention arm of EVIDEM-E, did not experience respite. On the contrary their responsibilities towards the person with dementia increased with their engagement with the study, therefore, respite provision cannot explain our findings.

One of the drawbacks of single-blind, behavioural trials can be participants' pre-existing preferences about group allocation (McCambridge, Kypri, et al., 2014). According to theories of behaviour change it can be hypothesized that carers who

agreed to participate in the trial were more motivated and/or ready to exercise in order to improve the BPSD of the person they cared for, than carers who refused participation. Furthermore, they probably found our intervention attractive and feasible and agreed to make a significant commitment in time and energy. Therefore, being assigned to the control arm may have been disappointing for some carers (Skingley et al., 2014). In fact a few carers allocated to the control arm asked if they could withdraw and re-enter the trial, and be re-assigned to the intervention arm. We can hypothesize that carers' disappointment about being allocated in the control arm may have either affected (biased) their ZBI responses or actually caused an increase in carers burden. This, however, remains an hypothesis that can be explored on future research.

Improvement in carers' burden for participants in the intervention arm may have occurred as a consequence of the beneficial effects of exercise on the carer, rather than due to any change in the person with dementia (King et al., 2002; Orgeta and Miranda-Castillo, 2014). In fact, exercise interventions are reported to be quite effective in improving the quality of life for carers of people with dementia and in reducing their burden (Castro et al., 2002; Connell and Janevic, 2009; Hirano et al., 2011; King and Brassington, 1997). It has been reported that carers of people with dementia have less time and opportunities to engage in preventive health activities such as exercise (Pinquart and Sörensen, 2007). Carers in the intervention arm of EVIDEM-E were given the opportunity to engage in such activity and this can be considered as an intervention on its own. Caring for someone with dementia is considered a chronic stressor given that the length of caring may range between 8

to 10 years (Moore et al., 2001), and regular exercise has been associated with reduction of negative physiological reactions to chronic stress (Netz et al., 2005; Vitaliano et al., 2003). Engaging in exercise has also been reported to improve sleep (McCurry et al., 2007) and increase stamina (King and Brassington, 1997), which are essential factors that affect daily caregiving activities.

Increased social interaction among intervention arm participants with the exercise therapist may also be a factor that could have affected carer's burden differentially. However, carer's burden was very similar in both arms during the peak of social interaction (week 6) for the intervention arm, and significant changes were only reported at week 12 when this interaction was at its minimum. Possible latent effects of social interaction may also have played a role in the findings. However, no examples of latent effects could be found in the literature. In addition, this was a complex intervention in which the social contact between the person with dementia and their carer formed an important component. Dyadic walking may have intensified habitual support from the carer, and this may partly explain the changes we observed for caregiver burden.

The input from the exercise therapist consisted of support for the participant's goal-setting and training participants to self-monitor and become self-efficacious. These activities are behavioural strategies and though not the direct focus of our intervention could have had an impact on carers' burden.

The ZBI is a self-reported measure and consequently carries the risk of being affected by response bias. Considering participants were not blinded to the

intervention, a tendency amongst carers in the intervention arm of the trial to give socially desirable answers may have had an impact in our findings. However, if such tendency existed it would be expected to have been present in other self-reported measures such as NPI, DEMQOL, GHQ etc which did not appear affected.

6.1.2.2 Carers' mental health

Carers on the intervention arm had a 58% decrease in odds of suffering from mental health problems (measured with the GHQ) than their control counterparts. This difference was statistically significant at week 6 only. At week 12, although this difference was no longer significant, there was still a 41% reduction in odds of experiencing mental health problems for carers in the intervention arm compared to carers in the control group.

6.1.2.3 Quality of life for people with dementia

People with dementia in the intervention arm were reported to have slightly better quality of life than those in the control arm. The median DEMQOL-Proxy score for the intervention group at week 12 was 2.62 points higher than in the control group, but this difference did not reach statistical significance.

Although DEMQOL-Proxy is considered to be one of the best available proxy measures for people with mild to moderate dementia, this instrument's validity has been criticised for several reasons (Smith et al., 2005). Firstly, DEMQOL-Proxy is based on health-related quality of life only and it lacks reference to social

consequences, environment and unmet needs, which according to psychological theories of BPSD are essential factors of its development and maintenance (Bowling et al., 2015). Secondly, five out of 31 items are reversed in order to minimise response bias, however considering the length of the questionnaire this approach may not be very effective (van Sonderen et al., 2013). Thirdly, quality of life is a subjective concept and as such its' scoring is influenced by the informant's characteristics, personality and relationship with person with dementia (Bowling et al., 2015).

Quality of life assessment should be an ideal approach to explore if an intervention has made a meaningful difference to participant's life, which is characterised by various domains. DEMQOL-Proxy does not asses many of these domains, especially 'unmet needs'. Instruments that assess 'unmet needs' as well as all domains of quality of life would be useful in similar research in the future.

6.1.2.4 Compliance with the intervention and BPSD

Adherence to the intervention was assessed through diarised entries that were completed by carer participants (Appendix 1.11 & 1.12). Diaries were returned by 69% of participant dyads (Figure 5.17). The reported reasons for unreturned diaries were that they were lost by the participants or lost in the post. The main predictors for returning diaries were carers' younger age and patients' milder dementia symptoms (Table 5.16). Assessment of adherence with the intervention is therefore potentially biased as a result of missing information from more than a quarter of the sample. The intuitive deduction is that those who did not return the

diaries may not have exercised. If this deduction is taken one step further it might mean that those who tried to adhere to trial requirements were supported by younger carers and had milder cognitive symptoms compared with those who did not abide by trial requirements. This assumption is consistent with behaviour change theories and the Unmet Needs model, according to which carer's support and perceptions of self-efficacy are central to engaging in exercise. Younger carers are likely to have less physical health problems, a lower risk of falls and be more physically active than older carers (Schutzer and Graves, 2004). People with milder cognitive symptoms of dementia, on the other hand, are also probably younger than those with more severe dementia and consequently overall have better physical and mental health status (including BPSD symptoms). As a result, these specific dyads may feel more autonomous, self-efficient and supportive of each other, and consequently may perceive themselves as at a lower risk of pain or injury when engaging in regular exercise. However, this remains a hypothesis that may be explored in future studies.

Another challenge to achieving intervention compliance may have rested with the involvement of dyads (as opposed to individuals) which may have held conflicting views about exercising. Thus, even when one person was willing to exercise and believed that it would be advantageous, the other person perhaps did not (or was perceived as such).

Adherence consisted of two elements: frequency - walking at least 5 times a week for 20-25 minutes each time; and intensity - reaching an RPE of 12 or above. Only 19% of the intervention participants were fully compliant. Compliance was higher

for frequency (40% walking compliant) than intensity (28% RPE compliant). Significant non-adherence with intensity suggests that participants either found the exercise physically challenging to achieve or they did not fully comprehend how to accomplish it. Nevertheless, literature indicates that frequency of exercise interventions rather than intensity is most strongly associated with mental health benefits (King et al., 1993).

Interestingly, Figure 5.20 shows a significant increase of BPSD symptoms at week 12 for RPE compliant participants in the intervention arm compared to RPE non-compliant participants in the same arm. RPE compliance and BPSD symptoms at week 12 were positively correlated ($r=+0.35$, $p=0.03$), which means that as RPE compliance increased so did BPSD symptoms or vice-versa. However, this correlation was weak and the direction of the relationship could not be confirmed because correlation does not imply causation (Judea, 2009). When baseline BPSD scores were controlled for in the multivariate analysis this difference became insignificant ($r=+0.29$, $p=0.09$). It can be assumed that the association between RPE compliance and BPSD symptoms at 12 weeks was partially due to differences in BPSD symptoms at baseline. However, the sample analysed was very small, which increases the probability of Type II error (not determining an effect when one exists).

Thirty percent of participants in the control arm of the trial walked 5 times a week or more. Surprisingly, there were no significant differences in walking frequency between the intervention and control groups, which may indicate two possibilities: the control group independently increased their walking or the intervention group

was non-compliant. The data suggests both these explanations may apply (Figure 3.14). Although the control group did not receive the prescribed intervention they were introduced to information regarding possible benefits of walking through information sheets and were asked to record their daily activity in diaries. Diaries on their own right are considered as significant motivational factors in enhancement of exercise (Bravata et al., 2007; Kang et al., 2009) and could have consequently affected the walking behaviour of the control group.

Although control participants initially increased their walking, by week 12 their walking times decreased by almost 8 minutes. Intervention participants, on the other hand retained their increased walking times (by 8 minutes) throughout the course of the trial. This may reflect the input and support from the exercise therapist designed to maintain increased levels of physical activity.

Figure 5.23 depicts an interesting tendency: intervention participants who adhered to walking 5 times a week reported fewer BPSD symptoms (4.63 points lower) at week 12 than those within the same intervention arm who did not walk. This pattern was reversed for control participants (7.73 points higher). This may indicate that walking can have a beneficial effect on BPSD only if it is supported by a trained therapist. Another explanation may be that carers in the control arm who looked after people with more BPSD symptoms may have been more motivated to alleviate BPSD, and walked more than their counterparts within the same arm with less BPSD symptoms to manage. Another explanation, in accordance with The

Theory of Reasoned Action, may be that carers in the control arm who looked after people with more or more severe BPSD symptoms may have been more motivated to alleviate BPSD, and walked more than their counterparts within the same arm with less BPSD symptoms. Campbell et al. (2001) reported that compliance with exercise was higher when the condition was perceived as more severe. They also state that a precondition for continued compliance is the perception that the intervention is effective in improving unpleasant symptoms.

6.2 Internal and external study validity

Internal validity of a study refers to the extent to which its findings are a result of the intervention being tested. External validity, on the other hand, relates to the degree those findings can be extrapolated from the study sample to other populations of interest. RCTs, compared to other study designs, have good internal validity because confounders and bias are limited through specific trial design, conduct, analysis and interpretation. The external validity of RCTs, however, is criticised especially in explanatory trials (Fahey, 1998; Rothwell, 2005).

In EVIDEM-E we attempted to maximise the precision and validity of the findings, and establish a good balance between internal and external validity. Both strengths and limitations of the trial that impinge on its internal and external validity are discussed below.

6.2.1 Population/sample

One of the main strengths of this study in terms of internal validity was the relatively large sample and low attrition rates, which provide sufficient power to detect an effect of clinically significant magnitude. However, the power calculation assumed a higher level of fidelity to the intervention than was actually achieved. EVIDEM-E employed limited exclusion criteria, consequently increasing its external validity. The recruitment of a clinically relevant sample in terms of age, ethnicity, diagnosis, severity of disease and mobility (Paragraph 5.3, pp. 165-97) allows greater generalisability to people with dementia and BPSD in the UK. Both prevalent and incident cases were recruited to the trial. Participant identification was carried out from a widespread geographic area in secondary and tertiary care provisions and from DemReg (Paragraph 3.3.2, pp 122). Patients in primary care services were not approached as previous research indicated that a very small number of GP patients with dementia were not in contact with secondary care services (Iliffe et al., 2011). Non-inclusion of primary care services in participant identification could have led to a sampling bias. Patients with dementia seen in primary care may be different from those reviewed in secondary and tertiary care (Sackett et al., 1991), therefore our sample is not representative of primary care patients.

More than half of our study participants (52%) were recruited from DemReg, e registry for people with dementia and their carers who have expressed an interest to participate in research (Iliffe et al., 2011). According to Heiman (2002), research volunteers tend to have a higher social status and intelligence, exhibit an increased

need for approval, and have a tendency to be less authoritarian and conforming than others that do not volunteer. People who volunteer to participate in research may also have outcomes and exposures (e.g. healthier status) that differ from those of non-volunteers (Rosnow and Rosenthal, 1997). Volunteering bias is one of the limitations of EVIDEM-E in terms of its external validity, because of the high prevalence of volunteering by DemReg participants. We do not expect volunteering bias to have affected study's internal validity as randomisation should have balanced both study arms.

6.2.2 Measurement

EVIDEM-E used well validated and clinically relevant outcome measures (see paragraph 3.4.1). Most measures were collected blindly by the researchers involved in the trial, thereby minimising information bias in the trial and strengthening its internal validity. The primary outcome (NPI) was collected by the author at baseline and by a different blinded researcher at 6 and 12 weeks. Inter-rater reliability was maximised through continuous training between both researchers and the PI. Although, individual differences could have affected scoring this would have happened equally for both intervention arms. Therefore it is not considered as a threat to study's internal validity. The NPI is a self-reported measure and as such is prone to response bias. However, since no other outcomes indicated being influenced by social desirable responses or their opposite, we do not think it is likely that possible biases would affect the two randomly allocated groups differently.

The choice of measurement methods was a trade-off between the available resources and feasibility. One of the trial's design weaknesses was using self-report in measuring exercise. Assessing exercise with minimum intrusion to study participants is challenging and we relied on participants' self-reports through daily diaries. Self-report is prone to information bias, especially when participants are not blinded to their group allocation (Bauhoff, 2011). We gave considerable thought to the issue of measuring physical activity. It was decided not to use such objective measurement instruments to avoid excessive intrusion and facilitate recruitment. This approach was thought to prevent use of such instruments affecting exercise behaviour in their own right (see paragraph 6.2.3).

Self-reports of exercise are criticized for over-estimating actual activity levels (Dyrstad et al., 2014). However, self-reported measures seem to correctly predict both self-reported and measured functional ability 3-5 years later (Young et al., 1995) and mortality in middle aged men 21 year later (Eaton et al., 1995).

Another limitation of the study design is failing to assess individual levels of activity prior to entering the trial. We assumed that everyone started exercising (planned, structured, and repetitive action for the purpose of improving health) at baseline. However, some participants were already physically active even though conceivably their activities may have not been strictly 'planned, structured, or repetitive actions for the purpose of improving health', while many others led sedentary lives. Although, we do not think that individual differences would have affected study arms differentially, it would have been useful to know if participants

in each group increased, maintained or decreased their physical activity after they joined the trial.

6.2.3 Intervention

We attempted to develop an individually tailored, pragmatic exercise regimen which did not require intense specialist training or equipment and was home rather than gym based (Cress et al., 2004; King et al., 1998).

A walking regime was decided upon, as it seemed more likely to be acceptable, applicable to a wider population and sustainable by our target population (Piercy et al., 2008). Walking does not require specific use of equipment, can be done almost anywhere and at any time at no extra financial cost. All these factors are crucial according to the Reduced Stress Threshold model of BPSD (Cohen-Mansfield, 2000) as they lower the environmental demands people with dementia face. By applying an intervention that is feasible, acceptable, sustainable, enjoyable and low cost we strived to lower the burden of engaging in exercise which, according to theories of behaviour change and current knowledge, is the main barrier to exercising (Schutzer and Graves, 2004).

The intervention was designed to be delivered in individuals' homes in order to maximise safety and to ensure that individuals exercised within familiar and comfortable surroundings. The home environment can enhance adherence to exercise interventions as it also reduces the time and financial commitment that participants would incur were they required to travel to an exercise facility (Chao et al., 2000). Furthermore, the home environment was considered as advantageous

in regards to exercise sustainability after the withdrawal of support from the exercise therapist. This decision is supported by the Environmental Vulnerability model (Cohen-Mansfield, 2000), which asserts that increasing the level of competence of people with dementia reduces their likelihood of being disturbed by the environment.

We endeavoured to control for the impact of therapist contact. Phasing out the effect of psychosocial contact (from the exercise therapist) from the exercise intervention appeared to allow a relatively successful control for contact between participants and the exercise therapist. Results were consistent across both time periods. However, withdrawing the exercise therapist six weeks after the intervention started may have been premature and may have had a negative effect on participants' compliance with the intervention and/or the trial. All theories of behaviour change and psychological theories of BPSD emphasise the importance of support and perceptions of self-efficacy when engaging in new behaviours, such as exercise, which are particularly difficult to maintain without ongoing support and encouragement (van der Bij, 2002). Perhaps separating social support from exercising interventions is not prudent and by endeavouring to do so we affected compliance with the intervention. As a result, the statistical power to detect a true difference in BPSD scores may have been reduced.

6.2.4 Fidelity to the intervention

Tailoring the intervention to the individual(s) is vital to maximising compliance, however, measuring the fidelity of tailored interventions is a major challenge.

Fidelity means that the intervention is carried out as planned and delivered comparably to all study participants (Horner et al., 2006). However this process becomes very complex when the intervention is not standard but tailored to individuals or in our case, dyads. Although the facilitation of the intervention by a single exercise therapist increases internal validity the fact that the intervention itself was tailored to each participating dyad makes it difficult to compare between participants. The fidelity of the EVIDEM-E intervention was affected because interventions consisted of multiple sessions, were delivered to heterogeneous groups (Kerns and Prinz, 2002), and the location of the intervention delivery varied (Soldano and Markell, 1997). While the exercise therapist had guidance on the components that could be modified in tailoring and the extent of those modifications, guidelines on when and how to record such modifications was lacking. Standard operating procedures for intervention delivery would have helped to set controls and tolerance levels. They could also have aided monitoring and limitation of intervention variability (Horner et al., 2006).

6.2.5 Blinding

The single-blind design of EVIDEM-E had the inherent and unavoidable risk of affecting control participants exercise behaviour and self-reporting of all participants. Additionally, there was also a risk that participants would divulge information about the group allocation to the researcher. We attempted to reduce this risk through the inclusion of a second, independent, researcher who blindly collected primary outcome data (NPI) at 6 and 12 weeks.

6.2.6 Analysis

Analysis was carried out blindly strengthening the study's internal validity. An analysis plan was devised with the assistance of a statistician prior to the analysis to avoid biases and 'data phishing'. Intention to treat analysis provides unbiased comparisons among intervention groups and avoids the effects of non-random attrition.

6.3 Future directions of research

The Evidem-E trial found that our intervention of walking did not have an effect on BPSD symptoms. This contradicts the meta-analysis reported by Heyn et al. (2004). Our finding may be related to the poor adherence to the full exercise regimen, premature withdrawal of the exercise therapist and/or the duration of the programme. Heyn et al. (2004) reported that the mean duration of exercise interventions that reached a large effect size was 14.5 weeks and a medium effect size was 23.4 weeks. Longer follow up periods and methods for increasing adherence might result in a significant effect, and this warrants further investigation.

Given that less than half the intervention group achieved the prescribed exercise frequency and intensity targets, further studies attempting to increase uptake are warranted, as are longer studies to measure the effects of reduced carer burden.

It may seem counter-intuitive that declining carer burden was attenuated in the treatment group given the absence of effect for BPSD. However, considering that

carers co-participated in exercise activity, we may hypothesize that their burden was improved as a direct consequence of their engagement in exercise (Orgeta and Miranda-Castillo, 2014). Feelings of mastery (or lack of in the control group), because of an anticipated positive effect of the intervention is another possible explanation; this could have methodological implications for the design of future research and should be explored along with other potential mechanisms and long-term effects. This will also be important for optimising this intervention and the development of other interventions. This finding is potentially important because improved physical and emotional conditions of carers contribute to patients' wellbeing and quality of life (Neil and Bowie, 2008). Carer burden mediates decisions to relocate the person with dementia to a care home (Dunkin and Anderson-Hanley, 1998), and is associated with greater use of services (Miller et al., 2010); consequently, it may provide a useful proxy measure of both a longer-term outcome and future service use. Furthermore, carers' effective coping styles can increase survival for people with dementia (McClendon et al., 2004), whereas, carers' burden is reported to be an independent risk factor for carers' mortality (Schulz and Beach, 1999).

Participants' exercise behaviour was measured through feedback from self-reported diaries. It was not possible for the research team to control the quality and quantity of data entry. Future studies measuring exercise should, if feasible, employ objective measurement(s) of participants' exercise behaviour such as pedometers, GPS watches, accelerometers, calorimetry.

In conclusion if I were to carry out the same study again I would consider the following:

- Conduct a larger, multicentre trial to increase the study power and its generalizability.
- Apply longer intervention and follow up periods (12-24 months).
- Consider employing narrower inclusion/exclusion criteria by excluding participants who are not likely to comply (e.g. participants with severe dementia and older carers), to minimise attrition and maximise compliance.
- Assess the stage of behaviour change for all participants in accordance with the trans-theoretical model using validated measures e.g. 'Exercise: Stages of Change' (Marcus et al., 1992).
- Record pre-trial activity level and lifelong activity habits (CHAMPS Physical Activity Questionnaire for Older Adults may be an option).
- Assess participants' preferences about arm allocation, which may potentially bias the findings (McCambridge, Sorhaindo, et al., 2014).
- Use objective measures of physical activity such as pedometers, actigraphs etc., as well as standardised questionnaires such as CHAMPS Physical Activity Questionnaire for Older Adults (Stewart et al., 2001), which is a widely used reliable and validated measure for older adults and is grounded on social cognitive theories, principles of self-efficacy and readiness to change, as well as motivational techniques (Harada et al., 2001).
- Include several exercise therapists to the trial to increase external validity.

- Withdraw the exercise therapist at a later period, after dyads had become confident enough to sustain intervention independently (as measured by specific outcomes).
- Establish fidelity monitoring for the exercise therapists. Train therapists in treatment delivery and also in the process of tailoring the intervention. Design clear Standard Operating Procedures identifying the extent to which modifications can be made and when and how to record such modifications.
- Tailoring should take into account the particular stage of behaviour change (readiness to change) of each dyad (Treasure, 2004).
- Exercise therapists to carry out the exercise programme alongside the dyad to increase compliance and to improve reliability in physical activity reporting.
- Measure the level of unmet needs through reliable and validated questionnaires such as Camberwell Assessment of Need for the Elderly (CANE) (Reynolds, 2000).
- Carry out qualitative interviews with participants and exercise therapists to explore feasibility, benefits, disadvantages, barriers and compliance issues.
- Consider offering the intervention to control arm participants at the end of the trial to improve recruitment rate, increase compliance and minimise response bias that may arise as consequence of being allocated into the control arm (Skingley et al., 2014). This approach would however bring about added costs and resources considering the extended engagement of the exercise therapists.

7 CONCLUSIONS

Previous studies have reported that exercise is beneficial in reducing some behavioural and psychological symptoms of dementia (BPSD), especially depressed mood and agitation and may also improve sleep and reduce 'wandering'. However, research evaluating the efficacy of exercise as a therapeutic tool for other important symptoms such as anxiety, apathy and repetitive behaviours is limited (Thuné-Boyle et al., 2012).

The EVIDEM-E trial evaluated the effectiveness of a walking intervention as treatment for BPSD. Although overall BPSD were lower at week 12 in the group that received the exercise in comparison to the TAU group, this difference was not statistically significant. There are several possible explanations for this: first, our exercise intervention is not a clinically effective therapeutic intervention for BPSD; second, the intervention has not had sufficient intensity and/or duration to have an impact on BPSD symptoms; third, the findings were biased by non-compliance in the intervention group and increased physical activity in the control group; fourth, the effect size was smaller than anticipated.

Our seemingly simple intervention of dyadic walking involves complex mechanisms and intricate consequences, which seem to support the main multifaceted psychological theories of BPSD such as The Environmental Vulnerability model and the Unmet Needs model.

Regular simple dyadic walking does not appear to be effective for reducing behavioural and psychological symptoms of dementia, although, it does appear to

help reduce carer burden. Given the absence of impact on behavioural and psychological symptoms, it is unclear why carers from the control group reported having a significant worsening of burden in comparison to those in receipt of the intervention. The increase may have been due to worsening burden because of BPSD, differential physical burden between the two groups (there was a slightly higher, statistically not significant, number of physical conditions in the control group at baseline) or unhappiness amongst carers about not being randomised to the intervention. Conversely participation in exercise in the intervention group may have attenuated the perception of burden directly or by enhancing carers' physical health or self-efficacy.

This study has shown that an acceptable exercise intervention for people with dementia can be developed and tested. However, future interventions need to make sure the intervention(s) can be sustainable and objectively measured.

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9 APPENDICES

Appendices Contents

1Study Design and Ethics

1.1 Participant and Carer Information

Re. 'EVIDEM-E: A randomised controlled evaluation of exercise therapy and its impact on behaviour, sleep and quality of life'

Dear Sir/Madam

Please take time to read the following information carefully.

What is the purpose of the study?

Dementia can cause many problems including difficulties with memory and thinking, and more commonly occurs in older people. Dementia can also cause changes in personality, mood and behavior and these are called ***Behavioural and Psychological Symptoms of Dementia (BPSD).*** This last group of symptoms can be very distressing for those who experience them as well as their families and carers. We recognize that managing these symptoms can have a very important role to play in everyday life.

Behavioural and Psychological Symptoms of Dementia can be treated with drugs in the short term, but in the longer term it is important to make use of other treatment and management strategies. One possible way, might be regular exercise and some previous research has shown that this might be a useful way of treating BPSD. In particular, exercise has been shown to help reduce symptoms of depression and aggression. These studies have often involved complicated exercise routines and have not looked at the impact on some important aspects of everyday life. Therefore, we have proposed a study that will test whether **going for regular walks** can improve sleep, behaviour and your life in general. We will also be looking at the impact on medication use and quality of life for both the individuals with dementia and their carers.

Why have I been chosen?

You have been identified as a person with dementia or a carer of someone with dementia, who might like to take part in the study. We hope to speak to about 146 people in a similar situation to you.

Do I have to take part?

No, it is entirely up to you whether you decide to take part or not. If you do decide to take part you will be given this information sheet to keep. If you would prefer not to take part, the way you access services will not be affected in any way. Once you have agreed to participate, you will still be able to withdraw at any time you like and you do not have to give a reason. If you decide to withdraw we will not gather any more information from you, **but** will make use of the confidential information you have given us up to the time of your withdrawal.

What will happen to me if I take part?

If you agree, we would put you into one of two groups. You would have an equal chance of being in either group and the research team can ***not*** choose who will be put into which group. One group will carry on as normal with no change of treatment. The second group will get tailored exercise therapy which will involve an exercise therapist visiting you at home.

If you are selected for visits by the exercise therapist, they will help you establish a programme of **walking outside** for you and your carer. This will be at a pace and distance to suit both of you. The exercise therapist will visit you on five occasions:

- three times during the first week;
- once, six weeks into the study;
- One final visit, 12 weeks into the study.

For this therapy to work, we believe that you will need to go out for a walk at least 5 times per week. Therefore, other than the five occasions that the exercise therapist

visits, you will need to go out for walks as a pair. During this time, you and your carer will be provided with a diary to record your exercise activities.

In order to find out if the exercise therapy has made any difference; a member of our team will need to take you through a series of questions designed to be used in studies like this. We will do this in person at your home, at a time convenient to you, no more than four times over one year from the start of the study; and by telephone no more than 3 times over one year from the start of the study. Each visit should last no more than two hours and each call no longer than twenty minutes. **It is important that we ask you these questions whether the exercise therapist visits you or not.** Also, your participation on the trial is expected to last for 12-18 weeks.

A few participants and their carers will be allocated to one further follow-up, where they will be asked questions about their experiences of the trial. This interview will be audio-recorded. If you agree to participate in this you will be given a separate information sheet and asked to sign a new consent form.

If at any time during the study you cannot continue with the exercise or the interviews, we can agree what will be best for you at that time. This could include taking a break, returning to the interview at a later date or withdrawing from the study.

What are the possible disadvantages and risks of taking part?

We are aware that some people might be at risk of falling and/or have other physical health problems. Therefore, a research worker will meet with you and your carer to assess possible risks before including you in the study. If we or your GP believe that you might be at risk of falling, you will not be able to be involved in the study.

The exercise therapist will assess your road sense and undertake location risk assessment (e.g. traffic density, kerb height, excessive noise), as well as the ability of your carer to support you.

What are the possible benefits of taking part?

Your participation in this study will help furthering our understanding of non-medical treatments for behavioral and psychological symptoms of dementia. Your support will help us improve the care people with dementia receive. You and you carer may benefit from walking exercises if drawn in the intervention group of this trial. Your help will be appreciated.

Will what I say in this study be kept confidential?

All information collected about you and your carer will be kept strictly confidential. Any information about our visits and your answers will be anonymous and a code will be used rather than your name. This information will be stored securely on a computer at Central and North West London NHS Foundation Trust and only members of the EVIDEM-E research team will have access to this. However, if we feel your health may be in danger, we may have to report your results to your GP.

What will happen to the results of the research study?

The trial will be published in a peer-reviewed medical journal. Abstracts will be submitted to relevant conferences to inform other researchers of the work. We'd be happy to provide you with a copy of the published research, should you wish to have one.

Who is organising and funding the research?

EVIDEM-E is part of a broader programme of research called 'Evidenced Based Interventions for Dementia' which is funded by The National Institute for Health Research's Programme: grant for applied research scheme. The grant code is RP-PG-0606-1005.

Contact for Further Information

If you would like further information, please do not hesitate to contact:

Arlinda Cerga-Pashoja
Research Worker
Tel: 020 3214 5886
acerga-pashoja@nhs.net

Dr David Lowery
Project Manager
Tel: 020 3214 5889
d.lowery@ucl.ac.uk

Address: CNWL NHS Foundation Trust, Greater London House, Hampstead Rd, London, NW1 7QY.

You can also visit our website: www.evidem.org.uk

Thank you for taking time to read this information sheet!

Yours sincerely

Dr James Warner
Consultant Old Age Psychiatrist

Evidem-E Study Team
Central and North West London NHS Foundation Trust
Stephenson House, 75 Hampstead Road, London NW1 2PL
Tel: +44 (020) 3214 5886 email: acerga-pashoja@nhs.net

EVIDEM-E

[Date]

Dear Dr **[name]**

Re: ***[Patient Name Surname]***

Following our letter dated **[date]**, regarding your patient's possible involvement in our study, we are writing to confirm that **[patient's name]** is eligible to participate in the study and has consented to become involved. We are forwarding you a copy of the signed consent sheet for your record.

As we have previously informed you, your patient will be involved in the study for a maximum of 26 weeks. He/she will be allocated into one of two groups: treatment as usual or exercise therapy. If **[patient's name]** is allocated into the intervention group he/she and his/her carer (he/she and the person he/she cares for) will meet with an exercise therapist on five occasions and go out on planned daily walks for 12 weeks.

- **We'd appreciate it if you could inform us of any changes in [patient's name]'s health, medication or treatment that may affect his/her participation in the study.**
- **We'd also kindly ask you to inform us of any Adverse Events (AE) or Serious Adverse Events (SAE) that may happen to [patient's name] that we might not be aware of.**

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the trial.

➢ *An AE does include a / an:*

✓ Exacerbation of a pre-existing illness.

✓ Increase in frequency or intensity of a pre-existing episodic event or condition.

- ✓ Condition detected or diagnosed after intervention even though it may have been present prior to the start of the trial.
- ✓ Continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

➢ *An AE does not include a / an:*

- ✓ Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.
- ✓ Pre-existing disease or conditions present or detected at the start of the trial that did not worsen.
- ✓ Situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received exercise intervention or usual treatment that results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation for non elective procedures
4. Sudden or rapidly progressive major disablement
5. An event that caused the participant to seek non-routine medical treatment.

I am attaching an Incident Reporting Form to report any AEs and a Serious Adverse Event Reporting Form to report any SAEs. **Should an AE or SAE occur, could you please return the corresponding form in an envelope marked AE or SAE to:**

Dr David Lowery

Project Manager

Tel: 020 3214 5889

d.lowery@ucl.ac.uk

Address: Medical Directorate, CNWL NHS Foundation Trust, Greater London House, Hampstead Rd, London, NW1 7QY.

Yours sincerely

Dr James Warner

Consultant Old Age Psychiatrist

1.3 Participant Consent Form

Participant Identification Number: ☐

Version: 1.1 April 2009

Title of Project: Randomized control evaluation of exercise on individuals with dementia and their carers

Principal Investigator: Dr James Warner, CNWL NHS Foundation Trust

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Please initial box to indicate agreement

1. I confirm that I have read and understand the information sheet dated March 2009 for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that my participation in the above study will not affect the standard of care I receive. ☐

4. I agree to my GP being informed of my participation in the above study. ☐

5. I agree to take part in the above study. ☐

6. I agree to be approached at a later date to take part in a tape-recorded interview about participation in this trial. ☐

Name of Participant	Date	Signature
Researcher	Date	Signature

☐ Participants' Copy

☐ Researchers' Copy

☐ GP's Copy

1.4 Participant-Carer Consent Form

Participant Identification Number: ☐

Version:1.1 April 2009

Title of Project: Randomized control evaluation of exercise on individuals with dementia and their carers.

Principal Investigator: Dr James Warner, CNWL NHS Foundation Trust

---

Please initial box to indicate agreement

1. I confirm that I have read and understand the information sheet dated March 2009 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that my participation in the above study will not affect the standard of care I receive. ☐
4. I agree to my GP being informed of my participation in the above study. ☐
5. I agree to take part in the above study. ☐
6. I agree to be approached at a later date to take part in a tape-recorded interview about participation in this trial. ☐

Name of participant	Date	Signature
Researcher	Date	Signature

☐ Participant's Copy ☐ Researcher's Copy

1.5 Assent Form

Participant Identification Number: ☐

Version: 1.1 April 2009

Title of Project: Randomized control evaluation of exercise on individuals with dementia and their carers

Principal Investigator: Dr James Warner, CNWL NHS Foundation Trust

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My carer knows about EVIDEM-E study and wants me to be in the study if I want to. I do want to be in the study, but I know that I can stop being in the study any time I want to. I know that the research worker can talk about the study with my carer, but will not talk about it with anyone else who is not working on the study unless I and my carer say it is OK. I can call the research worker any time I have any questions.

I was present when _____ read this form and gave his/her verbal assent.

Please initial box to indicate agreement

☐ I have solicited the assent of the participant.

_____ _____ _____

Name of Researcher Date Signature

Consent of Carer:

Please initial box to indicate agreement

☐ I agree with the manner in which assent was solicited and given by the participant.

☐ Although the participant could not give his/her consent, I agree to have him/her participate in the study.

☐ I will be given a signed copy of this Assent Form.

_____ _____ _____

Name of Consultee Date Signature

Relationship to Participant _____

☐ **Participant's Copy** ☐ **Researcher's Copy** ☐ **GP's Copy**

1.6 Consenting Protocol-Standard Operating Procedures

It is important to establish whether the potential participant and their carer have the capacity to provide informed consent at each interview. It is vital that the carer can provide informed consent. If the potential participant does not have the capacity to provide informed consent, they must still provide their assent (agree to participate) alongside the informed consent of their carer.

Assessment of capacity is based on Current case law applicable in England. To determine whether the individual is capable of providing informed consent, it is important to test whether pertinent information about the trial and the alternative (i.e. no trial) can be **understood**; if it can be **retained** for a sufficient amount of time to **weigh in the balance** and reach a decision about participation; and that the person can **communicate their decision** to participate free from coercion. The process for doing this is as follows:

1. **Understanding** the trial. As well as providing written information sheets, the main points of the trial and the alternative (i.e. no trial) should be provided (and discussed) verbally *in a way the potential participant can understand*. These points are:

a. Dementia causes problems with memory and thinking as well as changes in mood and behaviour.

b. Problems with mood and behaviour are usually treated with drugs, which can sometimes have a negative impact on the person taking them.

c. There is some evidence that exercising may be a safe, alternative treatment to behavioural and psychological symptoms of dementia.

d. Walking is a safe way of exercising.

e. Participants will be randomly allocated into two groups: to receive either Exercise Therapy or care as usual for 12 weeks. There is an equal chance (50:50) of receiving either of these

two allocations. This is because we do not know for sure whether Exercise works.

f. A few participants and their carers will be allocated to one further follow-up, where they will be asked questions about their experiences of the trial. This interview will be audio-recorded.
g. A final telephone contact will occur at week 26, where all participants from the Exercise-Therapy group will be asked a few questions about their current activity levels.
h. Participation is for 12-26 weeks but participants can withdraw at any time without having to give a reason.
i. Participants at risk of falling or who have other physical health problems that may unable them to carry out a walking programme will not be included in the study.
j. An exercise therapist will visit participants at home and establish a programme of walking outside for the participant-carer dyad.
k. The walking programme will be at a pace and distance to suit both the participant and his/her carer.
l. The exercise therapist will visit participants on five occasions. Each visit will last approximately 1-2 hours and will take place in the home of either the participant or their carer.
m. A research worker will visit participants on three or four occasions. At each visit, we will complete various questionnaires.
n. All information held about them will be strictly confidential and it will not be possible to identify them from published project data.
o. They do not have to take part and if they don't, the medical care they receive will in no way be altered. They can withdraw at any time.

2. **Retain and weigh in the balance of** the information. The length of time they need to retain this information for depends on the individual. If they are happy to give a decision immediately, then they only need to retain the information for that amount of time. Similarly if they ask to think about it and say that they will decide the next day, then they need to retain the information until the next day. The best way to test belief and retention of information is to ask the participant to repeat back the relevant information.

3. **Communicate a decision** free from coercion. The individual needs to communicate their decision on participation without any pressure from the carer (if applicable) or the researcher attempting to obtain informed consent.

Once this procedure is followed, the researcher can then assess whether they feel that the individual has the capacity to give informed consent. If it is decided that they are not so capable, then the potential participant may be able to participate but still needs to give their assent to the study (confirmation that they are happy to participate in the absence of full capacity). Therefore, an Assent Form will be completed. Three copies of the assent form are then made: one to go to the participant's GP; one to go to the carer; one to be kept at the study centre.

Participants with established capacity to consent will complete Participant's Consent Form. One copy of the form will go to the participant's GP; one to the participant and one to be kept at the study centre.

The carer will complete a Participant-Carer Consent Form, at all occasions. One copy will be kept by the carer and one will be kept at the study centre.

Classification of event

All adverse events will be classified by the Principal Investigator as either:

- Adverse Event (AE): any unfavourable and unintended sign, symptom or disease temporarily associated with the use of an investigational product, whether or not considered related to the investigational product.
- Serious Adverse Event (SAE): an AE that results in death; or is life threatening; or required in-participant hospitalisation; or results in persistent or significant disability or incapacity;

Classification of intensity

Regardless of the classification of adverse events as serious/non-serious, the *maximal intensity* of the event is to be evaluated by the responsible clinician, after consultation with the participant, carer and participant's GP:

mild: no impairment of normal daily activities;

moderate: impairment of normal daily activities;

severe: unable to perform normal daily activities.

Classification of causal relationship

Each adverse event (AE) must be classified on the basis of the available data with regard to the presumed *causal relationship* to one of the following categories:

1 = probable

Rational relationship to the time of intake of the investigational medication

AE is already known to be a side effect of the investigational medication or may be expected

Regression or disappearance of the AE after discontinuation of investigational medication or dose reduction

Reappearance of the AE after repeated exposure

AE cannot be explained in a reasonable manner by the clinical state of the participant

2 = possible

Rational relationship to the time of intake of the investigational medication

AE is already known as a side effect of the investigational medication or may be expected

AE could be explained by numerous other factors

3 = improbable

Rational relationship to the time of intake of the investigational medication

AE has not been reported so far as a side effect of the investigational medication or cannot be expected

AE persists after discontinuation of the investigational medication or dose reduction

Repeated exposure does not lead to reappearance of the AE

AE could be explained by numerous other factors.

4 = no relationship

No rational relationship to the time of intake of the investigational medication

AE is evidently caused by other factors, e.g. symptom of a concomitant disease.

5 = unable to evaluate

Amount and content of data do not permit a judgement of the relationship to the investigational medication.

1.8 Adverse Event Reporting Form

<table>
<tr><td colspan="2">Name :</td></tr>
<tr><td>Date of Incident :</td><td>Member of Staff Incident reported to :</td></tr>
<tr><td colspan="2">Details of the Incident

Action Taken

<u>Witness Name and Role in Trial</u></td></tr>
<tr><td colspan="2"><u>Outcome</u></td></tr>
<tr><td>Name of Member of Staff
…….</td><td>Witness Signature
……..</td></tr>
<tr><td>Signed
……...</td><td>Dated
……
……</td></tr>
</table>

1.9 Serious Adverse Event Reporting Form

Patient ID: _ _ _ **Patient Initials:** _ _ _

Patient Date of Birth: _ _/_ _/_ _ **Allocation** **Group:**

Intervention/Control

Date form completed: _ _/_ _/_ _

Death (any cause): Yes ☐ No ☐

Description: _____

Date of occurrence _ _/_ _/_ _

Hospital Admission: Yes ☐ No ☐

Description: _____

_____

Was the admission as a result of a fall? Yes ☐ No ☐

Injurious fall without Admission: Yes ☐ No ☐

Description: _____

Fall During the exercise sessions:

Did a fall or medical event occur during an actual exercise session, requiring medical attention? Yes ☐ No ☐

Form completed by:

_____ (Print name) Date_ _/_ _/_ _____ (Signature)

Form reviewed by

_____ (Print name) Date_ _/_ _/_ _ _____ (Signature)

For Principal Investigator

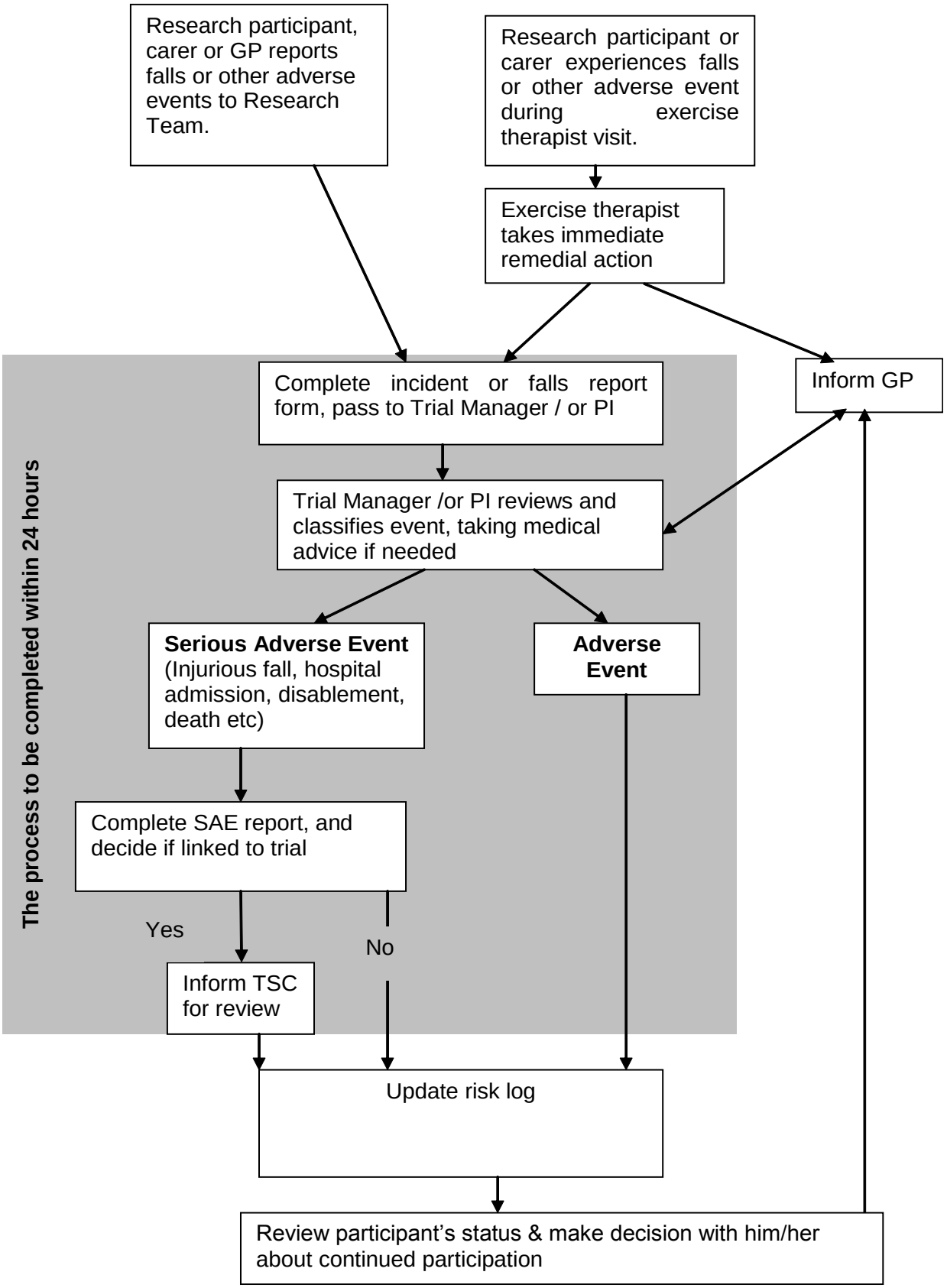
Is this event an SAE relating to patient safety in the trial?

☐ Yes – inform TSC, convene meeting to discuss trial safety

☐ No – no further action required

Signed by Chair of TSC **Date**

1.10 Risk Management Pathway



9.1 1.11 Intervention Diary

Monday **Date**	Did you go out for a walk today? **Yes/No**	How many times?	How long was each of your walks? (in minutes) **[e.g. walk1=10mins; walk2=20mins, etc]**
What RPE did you achieve? **Rating of Perceived Exertion** (Please circle below) ___**6**___7___8___**9**___10___**11**___12___**13**___14___**15**___16___**17**___18___**19**_____**20**___ **no exertion** **very light** **light** **somewhat hard** **hard** **very hard** **extremely hard** **maximal exertion**			
What did you enjoy about your walk/s?	What did you NOT enjoy about walk/s?	Did you complete the course set by the exercise therapist? **Yes/No**	
If you did NOT go out, why not? Please circle below **Didn't feel like it / Something stopped me (i.e. pain, agitation, weather conditions)/ Carer unavailable/ Other** (please describe below)			
Tuesday **Date**	Did you go out for a walk today? **Yes/No**	How many times?	How long was each of your walks? (in minutes) **[e.g. walk1=10mins; walk2=20mins, etc]**
What RPE did you achieve? **Rating of Perceived Exertion** (Please circle below) ___**6**___7___8___**9**___10___**11**___12___**13**___14___**15**___16___**17**___18___**19**_____**20**___ **no exertion** **very light** **light** **somewhat hard** **hard** **very hard** **extremely hard** **maximal exertion**			
What did you enjoy about your walk/s?	What did you NOT enjoy about walk/s?	Did you complete the course set by the exercise therapist? **Yes/No**	
If you did NOT go out, why not? Please circle below **Didn't feel like it / Something stopped me (i.e. pain, agitation, weather conditions)/ Carer unavailable/ Other** (please describe below)			

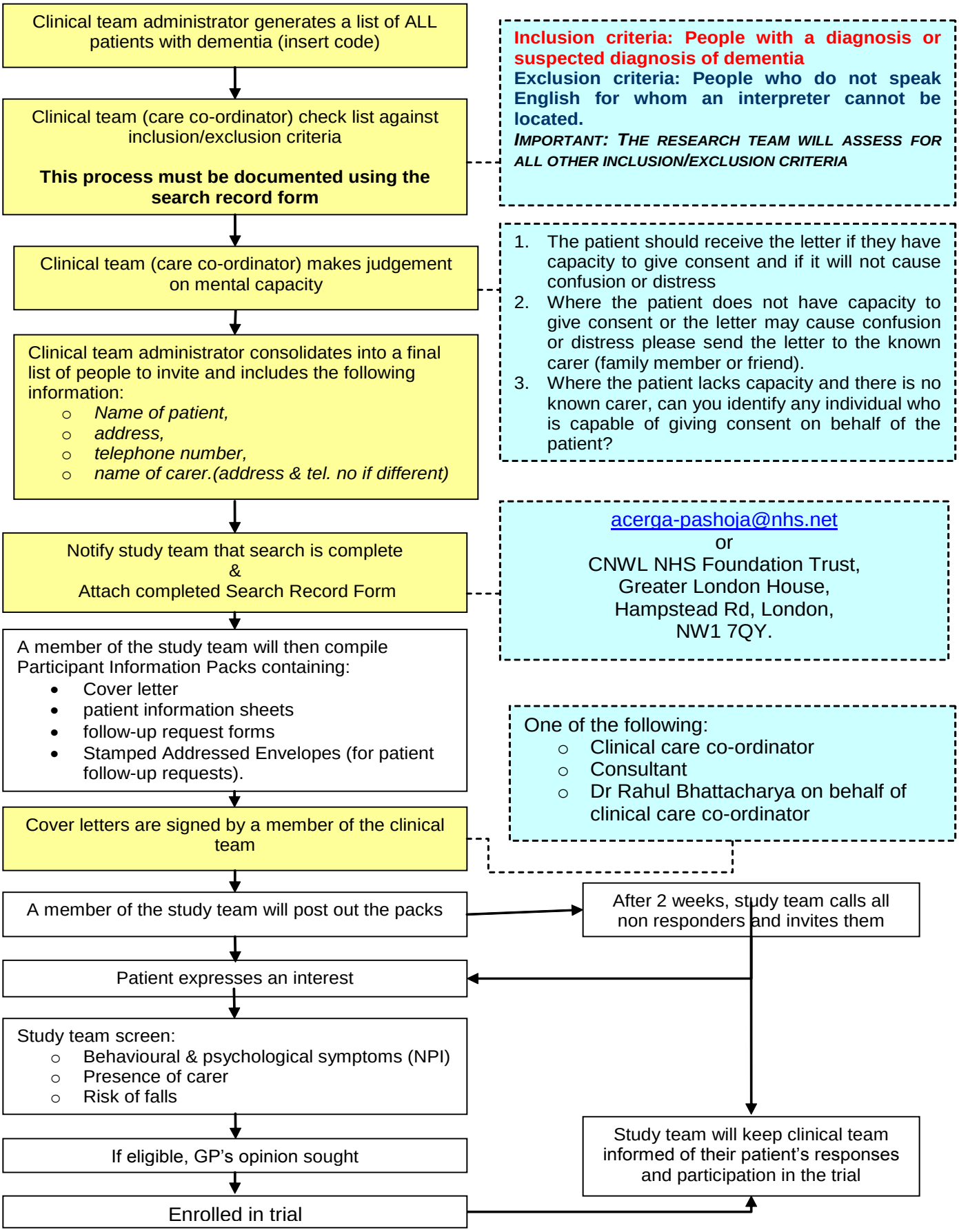
1.12 Control Diary

Week 1			
Monday **Date**	Did you go out for a walk today? **Yes/No**	How many times?	How long was each of your walks? (in minutes) **[e.g. walk1=10mins; walk2=20mins, etc]**
What did you enjoy about your walk/s?		What did you NOT enjoy about walk/s?	
If you did NOT go out, why not? Please circle below **Didn't feel like it / Something stopped me (i.e. pain, agitation, weather conditions)/ Carer unavailable/ Other** (please describe below)			
Tuesday **Date**	Did you go out for a walk today? **Yes/No**	How many times?	How long was each of your walks? (in minutes) **[e.g. walk1=10mins; walk2=20mins, etc]**
What did you enjoy about your walk/s?		What did you NOT enjoy about walk/s?	
If you did NOT go out, why not? Please circle below **Didn't feel like it / Something stopped me (i.e. pain, agitation, weather conditions)/ Carer unavailable/ Other** (please describe below)			

1.13 Assessment Schedule of Delineation of Responsibility

	Exercise Therapist (ET)	**Research Worker (RW)**	**Independent Researcher 1 (IR1)**	**Independent Researcher 2 (IR2)**
	Exercise group only	All participants	All participants	All participants
Baseline T -1		Screens for eligibility; Obtains consent; Outcomes assessed; Demographics and medication BP & HR at rest assessed		
				Randomisation & mails diaries and phone contact to provide instruction about diary completion
Week 1	RPE, walk, support to complete diary			
	RPE, walk, support to complete diary			
	RPE, walk, support to complete diary			
Week 2	Telephone contact			
Week 4	Telephone contact			
Week 6	RPE, walk, support to complete diary	Visits: Outcomes; Medication BP & HR at rest assessed	Telephone to complete NPI, remind diary completion	
Week 12	RPE, walk, support to complete diary	Visits: Outcomes; Medication BP & HR at rest assessed	Telephone to complete NPI, remind diary completion	
Week 13		Collects sealed diaries		
Week 26		Telephone contact Change in domicile? Still exercising? Mortality assessment		

1.14 Recruitment diagram



1.15 Output Strategy

JW James Warner; DL David Lowery; ITB Ingela Thune-Boyle; ACP Arlinda Cerga-Pashoja; JL James Lee; SI Steve Iliffe; RB Rahul Bhattacharya

Pub Publication; Pre Presentation; Pos Poster; Pro Promotional materials; Sym Symposium; OR providing advice for others; Med Media; Ed Produced for educational assessment

Theme/Purpose	Audience	Title/Description	Lead	Type	Target	When
BPSD, consequences & Management	Mixed: practitioners, public	The Use of Anti-Psychotic Medications in People with Dementia	JW	Pre	EVIDEM Summer School	2008
Methodology	Researchers	EVIDEM-E: A randomized controlled evaluation of a tailored exercise package for individuals with dementia and their carers. The impact on sleep, behaviour and quality of life	DL	Pos	DeNDRoN Ann' Conference, Newcastle	2008
BPSD, consequences & Management	Commissioners	Behavioural and Psychological Symptoms of Dementia (BPSD): the personal and practical costs of dementia	DL	Pub	Journal of Integrated Care Vol 17(2)	2009
Raising Awareness	Public	Exercising your mind	JW	Pre	Enfield over 50's Group	2009
Methodology	Mixed: providers, public	Symposium on Activities and Therapeutic Interventions. EVIDEM-E: A randomised controlled evaluation of a tailored exercise package for individuals with dementia and their carers. The impact on sleep,	DL	Pre	The DSDC 3rd International Conference, York	2009

		behaviour and quality of life				
BPSD, consequences & Management	Mixed: practitioners, public	The motion: People in the terminal stages of dementia are wasting their families' lives and the resources of the NHS, as opposer	JW	Pre	Dementia Congress, Harrogate,	2009
BPSD, consequences & Management	Clinicians CNWL patch	Behavioural & Psychological Symptoms of dementia and their management	JW	Pre	EVIDEM Summer School	2009
BPSD, consequences & Management	Mixed: researchers, practitioners	Challenging Behaviour: Meaning and (Care) Management	DL	Pre	Making research Count, National Dementia Strategy Practice Perspectives: One year on – King's College London	Mar 2010
Methodology	researchers	Evaluation of Exercise on Individuals with Dementia and their Carers: A Randomized Controlled Trial	ACP	Pre	PRIMENT Clinical Trials Unit Seminar	2010
Methodology	researchers	EVIDEM-E: A randomised controlled evaluation of exercise as a therapy for behavioural and psychological symptoms of dementia	ACP	Pub	BMC Trials Volume 11 (53)	May 2010
Raising Awareness	Public	Evidence based interventions in dementia: Opportunities to take part and change practice in dementia care in the community	DL	Pre	Hillingdon Admiral Nurse Service Carers	Jul 2010

					Information Day, Hillingdon Civic Centre	
Raising Awareness	Public	The importance of Behavioural & Psychological Symptoms of Dementia & a possible therapy: An invitation to participate in EVIDEM-E	ACP	Pre	As Above	Jul 2010
Raising Awareness	Mixed: practitioners, participants	Newsletter – Raise awareness and provide update on project progress	ACP	Pro	Clinicians and participants – mailing list	Biannu al'
Raising Awareness	Public	Exercise & Dementia	DL	Pub	Alzheimer's Society Newsletter: Living with Dementia	July 2010
Raising Awareness	Public	Scientists assess whether exercise helps combat dementia	DL	Med	BBC One Breakfast News + Radio 4 today programme	April 2011
Methodology/ Capacity	researchers	WHELD NIHR Programme – Developing and testing a multi-component intervention for people with dementia in care homes. Expert Therapy Development Group	DL	OR	Oxfordshire & Bunkinghamshire Mental Health NHS Foundation Trust and King's College	Oct 2010

					London	
Summarizing the literature	Researchers & practitioners	The effect of exercise on behavioral and psychological symptoms in dementia: Towards a research agenda	ITB	Pub	International Psychogeriatrics	2011
Summarizing the literature	practitioners	Physical Activity: a tool for improving outcomes for people with dementia	DL	Pre	Chartered Society of Physiotherapy Annual Congress	2011
Methodology	Research network commissioners	Developing a Dementia Registry: a descriptive case study from North Thames DeNDRoN and the EVIDEM Programme	SI	Pub	BMC Medical Research Methodology	2011
Methodology	Researchers	Evaluation of Exercise on Individuals with Dementia and their Carers: A Randomized Controlled Trial – Presentation for Conversion to PhD	ACP	Ed	Department of Primary Care & Population Sciences	Feb 2011
Methodology	Researchers, practitioners	Clinicians as recruiters to dementia trials: lessons from the EVIDEM-E project	DL	Pub	Letter to International Journal of Geriatric Psychiatry	Apr 2011
Methodology	researchers	Methodological challenges of conducting research in the NHS	ACP	Pre	Society for Academic Primary Care Regional	Feb 2011

Raising Awareness	Public	'Taking a stroll beyond memory lane: can walking help with symptoms of dementia?'	DL	Pre	Memory lane café – Alzheimer's Society	June 2011
Implementation	Practitioners	Managing Behavioural & psychological symptoms of dementia: training our colleagues to identify causes and consequences	JW	Pre	EVIDEM/CNWL Training event	2011
Implementation	Public, practitioners	Providing People with Dementia and their Carers with Tools to improve their levels of Physical Activity	DL/ JL	Pre	Dementia Care Congress -	2011
Implementation	Public	Invited to review and make recommendations for the Alzheimer's Society UK factsheet on exercise and dementia	ACP	OR	Alzheimer's Society UK Website	2011
Methodology	Researchers, practitioners	Factors Affecting Clinician Engagement in Recruitment for Dementia Trials	DL	Sym	Gerentological Society of America Annual Scientific Meeting, Boston	Nov 2011
Raising Awareness	Public	'Your say, your day'	RB/A CP	Pre	Service Users forum in east London	Nov 2011
Methodology/ Capacity	Basic science undergraduate students	The Role of Applied Health Research: experiences of implementing an intervention within a trial of exercise as a therapy for symptoms of dementia	JL	Ed	University of Brighton	2011
Methodology/ Capacity	Policy makers	DeNDRoN helps shape government dementia research strategy – feature article in network magazine	DL	Pro	National Institute for Health Research	2011

Recruitment/ Methodology	Researchers/ Practitioners	The Acceptability of exercise as an intervention across ethnicities/ cultures	RB		Cultural Psychiatry conference	2011
Raising Awareness	Practitioners/ Participants/ Reasecrhers	Evidem-E Newsletter	ACP/ DL		Evidem-E	Dec 2011
Recruitment/ Methodology	Providers/ Researchers	News from the network	DL	Pub	NIHR	Jan 2012
Outcome	Researchers/ Practitioners	Cross-cultural efficacy of exercise as an intervention for BPSD	RB			2012
Methodology/ Research Capacity	Academic	[insert Arlinda thesis title] Submission for examination for Doctorate of Philosophy	ACP	Ed	University College London	2012/13
Outcome	Researchers & practitioners	EVIDEM-E: Exercise as a therapy for behavioural and psychological symptoms of dementia: a randomized control trial of clinical and cost effectiveness	DL/ JW	Pub	International Journal of Geriatric Psychiatry	2012
Implementation	practitioners	Physical Activity: effects for people with dementia and their carers	DL	Pre	Chartered Society of Physiotherapy Annual Congress	2013

9.2 2.1 Evaluation of exercise on individuals with dementia and their carers: a randomised controlled trial

Cerga-Pashoja et al. Trials 2010, 11:53
http://www.trialsjournal.com/content/11/1/53

TRIALS

STUDY PROTOCOL Open Access

Evaluation of exercise on individuals with dementia and their carers: a randomised controlled trial

Arlinda Cerga-Pashoja[1,2], David Lowery[1,2], Rahul Bhattacharya[3], Mark Griffin[2], Steve Iliffe[2], James Lee[4], Claire Leonard[5], Sue Ricketts[4], Lyn Strother[6], Fiona Waters[1], Craig W Ritchie[7] and James Warner*[1,7]

Abstract

Background: Almost all of the 820,000 people in the UK with dementia will experience Behavioural and Psychological Symptoms of Dementia (BPSD). However, research has traditionally focused on treating cognitive symptoms, thus neglecting core clinical symptoms that often have a more profound impact on living with dementia. Recent evidence (Kales et al, 2007; Ballard et al, 2009) indicates that the popular approach to managing BPSD - prescription of anti-psychotic medication - can increase mortality and the risk of stroke in people with dementia as well as impair quality of life and accelerate cognitive decline. Consequently, there is a need to evaluate the impact that non-pharmacological interventions have on BPSD; we believe physical exercise is a particularly promising approach.

Methods/Design: We will carry out a pragmatic, randomised, single-blind controlled trial to evaluate the effectiveness of exercise (planned walking) on the behavioural and psychological symptoms of individuals with dementia. We aim to recruit 146 people with dementia and their carers to be randomized into two groups; one will be trained in a structured, tailored walking programme, while the other will continue with treatment as usual. The primary outcome (BPSD) will be assessed with the Neuropsychiatric Inventory (NPI) along with relevant secondary outcomes at baseline, 6 and 12 weeks.

Discussion: Designing this study has been challenging both ethically and methodologically. In particular to design an intervention that is simple, measurable, safe, non-invasive and enjoyable has been testing and has required a lot of thought. Throughout the design, we have attempted to balance methodological rigour with study feasibility. We will discuss the challenges that were faced and overcome in this paper.

Trial Registration: ISRCTN01423159

Background

> *"Country air, moderate exercise, and a tonic regimen may retard the progress of senile dementia and suspend to some extent its termination*[1]". J.E.D. Esquirol, 1845

Dementia is a degenerative disease of the brain that leads to impairment of memory and global intellectual deterioration without affecting consciousness [2]. The prevalence rises sharply with increasing age: 5% of those over 65 and 20% for those aged over 80 will have dementia [3]. Dementia is also associated with a cluster of non-cognitive symptoms and behaviours that are an integral part of the syndrome. Commonly described as Behavioural and Psychological Symptoms of Dementia (BPSD), they include disturbed perception, thought content, mood or behaviour that frequently occur in patients with dementia [4]. Although recognised as core to the phenomenology of dementia in Alzheimer's seminal case studies [5], these symptoms have received relatively little attention from the research community. This is surprising given that upwards of 80% of people with dementia will experience BPSD at some point during the course of

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their illness [6]. Apart from the obvious distress for the person, BPSD are commonly associated with reduction in the quality of life for the person as well as their caregivers [7]; increase of caregiver stress [8], costs of care [9]; and unsurprisingly premature institutionalization [10].

Although there is some evidence supporting the treatment of BPSD with antipsychotics, there have been increasing concerns over the safety of these drugs for people with dementia. Two recent studies indicate that there is a long-term risk of mortality in patients with dementia who take antipsychotic medication [11,12]. Non pharmacological alternatives that have been reported to have a positive effects include music therapy, bright light therapy, behavioural interventions and exercise[13]. As well as the potential improvement in physical well being exercise has been demonstrated to have a positive effect on cognitive symptoms and mood [14,15]. Interventions such as exercise may offer a safer effective alternative to pharmacological treatments and could also be empowering to individuals with dementia and may reduce carers' burden.

Heyn et al carried out meta-analysis of exercise in dementia and reported data on 30 trials of exercise [16]. The authors reported on trials that included strength, cardiovascular or flexibility regimes; and analysed for functional, cognitive or behavioural outcomes. A significant positive effect of exercise on behavioural outcomes was reported (Effect Size = 0.54; 95% Confidence Interval = 0.36-.72). However these trials do not provide a full picture of the effectiveness of exercise on BPSD for a number of reasons. There was considerable heterogeneity in terms of the interventions, and exercise was often combined with other behavioural interventions. Thus, it is difficult to isolate the impact that exercise has had on behavioural outcomes. Some regimes were quite complex and require a high degree of physical fitness that would preclude many older adults with complex physical problems and moderate or profound dementia from performing them. Moreover, they were potentially unsustainable without the support of trained therapists. Finally, the relatively high cost of delivery and specialist input required may prevent the interventions being used more widely. Most trials included in the analysis were relatively small, with only two of the eight studies that reported effects on behaviours having samples in excess of 100 participants.

We have designed a study that aims to evaluate the effectiveness of exercise as a therapy for behavioural and psychological symptoms of dementia. This will be a pragmatic randomised trial conducted in a community cohort in the UK nested within a larger programme of research. The overarching programme investigates the impact of various psychosocial interventions for people with dementia, those who care for them and professionals that support them (Evidence Based Interventions in Dementia-EVIDEM). This has been a challenging design process, which has seen the project team - supported by an independent steering group - attempt to strike a balance between achieving a feasible and sustainable intervention, which could be widely adopted in the target population while maintaining scientific rigour in its evaluation. In the following, we describe the resultant and final methodology and discuss the benefits & limitations to our approach.

Study hypothesis

A programme of tailored incremental exercise (through walking) improves the symptoms and outcome of Behavioural and Psychological Symptoms of Dementia

Methods/Study Design

This trial has been granted ethical approval by the Outer North East London Research Ethics Committee, REC reference number: 09/H0701/67.

We will undertake a pragmatic, randomised, controlled, single-blind, parallel-group trial. Community-dwelling individuals with a diagnosis of dementia or suspected dementia who also have a carer willing and able to be a co-participant in the exercise regime will be recruited to this evaluation.

Participants will be randomly allocated to one of two arms: the treatment arm, which includes receipt of an individually tailored regime of walking (the intervention; exercise therapy-ET) in addition to treatment as usual (TAU) or the control arm which receives treatment as usual only (see Figure 1). Treatment as usual may include home care, attendance at day care facilities, visits by health professionals, receipt of medication, respite care etc.

Both the treatment and control arms will be re-assessed for all outcomes at weeks 6 and 12. Further telephone contact will occur at 26 weeks to assess adverse events, mortality, change in domiciliary status and adherence to exercise regime. The randomisation ratio for the two groups will be 1:1 (ET:TAU). An Independent randomisation officer will use a computer algorithm to perform the randomisation centrally after the initial interview, and will communicate the results to the participants, the GP and to the exercise therapist; but not to those collecting research data.

Primary Objective

To determine the effectiveness of physical exercise delivered through a programme of incremental walking for treating behavioural and psychological symptoms of dementia (as defined by Neuropsychiatric Inventory scores) compared with treatment as usual (TAU).

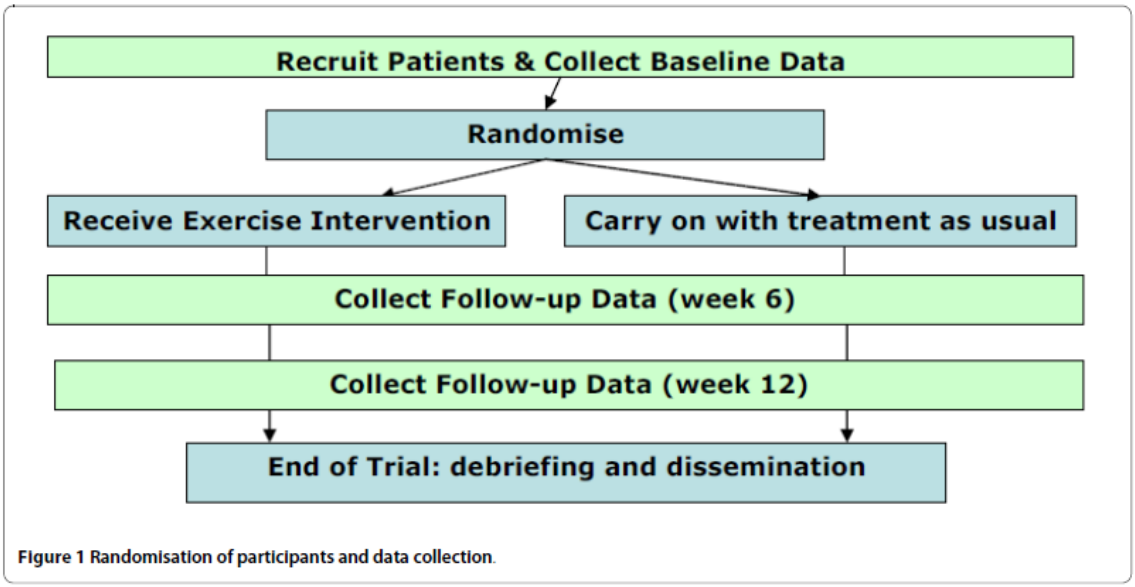

Figure 1 Randomisation of participants and data collection.

Secondary Objectives

To determine the effect of exercise on 1) the quality of life of people with dementia; 2) psychotropic medication usage; 3) move to a residential care facility; 4) mortality levels; 5) caregivers' perceived level of burden. We will also carry out an economic evaluation of the intervention and qualitatively explore participants' views about the intervention and barriers to treatment.

Recruitment

The selection criteria for participation in the Evidem-E trial are outlined in Table 1 (Table 1). Participants with a clinical diagnosis of dementia or 'suspected dementia' with at least one significant BPSD symptom defined by the Neuropsychiatric Inventory (NPI)[17] (excluding the domains of delusions and hallucinations) will be eligible for the trial. Diagnosis of dementia will be confirmed in accordance with ICD-10 Diagnostic Criteria for Research (DCR-10). A risk assessment will be performed to assess the suitability of participants for the intervention at baseline. This assessment will include measurement for risk of falls through the Falls Risk Assessment Tool (FRAT) [18] and Timed Unsupported Steady Standing (TUSS) [19].

Individuals with dementia known to the General Practitioner or secondary care will be identified and suspected new cases will be assessed to confirm diagnosis. Regular reminders about the study will be sent to participating practices and secondary care teams within the network catchment's area. A central register of all referrals will be maintained.

There are four potential sources of recruitment:

- The locally adopted Dementia Registry (DemReg) of people with dementia interested in participating in research.
- GP practices that are affiliated to the EVIDEM Research Group
- Memory assessment services and community mental health services (e.g. Admiral Nurses) recruited via CNWL NHS Foundation Trust
- Self referral

Interventions

Physical exercise will be delivered as an individually tailored regime of walking designed to become progressively intensive and last between 20-30 minutes. This will be facilitated by a qualified exercise therapist and delivered to participants in the treatment arm of the trial (Figure 2) in the area around their own home. The exercise therapist will facilitate physical exercise in the participant-carer dyad with the expectation that the dyad will perform the exercise regime regularly and independently of the therapist at least 5 times per week. The intervention has been structured so that the therapist adopts a phased withdrawal approach utilising both face-to-face contacts and telephone support contacts.

The dyad on the intervention group will also be asked to complete a visual analogue scale called the Rating of Perceived Exertion (RPE) [20]. Perceived exertion is based on the physical sensations a person experiences during physical activity, including increased heart rate, increased respiration or breathing rate, increased sweating, and muscle fatigue. Although this is a subjective measure, a person's exertion rating may provide a fairly

Table 1: Selection criteria for inclusion/exclusion from the Evidem-E trial

Inclusion criteria	*Exclusion criteria*
Diagnosis of: a. Dementia in primary or secondary care OR b. Suspected dementia confirmed by the researcher to ensure the DCR-10 criteria are met; Presence of a carer (professional, friend or family member, who does not necessarily have to live with the participant); Presence of BPSD measured through NPI. [NPI score in any one sub-set (except only hallucination or delusion) more than or equal to 2 in severity and more than or equal to 2 in frequency]; Consent of participant, or in the case of an individual who is not capable of giving informed consent, the assent of the participant with agreement of carer; Consent of carer.	Cardio-respiratory condition, neurological or musculo-skeletal condition of a degree that prevents participation to even the modified exercise regime unsafe or not possible. Three or more falls in the previous year ("frequent fallers") assessed by FRAT or high falls risk defined by TUSS; Uncontrolled medical problems, which the GP considers would exclude participants from undertaking the exercise programme; for example, acute systemic illness' such as pneumonia, poorly controlled angina, acute rheumatoid arthritis, unstable or acute heart failure; Sensory impairment to an extent that prevents dyad facilitated exercise; Participant or carer dissent to engage in the exercise programme.

good estimate of the actual heart rate during physical activity (Borg, 1998). The exercise therapist will not only assess the RPE but train participants to evaluate themselves and will encourage the dyad to extend walking exercise to 60-70% of RPE.

The participants in the treatment arm will be asked to record their daily activities and RPE throughout the 12 weeks of their participation using a diary designed to meet the specification of this study.

Outcome Assessments

Assessments will be conducted according to Figure 1. Participants will be visited in either their own homes, or a mutually acceptable convenient location (e.g. GP's clinic), by a trained research worker (RW) masked to arm allocation.

The primary outcome measure will be changes to behavioural and psychological symptoms measured by the Neuropsychiatric Inventory (NPI) at baseline as well as 6 and 12 weeks of participation.

Secondary outcome measures will be changes to: participants' mental health (GHQ)[21], participants' quality of life (DemQOL-Proxy)[22], and caregivers' burden of caring (short ZBI) [23]. The secondary outcomes will also be measured at baseline, 6 and 12 weeks into the trial.

Participants' level of physical activity and compliance with the intervention will be measured through daily diaries, Rate of Perceived Exertion (RPE), blood pressure and heart rate monitoring. Diaries will also provide qualitative information in regards to participants' views about the intervention.

We will also carry out an Economic Evaluation through the Client Service Receipt Inventory [24], which will be administered at baseline and 12 weeks into the trial.

Domicile and mortality change will be measured at follow-up, 26 weeks into the trial via a structured telephone interview.

The exercise programme will be initiated and supervised by the Exercise Therapist. Baseline and subsequent evaluations will be undertaken by RW. An independent researcher (IR) will collect the primary outcome data (NPI) at weeks 6 and 12, which will be completed by telephone with the aim of minimising the risk of un-blinding group allocation to research workers.

Sample size

Based on anticipated between-group absolute risk difference of 30% in number of people with BPSD symptoms measured by the NPI, a sample size of 146 participants will give 90% power to detect this difference with 95% confidence. This calculation includes a 20% attrition estimate. The sample size calculations have been described in Table 2.

(calculated by http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html)

Statistical Methods

Baseline demographic and outcome data will be compared between the two randomisation groups. Categorical data will be analysed using the chi-square test. Continuous data will be analysed using the t-test or if the data is found to be non-normally distributed, we will use the Wilcoxon Rank-Sum test.

Outcomes at 6 and 12 weeks will be compared between randomisation groups using analysis of co-variance (ANCOVA) for continuous data. The relevant baseline scores will be included as the co-variate in order to adjust for any potential baseline differences in the respective outcome. Categorical outcomes will be compared using the chi-square test.

All data will be analysed on an intention-to-treat basis, where appropriate imputation of missing data will be implemented. Under the assumption that data are missing at random multiple imputation will be used.

All analyses will be completed using the statistics package STATA.

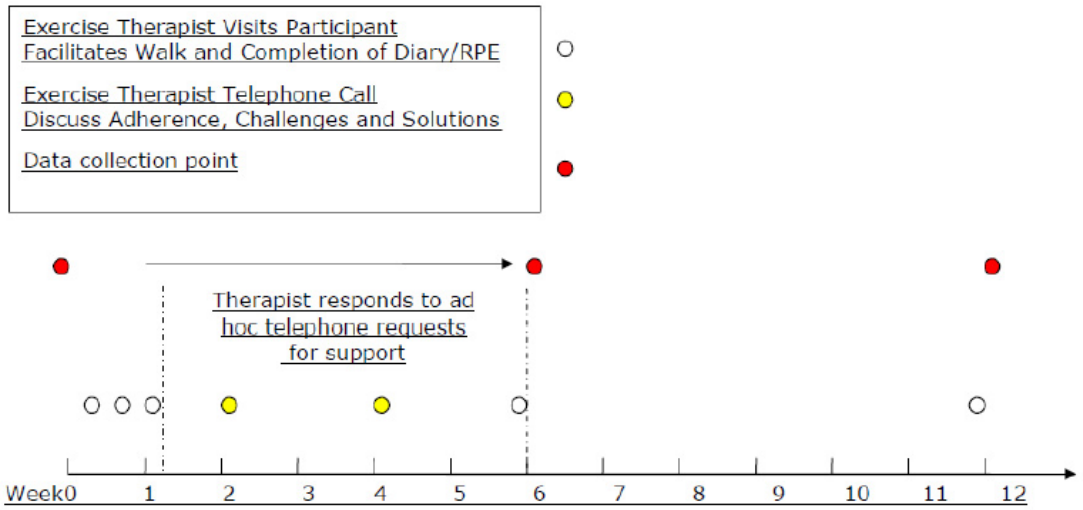

Figure 2 Intervention schedule.

Discussion

Behavioural and psychological symptoms are an intrinsic feature of dementia that are often treated with drugs such as antipsychotics, which are potentially unsafe to use in this population. Alternative treatments for BPSD are required but there is a dearth of research in the area. We have tried to design a trial of exercise as therapy for BPSD. Designing such a trial provides challenges that drugs trials do not, such as: defining the treatment, maintaining blinding, defining clear measurable outcomes and ensuring the intervention is feasible and sustainable.

Exercise provides a promising intervention for BPSD, but further work is needed. Previous studies have reported the use of relatively complex exercise regimes including aerobic, strength, flexibility and balance training [25,26]. Most ageing individuals suffer from physical conditions such as cardio-respiratory illness, arthritis, and sensory and mobility impairments. It is important, therefore, that exercise therapy for this patient population is sensitive to this. Our study group and the independent Steering Group, which monitors and advises us, agreed that 'walking' is a feasible, sustainable and cost effective way of exercising. Walking is a simple way of exercising which enjoys all the benefits of more complex exercises but with the advantage of being sustained independently even by individuals with moderate to severe dementia and other physical conditions.

Careful consideration was taken in regards to blinding the researcher to the allocation status of the participants. The single blind design leaves us vulnerable to unmasking group allocation during the interaction between researcher and participant during visits. This everyday conversation is essential to building a rapport with participants and ensuring they feel comfortable in participating. All study personnel including researchers and therapists will repeatedly remind participants of the importance of not disclosing their group allocation. However, the risk will remain, and so we decided to include a second 'independent' researcher whom would collect our primary outcome data (NPI) at 6 and 12 weeks. The premise for this approach is that this researcher can take a less 'personal' tone and thus minimize the risk of con-

Table 2: Power calculations

Control	Intervention	Difference	N (including compensation for 20% attrition)
0.8	0.4	0.4	70 (88)
0.8	0.5	0.3	116 (145)
0.8	0.6	0.2	238 (298)

versation with the dyad that might un-blind group allocation. However, there remains a risk that the dyad will divulge information about the group they have been allocated to. Therefore the efficacy of blinding will be assessed at each time point, by personnel collecting data who will record which arm they believe each dyad is randomised to.

Separating the effect of psychosocial contact (from the exercise therapist) from the exercise intervention has proved to be the biggest challenge in our study. We decided to address this problem by introducing two periods during the intervention: 1-6 weeks whereby the participants in the intervention group will be trained and supported by an exercise therapist and 6-12 weeks when participants will receive absolutely no contact with the therapist. This stage will also help to assess the intervention's feasibility and sustainability in a community population. The symptoms of BPSD tend to be relatively stable over short time periods (i.e. months) so the two windows provided by this method should detect responses influenced purely because of exercise and not by any residual benefits of interaction with the therapist. Although we have tried to control for contacts between participants and the exercise therapist, we could not control for the social contact between the person with dementia and their carer. Dyadic walking may encourage not just physical activity but psychosocial support from the carer as well.

In terms of outcomes, we are using measures that are validated and widely used in research with individuals with dementia. We also gave considerable thought to the issue of measuring physical activity. Particular consideration was given to the use of equipment by the participants to record their individual activities e.g. Global Positioning System receivers and pedometers. The following issues were identified:

- Measurement accuracy and information bias (participants are likely to forget to wear their equipment or they may continue to wear equipment during non-activity time);

- Practicality and intrusion (wearing equipment for 12 weeks on daily basis can be intrusive and this may affect participation in the study and may give rise differential attrition);

- Methodological problems (introducing a self administered assessment of physical activity within the control group could constitute an intervention in its own right. There is potential for this to promote increased levels of physical activity within the control group and thus reduce the detectable effect size).

Therefore, we agreed to evaluate participants' level of physical activity through measurements of the participants' self reported Rate of Perceived Exertion (exercise group only). A proxy measure of fitness will be utilised to assess for compliance with intervention. Heart rate at rest will be assessed at the beginning, middle and end of the trial for all participants. We expect that should participants adhere to the prescribed exercise regime, their fitness will improve and ergo their heart rate at rest. We hypothesise that with such an increase in activity we may observe a reduction of BPSD. However we recognise that detecting such changes in cardiovascular health may be overambitious.

Assessing physical activity with minimum intrusion to study participants is challenging and we are relying on participants' self reports through daily dairies. Self-report is prone to information bias, especially when participants are not blinded to their group allocation. We may also encounter a significant Hawthorn effect whereby participation in the study and study hypothesis in particular may affect the behaviour of study participants. Thus, participants in the control group who believe they may benefit from regular exercise might increase their physical activity during the study period, which in turn may reduce any detectable effect due to the intervention.

Antipsychotic drugs, as discussed above, provide limited efficacy in treating BPSD as well as having established safety concerns. Exercise, on the other hand, may be effective but could also be associated with unknown risks. At present we can not discern whether the unconfirmed risk of the exercise is more substantial than the demonstrated risk of drugs. However, we have attempted to develop a design with robust risk event detection to mitigate this.

Designing the Evidem-E trial has proven to be very challenging but we have attempted to overcome the challenges without compromising scientific rigour or study feasibility. This trial is in accordance with the UK government's action plan to tackle the over-prescribing of antipsychotic drugs to people with dementia.

If this trial is successful, its findings may be applicable to a wide base of people diagnosed with dementia with minimal costs.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JW conceived of the study, and along with DL, MG & RB developed the first draft of the protocol. AP wrote the first draft of the paper for publication. All authors significantly contributed to subsequent drafts and the final version submitted for ethical approval. All authors contributed to the design of the study, and have seen and approve of the final version. The quote from Esquirol was contributed by Dr Claire Hilton.

Acknowledgements

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Designing the Evidem-E trial has proven to be very challenging but we have attempted to overcome the challenges without compromising scientific rigour or study feasibility. This trial is in accordance with the UK government's action plan to tackle the over-prescribing of antipsychotic drugs to people with dementia.

If this trial is successful, its findings may be applicable to a wide base of people diagnosed with dementia with minimal costs.

Competing interests

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Authors' contributions

JW conceived of the study, and along with DL, MG & RB developed the first draft of the protocol. AP wrote the first draft of the paper for publication. All authors significantly contributed to subsequent drafts and the final version submitted for ethical approval. All authors contributed to the design of the study, and have seen and approve of the final version. The quote from Esquirol was contributed by Dr Claire Hilton.

Acknowledgements

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9.3 2.2 Clinicians as recruiters to dementia trials: lessons from the EVIDEM-E project

Clinicians as recruiters to dementia trials: lessons from the EVIDEM-E project

'Evidenced based interventions in dementia' (EVIDEM: www.EVIDEM.org.uk) is a 5-year research & development programme aiming to explore, evaluate and improve the quality of community based dementia care (Iliffe *et al.*, 2008). The EVIDEM programme, like most clinical trials, relies on clinicians to recruit participants. Key NHS Stakeholders support was strong for EVIDEM and so we anticipated straightforward recruitment. However, this has not been the case; from a population exceeding 2000 people with dementia, one EVIDEM trial (EVIDEM-E: http://www.evidem.org.uk/projects/evidem-e.htm) recruited 6 participants over 6 months through clinical teams, despite minimal exclusion criteria. Our enquiries suggested that this was due to clinicians not distributing invitations, rather than a lack of interest from people with dementia and their carers. With recruitment alarmingly low and struggling to understand the incongruity between verbal support and limited promotion of the study, we invited team managers, nurses, occupational therapists, physiotherapists and psychologists to a facilitated round-table discussion on their perceptions of research, impediments to their role as recruiters and ways to enhance recruitment.

The group described clinicians being challenged by patients 'informed about the latest research' reported in the mass media; this sometimes required provision of contrary opinion and reminders for patients that application of research findings are dependent on the quality of the research and clinical nuances. When recruiting to research, the group felt responsible as the source of the invitation, assuming a degree of accountability for the project's value and conduct (Table 1a). This was seen as unreasonable as they had no part in its design and administration, and so recruiting might be perceived as potentially unrewarding or worse, detrimental to patients. While the group perceived the value of research, they also identified several concerns about recruiting their patients to EVIDEM-E (Table 1b–d). Understandably, recruitment was regarded as a low priority in consultations and easily 'slipped off the radar' (Table 1e). The group made 3 suggestions aimed to enhance the participants' experience opposed to theirs as recruiters; the first suggestion involved increasing clinician workload (Table 1f–h). With regard to the second, the EVIDEM programme attempts to ensure comprehensive stakeholder involvement (e.g. http://www.evidem.org.uk/events/ss08-details.htm) (Iliffe *et al.*, 2009; Cerga-Pashoja *et al.*, 2010), but this does not seem to have influenced this group's experiences. The final suggestion is outside the remit of EVIDEM, but is consistent with the overall themes of patient protection and making research involvement profitable for participants.

The NHS appears a fertile environment in which to recruit to clinical and healthcare research; within a society that often undervalues older people, many clinicians and researchers are passionate advocates of broadening patient choice, including opportunities to participate in research. All participants are expected to give their informed consent and safeguards exist for those who are unable to. In our experience, people take part in research for many reasons, not always obvious, but include altruism and heterotelism; and, people who are not interested have a range of direct and indirect ways of showing this. Despite all this, clinicians appear apprehensive to recruit to low-risk research. Therefore, we support recent calls to quantify clinicians' impact on recruitment and test ways of improving accruals (Rendell *et al.*, 2007). We also agree more is needed to understand the experience of participating as a 'control', particularly in trials utilising a single blind design.

There are several ways researchers can incentivise clinicians' involvement in research. The group indicated their involvement should bring tangible reward for clinicians and participants (Table 1i). It is not enough that NHS Trusts financially gain through research involvement; how these resources enhance clinical services should be made explicit. Encouraging investment by including clinicians on research advisory groups may garner support; however, it is likely that a more widespread and involved approach is needed to improve practitioner engagement. Consulting clinicians on dissemination strategies might help them see the path from project to practice. Finally, developing flexible quick guides to recruitment may instill confidence when discussing individual projects with patients. These approaches all maintain clinicians as central to recruitment; an alternative could be direct contact between researchers and patients. This could potentially resolve many

Table 1 Themes emerging from group discussions about recruitment

a. Clinician accountability for research	'What if they agree due to your relationship with them, when you've said this thing is going to be great...?'
b. Overburdening 'vulnerable' participants	'I was just wondering if you could take it [information pack] out and talk them [participants] through, rather than this big pack arriving. I'd be thinking "uau" I thought I was just going out on a walk...'
c. Anxiety over the patients' feelings after researcher withdrawal	'From our perspective they have participated in research... but they got nothing to say: thank you very much. I think that kind of puts people off'.
d. Concern that participants would be dissatisfied when allocated to a control group	'We have to tell the client what is it they get out of this... what if they go on the control group and get nothing?'
e. Low priority in individual clinical context	'I don't see it as likely that patients that will be offered some sort of treatment will ask: "why are you saying this is the best treatment?" and ask for a justification. Many of our patients would be grateful because what they are looking for is an outcome, they are not interested how we get there. They just want positive outcome'.
f. Continuation of treatment – themselves to be trained to deliver the EVIDEM-E intervention	'I think it would be really useful if we could do it [exercise intervention] ourselves and have a go. With proper training and under you observing it, I don't see a reason why we couldn't'.
g. Feedback provided face to face to participants	'You need to talk to people. The feedback is very important, whether it [the study] has success or not. At the end they [participants] should be given some feedback'.
h. Provision of carer respite	'I think that whilst... they might want to be involved and participate, but if the services are not going in to enable them to have a good night sleep... A lot of times carers will actually say: I want a break... That's the expectation of the carer, that someone will do that. That'll be the motivation'.
i. Tangible rewards	'What's in it for us?'

recruitment challenges for clinician and researcher, while improving patient choice. In collaboration with North Thames Dementia & Neurodegenerative Diseases Research Network (DeNDRoN), we helped develop a Registry of people with dementia interested in research ('DemReg') (Ritchie and Rait, 2009); this is operational, but requires testing and refinement. Preliminary experience suggests it is an effective recruitment mechanism; 8 participants in 6 weeks were recruited from the Registry to EVIDEM-E.

Declaration of authorship

DL & AP were responsible for the idea and acquisition of the data. DL prepared the first draft, and as such takes responsibility for the integrity of the work from inception to the final version. All authors made substantial contributions to analysis and interpretation of data, revising the manuscript critically for important intellectual content and approve of the final version.

Conflict of interest

None of the Authors have any conflicts of interest to declare. The study sponsor has played no part in the study design, in the collection, analysis and interpretation of data, in the writing of the report and in the decision to submit the report for publication.

Ethical approval

This work was conducted as part of the EVIDEM-E project which received ethical approval from East London 3 NHS REC (Ref: 09/H0701/67).

Key Points

- Clinicians are the link between NHS patients and healthcare researchers and so are central to recruitment to health care research.
- Recruitment rates from clinicians often do not meet the expectations of researchers and can significantly impact on the timetable of research projects.
- Many clinicians are uncomfortable recruiting to research as they feel they are not familiar with the research topic, fear a negative impact upon their clinical relationship with the patient and believe that such work is a low priority in the clinical situation.
- Involving the clinician later in the recruitment process may provide a solution.

Acknowledgements

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9.4 2.4 Presentations

Title	Location and Date
Evaluation of Exercise on Individuals and their carers: A randomised controlled trial.	PRIMENT Clinical Trials Unit, 2010, UCL, UK.
Evaluation of exercise on individuals with dementia and their carers: A randomised controlled trial.	Presentation for conversion to PhD. Department of Primary Care and Population Health, 2011, UCL. UK.
Methodological Challenges of conducting research in the NHS.	Society for Academic Primary Care Regional Meeting, 2011. Cambridge. UK
The importance of Behavioural & Psychological Symptoms of Dementia and a possible therapy: an invitation to participate in EVIDEM-E.	Hillingdon Admiral Nurse Service Carers Information Day. Hillingdon Civic Centre, 2010, UK

9.5 2.5 Newsletter 1

EVIDEM-E:

A Trial of Exercise as a Therapy for the Behavioural & Psychological Symptoms of Dementia

Newsletter 1 Summer 2010

www.evidem.org.uk

EVIDEM

Welcome

Welcome to the First edition of the EVIDEM-E newsletter. On these pages you will find an introduction to the trial, the people working on it, and some feedback from volunteers.

The Team

Dr James Warner Chief Investigator
James is a clinical lead for organic psychiatry for CNWL NHS Trust
Dr David Lowery Trial Manager
Arlinda Cerga-Pashoja *Researcher*
Dr Ingela Thune-Boyle *Researcher*
James Lee *Exercise Therapist*
Dr Alex Bailey *Randomisation Officer*

The project team are supported by an Independent Steering Group of family carers, older people, clinicians, and representatives of volunteer organisations

What's it like to be a recruiter?

The project team would like to invite members of clinical teams for lunch time discussions on recruitment to research.

- **What are the challenges of being a recruiter?**
- **How much time have you had to spend on recruitment?**
- **How can researchers improve the way they recruit?**

20th July—Bentley House 1pm-2pm
21st July—Redwood Mtg Rm, Nightingale House, St Charles Hospital.

LUNCH PROVIDED : LIMITED PLACES
RSVP TO ARLINDA (CONTACT BELOW)

Feedback from the Trial

"My husband and I are delighted with the trial."
Mrs F, our first trial participant

"The general impression I get from speaking with carers of patients with dementia is that taking part in this study has been a very positive experience. People are really happy to help and hope that their participation will also help someone else who find themselves in a similar situation." *Dr Ingela Thune-Boyle*

For more information or to get involved in EVIDEM-E please contact:
Arlinda Cerga-Pashoja 020-3214-5886/acerga-pashoja@nhs.net
Medical Directorate, CNWL NHS Foundation Trust, Greater London House, Hampstead Rd, NW1 7QY

Central and North West London NHS
NHS Foundation Trust

Has dementia brought you challenges other than those of thinking or memory?

Is your loved one perhaps more irritable, anxious or sad?

Does one of your clients have trouble sleeping or sleep at odd times?

If you answered yes to any of these questions then the person might be experiencing Behavioural and Psychological Symptoms of Dementia (BPSD). These can be very distressing and managing them can be critical to living well with dementia .

TREATMENT

These symptoms can be treated with drugs, but they are short term measures and can sometime have a negative impact on the person taking them. Therefore, making use of alternative treatment could be crucial. Some previous research has shown that **exercise** might be a useful way of treating Behavioural and Psy-

THE RESEARCH

Our project is examining whether **regular walking** can be used to treat Behavioural and Psychological Symptoms of Dementia; whether it has as impact on medication use and quality of life for both the individuals with dementia and their carers.

YOUR INVOLVEMENT

People may be eligible to participate in the trial if they meet the following criteria

- Have a diagnosis of dementia or suspected of having dementia
- Have the presence of a professional, friend/family member, or carer—willing to take part in the trial.

Commitment required: Participants are put into one of two groups:

1. One group would carry on as normal with no change of treatment.
2. The second group receives a tailored and gentle exercise therapy programme. The therapist helps the person with dementia and his/her carer to establish a programme of **walking outside** their homes. This is at a pace and distance to suit both participants. The exercise therapist will visit participants on **five occasions over 3 months.**

A researcher will also visit the participant to monitor for key changes on **four occasions**

SELECTED REPORTS FROM EVIDEM-E

Behavioural and Psychological Symptoms of Dementia (BPSD): the personal and practical costs of dementia *Lowery D & Warner J (2009)* ***Journal of Integrated Care 17 (2)***

Evaluation of exercise on individuals with dementia and their carers: a randomised controlled trial *Pashoja A, et al (2010)* **BioMed Central Trials** *Volume 11: 53*

For more links, presentations and publications from EVIDEM-E, please visit: www.evidem.org.uk/reports/bpsd

9.6 2.6 Newsletter 2

EVIDEM-E:

A Trial of Exercise as a Therapy for Behavioural & Psychological Symptoms of Dementia

Newsletter Number 2 (Winter 2010/11)

www.evidem.org.uk

Welcome to the Second edition of the EVIDEM-E newsletter. On these pages you will find an introduction to the trial Steering Group, an update on recruitment and feedback from clinicians about recruitment issues.

Introducing the EVIDEM-E Steering Group

The Steering Group acts in the interest of the public; it provides independent monitoring of the trial, focussing on aspects of safety, progress and reporting. The group meets quarterly and includes members from a range of backgrounds. Here, three of the members tell us a little bit about the experience they bring to the group.

"I am the Physiotherapy Professional Lead of Older Peoples Services for a Mental Health Partnership Trust. For 16 years I have worked and developed a specialist interest in Dementia care. I am passionate about enabling people with dementia to have the best quality of life; maintaining independence for as long as possible and promoting mobility alongside positive risk management." **Clare Leonard**

"My husband was diagnosed with Alzheimer's in 2005. With hindsight, I realize he was suffering many years before. Unfortunately, his behaviour became unmanageable and we were both considered at risk. He went into residential care in February 2010 and is safe, well cared for and contented. Our son and I visit regularly. My husband has participated in research, and I am now a moderator for Talking Point, the Alzheimer's Society's Forum for people with dementia and their carers" **Sylvia Gupta**

"I am Chair of the Steering Group with an academic and clinical interest in dementia and cognitive impairment. I have been involved in designing and running clinical trials in dementia for over 15 years. I am also Research and Development Director at West London Mental Health Trust." **Dr Craig Ritchie**

Other members include:

Lyn Strother, Director of Greater London Forum for Older People;

Fiona Waters, Occupational Therapist, South Kensington and Chelsea;

Natalie Fox, Service Director for Older Adults at CNWL.

Central and North West London NHS
NHS Foundation Trust

The CNWL NHS Foundation Headquarters including the Evidem-E study team have now successfully moved to a new address:

Stephenson House , 75 Hampstead Road, London NW1 2PL

After an initially slow start to recruitment back in 2010, we have been working hard to invite as many people as possible. Lots of people have volunteered to take part in the study, but it will be difficult to reach our recruitment target on time. We sought permission from our funder (The National Institute for Health Research) to extend our recruitment period until June 2012. This will allow us to have good confidence in our findings. Therefore, we are happy to report that we will be continuing to invite research volunteers until June 2012.

Our area of recruitment is expanding. We welcome **Surrey and Borders Partnership Foundation Trust** as our newest recruitment centre.

RECRUITMENT PROGRESS
TARGET: 146
RECRUITED: 91

- **Participant Recruitment Centres & Primary Investigators**
  - CNWL->Dr James Warner
  - WLMH ->Dr Sujoy Mukherjee
  - East London -> Dr Rahul Bhattacharya
  - SBP ->Dr Ramin Nilforooshan
- **Participant Identification Centres**
  - Barnet Enfield & Haringey
  - Luton

SELECTED REPORTS FROM EVIDEM-E

The effect of exercise on behavioural and psychological symptoms of dementia: towards a research agenda I. Thuné-Boyle, S. Iliffe, A. Cerga-Pashoja, D. Lowery and J. Warner (2011) *International Psychogeriatrics*

Providing People with Dementia and their Carers with Tools to improve their levels of Physical Activity D. Lowery & J. Lee (2011) Workshop demonstration, Dementia Congress

Physical Activity: a tool for improving outcomes for people with dementia D. Lowery (2011) Chartered Society of Physiotherapy Annual Congress

Factors Affecting Clinician Engagement in Recruitment for Dementia Trials D. Lowery (2011) Gerontological Society of America Annual Scientific Meeting

For more links, presentations and publications from EVIDEM-E, please visit: www.evidem.org.uk/reports/bpsd

9.7 2.7 Newsletter 3

EVIDEM-E:

A Trial of Exercise as a Therapy for the Behavioural & Psychological Symptoms of Dementia

Newsletter 3 Winter 2011

www.evidem.org.uk

EVIDEM

We here at the Evidem-E team wish to extend our warmest holiday wishes. We would like to thank everyone who has contributed to the trial. We hope you will have a healthy and rewarding year ahead filled with joy and happiness

For information or to get involved in EVIDEM-E please contact:
Arlinda Cerga-Pashoja 020-3214-5886/acerga-pashoja@nhs.net
Medical Directorate, CNWL NHS Foundation Trust, Stephenson House, 75 Hampstead Rd, NW1 2PL

Central and North West London NHS
NHS Foundation Trust

9.8 2.8 Newsletter 4

EVIDEM-E:

A Trial of Exercise as a Therapy for Behavioural & Psychological Symptoms of Dementia

Central and North West London NHS

NHS Foundation Trust

Final Newsletter 2013

www.evidem.org.uk

EVIDEM

EVIDEM-E started in 2010 with the idea that walking might be a useful way of helping people with dementia and those who care for them to feel better. We would like to share what we found and how this might be used to improve the way we provide care.

What we wanted to find out

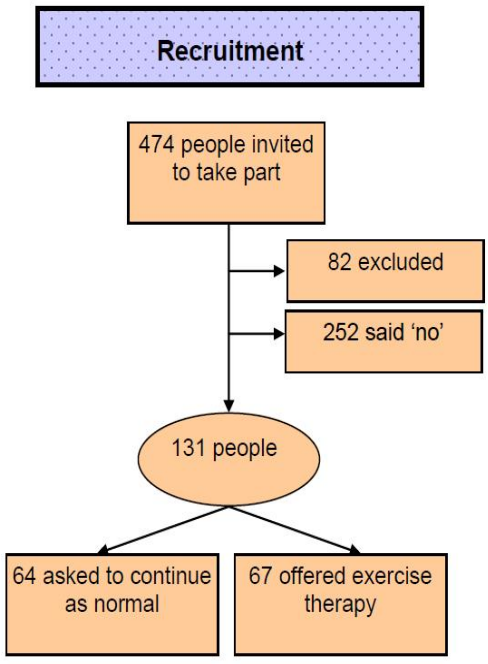
⇒ If regular walking helps reduce symptoms like agitation, depression and disturbances of sleep for people with dementia.

⇒ If walking helped carers to feel more able to cope.

What we did

People with dementia took part in the study with their carers, for 12 weeks.

- Some people were given exercise therapy (exercise group) and others were asked to carry on as normal (control group).
- A computer was used to decide which group (exercise or control) each person was asked to join.
- We asked everyone a list of questions before they entered the study, then again after 6 and 12 weeks.
- The answers to these questions were converted into scores that we could analyse.



For participants only

Walking Programme

James Lee - the exercise instructor - visited people with dementia in the exercise therapy group and helped them start a routine of walking. James recommended:

- Walking 5 times per week for 20-30 minutes.
- Increase speed until the person becomes a little breathless while talking and walking.

Analysis

We used statistics to see if the two groups gave different answers at the end of the study.

We predicted that if walking was effective:

- more people in the exercise group would improve after 12 weeks, compared to those who were asked to carry on as normal.
- Carers of those who exercised would feel more able to cope after 12 weeks than carers of people who were asked to carry on as normal.

What we found at the end of the study	Group	
	Control	Exercise
Improvement of behavioural and psychological symptoms	58%	66%
Caregiver reported coping difficulties	32%	17%

What we found at the end of the study

- Behavioural and psychological symptoms improved in 58% of the control group and 66% of the exercise group.

Although this looks like those who exercised were more likely to have an improvement in their behavioural and psychological symptoms, analysis indicated that this difference may be due to chance.

- Almost twice as many carers in the control group had difficulty coping compared to those in the exercise group. Our analysis showed that this was a real finding and not due to chance.

What we think

It is difficult to explain the results of our study. We found that one out of five people in the exercise group walked as often and at the pace we recommended.

We may have asked too much of the walkers, but there may have been other reasons.

We cannot be sure whether exercise could be helpful. We need to find out if we can better support people with dementia to walk more often at a suitable pace.

Conclusion

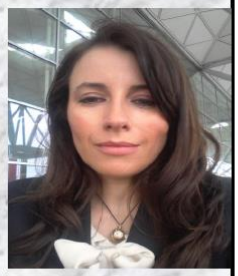
Although the results for this study were mixed, we will use them to help improve care for other people with dementia. We will publish our findings and we will recommend more work to help find out the best ways of supporting people with dementia and those who care for them.

We would like to thank you for your support over the last few years. This work would not have been possible without your generous contribution of efforts and time

Arlinda Cerga Pashoja -Research Worker

Dr David Lowery -Research Manager

Dr James Warner -Principal Investigator



3 Minutes of the Meetings

9.9 3.1 Project Management Meetings

3.1.1 27 March '09

Attendees: A Cerga-Pashoja, R Bhattacharya, D Lowery, J Warner

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Aims, Scope & Membership of this Group

The project management meeting will meet monthly to discuss and review:

- Protocol
- Recruitment process
- Adverse events
- Troubleshooting
- Analysis
- Audit (regular audit of data entry and security)

It was agreed that longer time will be set aside during analysis stage for number crunching. Contingency meetings will be arranged every three months.

Mark Griffin (statistician) and the exercise therapist will also be invited to attend project management meetings.

Gantt Chart

DL presented the Gantt Chart indicating the project has been progressing within arranged timeframes. ***Action: DL to update.***

Protocol – Final Thoughts Before Peer Review

Diaries were reviewed and suggestions from RB, DL and JW were incorporated. Each dyad will complete one common diary collaboratively instead of separate ones. ***Action: AP to finalize the diaries and send them to the steering group for review and piloting.***

Use of Pedometers was discussed and JW suggested both groups wear pedometers as a way of comparing between and within groups level of physical activity.

Qualitative methods were discussed and it was agreed that qualitative interviews are deemed more appropriate than focus groups for this trial.
Action: AP to finalize the protocol and send to JW for review.

Ethical Application

It was agreed that before submitting the Ethical application the protocol will be sent for peer review. JW suggested a few people that may conduct the peer review i.e. Craig Ritchie, Rob Howard and Roger Bullock.

Action: DL to register EVIDEM-E with the Register of Clinical Trials.

Dissemination, Outputs & Building Awareness

a. DSDC abstract
b. Expressions of Interest Flyer

AOB & Dates of future meetings

Recruitment of exercise therapist and funding for this purpose was discussed. ***Action: DL to follow up.***

Project management meetings will happen on the first Tuesday of each month.

Next meeting: 4th May 2009 at 9.30am at Fitzroy in Totenham Court Road.

3.1.2 04 May '09

Attendees: A Cerga-Pashoja, R Bhattacharya, D Lowery, J Warner

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Minutes, progress and updates from last meeting (DL)

- AP has finalized the diaries and sent them to the Steering Group for review and piloting.

- The Demographic Questionnaire was reviewed in the meeting and it was agreed that version 1 will be used.

- It was decided that pedometers will not be used but heart rate at rest will be measured instead.

- DL has registered EVIDEM-E with the Register of Clinical Trials.

Sponsoring

Action: DL to obtain a letter from John Green stating that CNWL is sponsoring Evidem-E.

Consent forms and access to medical records (AP)

It was agreed that access to medical records will not be sought. Consent and assent forms were reviewed and updated.

Economic Evaluation

Economic evaluation and Client Service Receipt Inventory (CSRI) were discussed.

Action: JW to contact Martin Knapp and clarify utilization of CSRI and economic evaluation.

Recruitment SOPs (AP)

Recruitment SOP's were discussed: it was agreed that recruitment will be made through:

- DeNDRoN
- Evidem Consortium (GPs)
- Memory Clinics and CMHTs

Action: AP to contact Tracy White (Information manager) and obtain mapping for older-people services in CNWL.

Action: DL to contact Tania Burke from DeNDRoN and ascertain what help will DeNDRoN offer us regarding recruitment.

Training and inter-rater reliability (DL)

Action: AP to arrange TUSS training. NPI inter-rater reliability to be arranged.

Kath Lowery has agreed to help us with piloting the study measures.

Randomization Generation

Randomization was discussed and in particular who will carry out the procedure. It was agreed that: a researcher independent of the study team will carry out a computerized random-number generation. ***Action: DL to discuss with Gira Patel.***

Ethics Application (AP)

Action: DL to send the final protocol to Maria Tsappsis from the R&D office and ask for an external review.

Action: AP to finalize the IRAS application, send it to JW and DL for review then send it for ethical approval.

Gantt Chart

DL presented the Gantt Chart indicating the project has been progressing within arranged timeframes. ***Action: DL to update.***

Exercise Therapist

Recruitment of exercise therapist and funding for this purpose was discussed. ***Action: JW to send a contract sample to DL and DL to follow up.***

Next meeting: 7th July 2009, 9.30am, at Fitzroy in Totenham Court Road.

3.1.3 02 June '09

Attendees: A Cerga-Pashoja, R Bhattacharya, D Lowery, J Warner, M Griffin

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Minutes, progress and updates from last meeting (DL)

- AP has piloted the measures with a volunteer from GLH. The screening might take longer than two hours to be administered. Should we break the first contact in two sessions?

- The Ethical Application was submitted to IRAS. The review meeting is set for 9th June 2009. JW to attend. DL and AP may attend as well.

Sponsoring

Action: Letter from John Green stating that CNWL is sponsoring Evidem-E has been obtained.

Economic Evaluation

Economic evaluation and Client Service Receipt Inventory (CSRI) were discussed.

Action: JW to contact Martin Knapp and clarify utilization of CSRI and economic evaluation.

Recruitment SOPs (AP)

Action: AP contacted Tracy White (Information manager) and obtained mapping for older-people services in CNWL.

Action: DL met with DeNDRoN representatives and discussed what help will DeNDRoN offer us regarding recruitment.

Data Analysis

MG went over the data analysis section and confirmed that it is accurate and no changes are needed. Data encryption was discussed and was taken further through CNWL IT department. MG stated that as long as the databases are integrated it doesn't matter which statistical package is used for data entering from AP.

Training and inter-rater reliability (DL)

Action: AP met with Jacqui Morris (Physiotherapist) and practiced TUSS procedures. NPI inter-rater reliability to be arranged.

Kath Lowery has agreed to help us with piloting the study measures. AP is meeting with Kath's team to pilot the measures on 16/07/09.

Randomization Generation

Randomization was discussed and in particular who will carry out the procedure. It was agreed that: a researcher independent of the study team will carry out a computerized random-number generation. ***Action: DL to discuss with Gira Patel.***

Ethics Application (AP)

Action: DL sent the final protocol to Maria Tsappsis from the R&D office and asked for an external review.

Gantt Chart

DL presented the Gantt Chart indicating the project has been progressing within arranged timeframes. ***Action: DL to update.***

Exercise Therapist

Recruitment of exercise therapist and funding for this purpose was discussed. ***Action: JW to send a contract sample to DL and DL to follow up.***

Next meeting: 4th August 2009, 9.30am, at Fitzroy in Totenham Court Road.

3.1.4 01 September '09

Attendees: A Cerga-Pashoja, D Lowery, J Warner, J Lee (exercise therapist)

- **Progress and updates from last meeting**
  - AP has piloted the measures with the IMPS Westminster Team. The length of the screening and baseline interviews seem problematic. The interview schedules were discussed and some of the possible solutions are:
    1. Drop the ZBI from the schedule.
    2. Carry out the NPI on the phone with the carer.
    3. Leave the GHQ (and CSRI?) with the carer for completion. Remind the carer to post them back (reminders: on the day and through telephone follow-ups).
    4. AP to observe JW when administering the NPI and MMSE with clients.
    5. JW to clarify with Martin Knapp the utilization of the CSRI (does it need to be competed at baseline or just at week 6; if so can it be left to be completed by the carer independently)

- **IRAS application and R&G**

  - On 9th June 2009 JW, DL and AP attended the Ethical Application review meeting. A favourable decision was received on 14 August 2009, after making some minor amendments to the protocol.
  - We are still waiting to hear from the Research Governance about the ethical clearance. We still have not had any feedback from the peer review, which was sent out in May. (**Action: DL to follow up**)

- **Recruitment**

- AP has obtained the organizational charts for Westminster and K&C.
- JW is attending a meeting with consultants in the trust where he will give a 10 minute talk about Evidem-E. JW recommended we make contact with consultants regarding recruitment. **Action: JW to give contact details of trust Consultants to DL.**

➢ **Recruitment of study personnel**

- James Lee, the exercise therapist, was welcomed to the team. Intervention phase was discussed. JL has CRB clearance and DL will add this to his contract. DL to finalise JL's contract. JL to keep a written log, which will be countersigned by DL or JW. **Action: DL to identify the independent researchers: IR1 and IR2.**

➢ **Economic Evaluation**

- Action: JW to contact Martin Knapp and clarify utilization of CSRI and economic evaluation.

➢ **DSDC Conference and BMC paper**

- DL has prepared slides for the DSDC conference. DL and AP to attend the conference 14-16 September 2009.
- DL and JW have made comments to the first draft of the BMC paper. **Action: AP to make suggested amendments.**

➢ **BPSD management strategies/Literature Review**

- Erkida Mehmetaj has volunteered to carry out the lit review. She is a psychology graduate who is currently carrying out an MSc in Health Psychology. **Action: DL to follow up.**

Next meeting: 13 October 2009, 1.00pm, at Greater London House.

3.1.5 13 October '09

Attendees: A Cerga-Pashoja, D Lowery, J Warner

- **Progress and updates from last meeting**

1. The ZBI will not be dropped from the schedule.
2. AP to carry out the NPI (baseline) on the phone with the carer.
3. AP to leave the CSRI with the carer for completion. Remind the carer to post them back (reminders: on the day and through telephone follow-ups).
4. AP has observed JW when administering MMSE with a client. AP to arrange observing JW administering the NPI.
5. JW has clarified with Martin Knapp the utilization of the CSRI. **It needs to be competed at baseline and week 12**.
6. JW has attended a meeting with consultants in the trust (who will help us recruit for the trial), where he gave a 10 minute talk about Evidem-E.
7. DL and AP attended the DSDC conference in York, 14-16 September 2009. DL's presentation on EVIDEM-E was very well received.
8. DL and AP attended the CNWL's Older Adults Conference and displayed Evidem banner, leaflets and newsletter.

- **IRAS application and R&G**

  - DL was informed that we need to complete a couple of other forms for R&G approval. SSI and R&D Supplementary Registration Form to be completed and sent as soon as possible to the R&D department (**Action: DL and AP to follow up**)

- **Recruitment of study personnel**

- Two researchers will be joining the Evidem-E team. Alex Bailey who is a trust teaching fellow at St Charls and Ingela Thune-Boyle, a research associate with UCL.

- **AP to update the signature log for the trial.**

➢ **Study Manual**

- AP has compiled the master file for the trial and a draft study manual. JW to go over the master file and make any further suggestions.

- JW to check with Rob what database was used in the Digger trial.

- The team discussed on the pros and cons of collecting the data electronically and in paper form. It was agreed that the data will be collected in paper form then transferred in the electronic databases.

Next meeting: 17 November 2009, 12.00pm, at Greater London House.

3.1.6 09 February '10

Attendees: A Cerga-Pashoja, D Lowery, J Warner

Apologies : Jose Trevino (DeNDrON)

Recruitment

We have recruited one person into the study. AP shared a table indicating the number of invitation packs sent to teams and to patients. There is a big discrepancy i.e. teams not sending packs to patients. JW suggested we follow up actively with teams and attend their meetings.

- DL suggested we recruit through the PCRN. **Action: DL to contact Lennis Lewis and enquire about obtaining R&D approvals from PCTs.**
- Recruitment to be discussed in the Steering Group meeting
- JW suggested we write an article for 'Living with Dementia' magazine. **Action: AP to contact Rachel Doeg enquiring if we can publish an article in Alzheimer's Society journal Living with Dementia.**

Databases

We have currently set up the databases in Microsoft Access. The forms in Access give the opportunity to record the data in a way that is similar to the hard copies, thereby reducing entry errors. **Action: AP to meet with Mark Griffin to discuss databases.**

Files and documentation

JW asked if the management team can gain access of a shared drive where all study documentation can be filed. **Action: AP to enquire with David Gulbrandsen about establishing a shared drive for Evidem-E management team.**

3.1.7 12 January '11

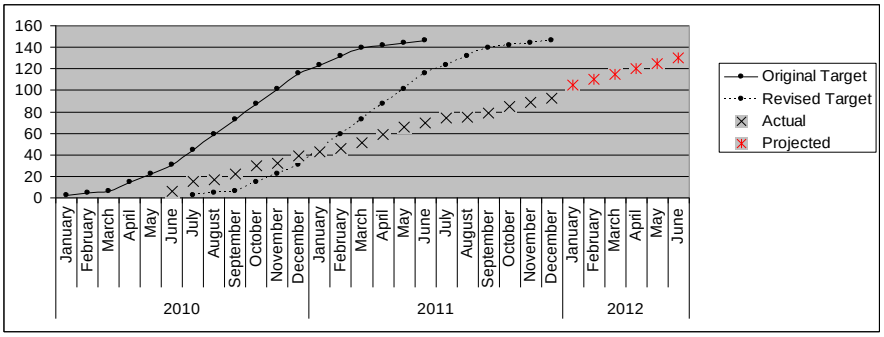
EVIDEM-E

Exercise as a Therapy for Behavioural & Psychological Symptoms of Dementia

James Warner, Arlinda Cerga-Pashoja & David Lowery

Central and North West London NHS Foundation Trust

EVIDEM
www.evidem.org.uk



NIHR: Programme Grant for Applied Research

Hosted by **Central and North West London NHS Foundation Trust**

Collaboration with University College London, King's College London, St. George's, University of London, Kingston University, London School of Economic and Political Sciences and The University of Hertfordshire

	WLMHT	CNWL	BEH (demreg)	Self referrals	Demreg Total	Total
Invited	324 (178D/146C)	303	24		202	651
Recruited	33 (31 D/2C)	25	4	2	34	64
Ineligible	10 (6D/4C)	18	2	2	8	32
Declined	68 (39D/14C)	46	12	3	51	131

9.10 3.2 Steering Group Meetings

3.2.1 23 February '09

Central & North West London NHS Foundation Trust, Greater London House, Boardroom

Attendees: Steve Iliffe (SI), James Lee (JL), Clare Leonard (CL), David Lowery (DL), Sue Ricketts (SR), Lyn Strother (LS), Fiona Waters (FW), Jane Wilcock (JW).

Apologies: Rahul Bhattacharya (RB), Sandra Brookes (SB), Mark Griffin (MG), Craig Ritchie (CR), James Warner (JR).

- **Welcome & Introductions**
- DL welcomedand thanked attendees – Apologised for not sending out the agenda and re-iterated the purpose of the meeting
- DL invited the group to introduce themselves

- **Previous Minutes**
- DL took the group through the minutes of the previous meeting point by point. – The group agreed that they were an accurate reflection of the discussion at the November meeting.
- At point 2 DL reminded the group that we had all agreed that the SG would benefit from the inclusion of a person with dementia. – LS nominated a potential representative, described his background to the group and agreed he was to be invited.

Action: LS to approach potential new member on behalf of SG

Chair & Membership

DL thanked the group for the input at the previous meeting and advised

that as a result the protocol had undergone significant development

DL informed the group that a sub-group of the EVIDEM management team had held a one of meeting to discuss the protocol and provide some critical advice. Two key points had been raised in reference to the SG: 1) The Chair of the group should be independent and 2) The membership for the group should hold a majority that do not have a direct interest in the outcome of EVIDEM

SI elaborated that the SG should have a responsibility for reporting if anything goes wrong and so it will be important that the Chair and the membership have an independent majority. SI further emphasised that it would be important that the chair have experience of leading formal meetings

DL nominated CR as Chair and CL as Vice Chair – The group agreed that these were good nominations – CL agreed so long as adequate guidance of the role would be provided

A count of the membership revealed that the ratio of independent member/non-independent members is 6/7 – JW offered to alter her role to non-participant observer, and DL reminded the group that should candidate identified by LS agree to join, the ratio would alter to 7/6. – The group agreed that this was satisfactory

During this discussion SR also expressed that she had felt the outcome of the previous meeting had been negative as the group had provided a significant amount of criticism – DL reminded the group that this had been overwhelmingly constructive and as a consequence had led to some positive advancements in the protocol. DL further emphasised that by opening the project to criticism at an early phase, the researchers would have an opportunity to tailor the design of the project to help avoid such criticisms at its conclusion.

Action: DL to approach CR to ascertain his willingness to fulfil this

role

Infrastructure – Appointments & Adoption

DL informed the group that we have applied for adoption by the North Thames Dementia and Neurodegenerative Diseases Research Network and that this network would likely be able to support the project with recruitment of participants.

DL informed the group that the trust had successfully appointed a research worker specifically for the project and gave the group details of the post and the successful candidate.

Methodology - Revised Design & Protocol

DL provided the group with a handout that included several figures and tables that summarize the proposed design. DL worked through the document asking for questions and comments

CL advised that the FRAT is good but instructions for TUG are sometimes too complex even for those with mild cognitive impairment – Described the '180 turn' as an alternative: 5-6 steps ok; 9 and above is indicative of someone who is at high risk of falling. CL can provide evidence

Another alternative – 'time steady stand test' - Can the participant stand unaided for 1 minute? CL

JL suggests that it will be important to know whether the participant will be able to perform the intervention or not – JL Described the 3 min 'step test'

CL – Most of population recruiting from are on multiple meds, have cardio vascular problems and so would be ruled out by the FRAT

FW – The home step test might be beyond the capabilities of potential participants on grounds of co-ordination

SR – Everyone will have different ability, so should measures be

individualized- yes

DL – reminded the group that at this point we were trying to determine whether to exclude someone as a person who is of high risk of falls – Should we:

Exclude on basis of either FRAT & 180 turn; or just the 'time-steady stand'?

CL - 180 turn may be adequate on own – if fail 1 minute standing they should be excluded – no matter what scores are on other assessments. To be completed without aids. There is a greater success rate if the participant is unaware of what they are being assessed for and are distracted

SI – The FRAT is nationally used and would allow description of the population

DL – Exclusion on the basis of one minute standing test and FRAT collected for completeness - agreed

DL – The participants' GP would be asked if they considered the participant unsuitable for the intervention on the basis of any existing cardio-vascular/pulmonary complaints

DL – Do the group want to assess for vital signs? – yes

JL asked if we were to include any operational assessment and criteria for exclusion based on sensory impairment – The group decided that the carer would be asked an over-arching question on whether they felt the person could participate in the intervention

DL – Highlighted that the protocol development group had advised that the risk assessments should also be undertaken for the carers as they would be performing the intervention also.

The group decided that utilizing the step test might be beyond some of the participants and so offered alternatives of attaching a heart rate monitor, or a pedometer.

The use of a pedometer was further discussed. JL – the more

expensive they are the more sensitive they are – this will be important within the population we're recruiting from with limited mobility; Pedometer also good for motivation to persevere with the intervention. Suggested the therapist might test out the accuracy of the pedometer with participant on 1st visit- DL advised that this would be difficult.

JL described the RPE and the group agreed that the target rate should be amended to 65%-70%, and that the participants should be encouraged to maintain this rate throughout the trial while extending the distance they cover.

SI - need to measure the dose and increase if you can.

Environment and terrain will have an impact, but the important point will be the RPE.

DL asked the group if the therapist should suggest a minimum time/distance – The group agreed that it would be important to record these but not set a minimum

There followed some discussion on the diaries, their purpose and who would complete them – the group were of the opinion that the diary should be structured in order to facilitate completion including the RPE – further, there should be separate diaries for carer and PWD to be completed individually where possible

DL described the assessment schedule – and drew the group's attention to the potential for accidental 'unblinding' the trial. DL informed the group that they had devised two strategies to minimize this risk 1) The use of a separate researcher who administers the assessment via a telephone and 2) the completion of a scale by research workers to assess for knowledge of participant groupings – The group agreed these were good strategies and that there would be little other way in which to minimize this risk

Action: 1. JL to investigate accuracy of pedometers and report

back to the group.

2. DL to amend protocol to reflect today's discussion and distribute to the group

Time line

The group worked through the projected timeline and the following additions were suggested: 1) the SG should see the final worked protocol by no later than May 2009 and this will be done electronically. 2) Ethical and governance applications should be made by no later than June 2009 – If this is not the case, an emergency steering group should be convened. 3) Otherwise the steering group should next meet in September 2009. The primary topic for that meeting will be recruitment.

Action: DL to distribute final worked protocol ASAP

- AOB and date of next meeting
- NO AOB and date of next meeting is as above

3.2.2 13 October ‘09

UCLH, Room 5

Attendees: Craig Ritchie (CR)(Chair), Arlinda Cerga-Pashoja (ACP), Mark Griffin (MG), Clare Leonard (CL), David Lowery (DL), Lyn Strother (LS), Jane Wilcock (JWk) James Warner (JWr),

Apologies: Rahul Bhattacharya (RB), Sandra Brookes (SB), Steve Iliffe (SI), James Lee (JL), Sue Ricketts (SR), Fiona Waters (FW),

---

- **Welcome & Introductions**
- CR welcomed and thanked attendees
- CR introduced himself to the group

- **Previous Minutes**
- CR took the group through the minutes of the previous meeting point by point.
- – LS informed the group that she was no longer comfortable with inviting her suggested person to the group due to circumstances surrounding that person’s experience of dementia. The group agreed that LS had made a wise decision. CR agreed to take this forward with his contacts.
- - CR asked and DL confirmed that the project is DeNDRoN adopted. CR suggested contact with Tania Burke to support the project recruitment
- - DL explained the decision not to use the pedometer: invasiveness, lack of sensitivity within our target population; and that we decided to use a proxy measure of heart rate at rest
- - DL informed the group that the project had received ethical approval in July and that we were working with the relative trust to gain final governance approval. This involves completing two forms, after which the approval should take only a matter of days.

- - There followed some discussion of Site Specific Information forms and recruitment in Primary Care Trusts. CR advised the team to contact Jo Burns at Greater London Primary Care Research Network.
- - There was some discussion on reporting accruals to the Comprehensive Local Research Network, JWk advised on processes and justification including recuperating service support costs for NHS Trusts; and CR described current policy on division of monies where complex research governance arrangements were in place
- - CR offers open assistance to facilitate approvals for the study
- - JWr informs the group that the project has also been registered with www.clinicaltrials.gov and describes the purpose of this

Action: DL to discuss possible network support with Tania Burke (DeNDRoN) and Jo Burns (PCRN).

CR to seek a for person with dementia representative for the SG

- **Infrastructure**
- DL updated the group on study personnel
- DL welcomed Arlinda Cerga-Pashoja (ACP) as research worker dedicated to the EVIDEM E project. JWr informed the group that ACP has registered to read for a PhD as part of this work with UCL.
- DL informed the group of the appointment of a research worker, Ingela Thune-Boyle, who is to work across two EVIDEM projects with 20% of her time specifically devoted to EVIDEM-E. Ingela is likely to collect Neuro-Psychiatric Inventory data by telephone.
- Also the management team decided to commission James Lee to provide the intervention part of the project on a consultancy basis. DL explained that JL would not be employed by CNWL, but rather would provide the service according to a detailed payment structure

- **Methodology**
  - DL tabled the scripts that form part of the trial master file.
  - The group agreed that the documents appeared to be fairly comprehensive, but the following issues were raised:
  - - LS The understanding and use of terms need to be checked
  - - JWk The use of the term dementia – JWk referred to the EVIDEM agreement to use 'memory problems and difficulty with thinking'
  - - CR Does the SG need to sign this off?

Action: ACP to Pilot the Scripts and the Project Management Group is to sign them off when happy they are fit for purpose

- **Outputs – Dissemination Plan**

DL informed the group that the project had produced several outputs to date including a poster at DeNDRoN conference in 2008, a paper in the Journal of Integrated Care in early 2009 and a presentation to the Dementia Services Development Centre's 2009 International conference. DL highlighted that there had been some important aspects of our experiences during the design and development process that were worthy or reporting. DL informed the group that ACP is drafting a manuscript for submission to BioMed Central Trials. DL also stated that it was his opinion that the SG membership should be included as authors given their contribution to the study design. JWk and JWr agreed with this position

There followed some discussion on authorship policy, the role of the steering group with regard to outputs and the appropriateness of appearing as authors. CR clarified the SG role as 1) monitor, to ensure the adequate reporting of results; 2) Arbitrator, where disputes arise in authorship and acknowledgement.

CR/LS/CL all stated that they did not expect authorship, and would leave this decision to the Project Management Group.

Action: DL to draft and table an authorship policy at the next SG

Recruitment

DL reminds the group of the three recruitment routes: 1. CNWL clinical teams; GP practices recruited to the EVIDEM programme; and North Thames DemReg. CR gave a description of NT DemReg its purpose, and current status. CR also suggested discussion with Tania Burke, and that Ali Featherman would be in an ideal position to support recruitment. DL explained EVIDEM's existing link with NT DemReg, through the operation of the pilot recruitment to the registry via GPs.

LS asked if the recruitment was to be conducted of people using day centres

- JWr informed the group that although participants wouldn't be excluded on the basis of living within care homes, these wouldn't be targeted as a specific source of recruitment
- DL/CR raised the issued of methodological issue of recruitment strategy. MG highlighted that it would be impossible to obtain a 'representative' population for any Randomized Control Trial

- **Time Line**
  - JWr described a sigmoidal accrual profile the management group has approved for the recruitment targets – CR requested that this be provided to the SG for the next meeting to help them monitor the recruitment progress
  - CR inquired about data quality – MG described the double entry process – CR suggested the management group talk to CTU

- **AOB and date of next meeting**
  - NO AOB and date of next meeting is as above

3.2.3 25 May '10

10:00 – 12:00

UCLH, 250 Euston Road

EVIDEM- E: Randomized Control Trial looking in the Impact of Exercise on Individuals with Dementia and their Carers.

Attendees: Craig Ritchie (CR)(Chair), James Warner (JWr), Natalie Fox (NF), Kalpa Kharicha (KK), Arlinda Cerga-Pashoja (ACP), David Lowery (DL),

Apologies: Steve Iliffe (SI), Clare Leonard (CL), Fiona Waters (FW), Mark Griffin (MG), James Lee (JL), Lyn Strother (LS).

Did not attend: Sue Ricketts (SR)

1) Welcome & Introductions

- CR welcomed and thanked attendees
- As there was an imbalanced representation from the independent members of the steering group, it was discussed whether to go ahead with the meeting or reschedule it for another date. CR proposed to carry on with the meeting but to avoid making any important decisions at this instance. JW suggested AP contacts Chris Bumstead (CNWL, Clinical Governance) regarding PPI involvement. KK suggested having a look at the Evidem self-referral list to identify possible PII representatives.

2) Previous Minutes

- CR took the group through the minutes of the previous meeting point by point. Previous minutes represented an accurate reflection of the meeting and were agreed by the group.

o Previous Actions

- DeNDRoN -ACP & DL met with Jose Trevino (DeNDRoN) on 26/02/2010, where Jose stated that he would enquire with his leads if he could assist

recruitment for the Evidem-E trial. Jose said that the Evidem studies would be included in the DeNDRoN pathways document. DL provided Jose with the information describing the Evidem studies. However, later on Jose informed DL and ACP that the Evidem studies have been dropped off the brochure. Jose said that he did not know the reason why. Jose also informed DL and ACP that he has been told by his managers that he cannot assist Evidem-E with recruitment. Action: CR to email Kath Mummery to clarify Evidem's position with DeNDRoN. DL to contact DeNDRoN manager and enquire about DeNDRoN's support to Evidem-E. CR to invite a representative from DeNDRoN to the next Steering Group Meeting.

3) Recruitment

- CNWL

Recruitment in CNWL continues to be slow. Six people have been recruited into the trial since December 2009. ACP & DL are actively visiting teams in CNWL and providing clinicians with information about the trial as well as information packs for their clients/patients. NF suggested raising the issue in her monthly meetings with the nurse leads. Action: ACP to provide NF with information regarding packs sent to teams and patients. ACP and DL to attend the next meeting with NF and admiral nurses. NF, JW and CR to email all trust OA clinicians about trial importance and recruitment.

Incentivising- CR enquired whether it is possible to present the champion team, who sends the most packs to participants, with a percentage of accrual rates from the money that goes to the trust. Action: JW to discuss with John Green.

- WLMHT

ACP has completed a new SSI form, adding West London Metal Health Trust as a new participant identification site. ACP does not require an honorary contract as the R&D office will provide her with a Letter of Access as soon as all the checks have been carried out. The first SSI form was not accepted by the R&D office as there was no ample information in the form regarding the research team in

WLMHT. Discussions ensued regarding who will be part of the team in WLMHT, and about JL contract and indemnity. CR thinks That ITB and JL do not need to be included in the SSI. ACP and DL have met with Dr Regan (WLMH site PI) and her team, who are ready to recruit for the trial. Action: CR to contact Lynis Lewis to clarify whom should we include in the SSI as working at the WLMHT site.

- Registry

DL informed CR that SI has emailed us the agreement letter regarding accruals. DL will email the letter to CR. Lisa Curry, the present manager can help with recruitment. CNWL will recruit for Demreg and Lisa Curry will act as coordinator for the site in the meantime. Action: DL and ACP to contact Lisa regarding recruitment for the trial. CR to ask Lisa to meet with JW regarding championing in his clinic to recruit for Demreg.

- Other

CR suggested exploring recruitment with other trusts such as Barnet, Enfield and Haringey. Action: JW to discuss new recruitment pathways with Liz Sampson from Barnet, Enfield and Haringey NHS.

4) Databases

ACP- The Access database was abandoned as data collection in it seemed problematic. Another database was set up in Opinio, UCL based database. This was abandoned as well as it presented limitations in regards to double data entry. MG and ACP met and the team agreed to use Epi-data. Action: ACP to set up a new database in Epi-data, with MG's help.

5) Timeline

DL explained that the study recruitment is running fairly late therefore, there is a slippage in timeline. CR set a target of having recruited a total of 16 participants in the trial by September.

6) AOB and date of next meeting

- Information sheets- ACP & DL were asked by clinicians of a team in CNWL to replace the word ‘dementia’ with ‘memory difficulties’. This was discussed in the group and it was decided that considering the forms were approved by the Ethics Committee, the wording remains the same.

- ACP & DL- during a visit at IMPS team the physio lead talked about a validated intervention where walking is part of the intervention. Can we recruit from this group? Action: We can recruit after the client has been discharged from the intervention.

- Adverse Events- One of our participants has, unfortunately, passed away. The death was unrelated to the trial. We have devised a letter to the GP to make sure the death was unrelated and to enquire whether there are any concerns about the trial. Action: AP to email the letter to CR.

- JW thanked the group for a very productive meeting that filled him with enthusiasm.

- The date of next meeting is 21 September 2010, 10:00-12:00. Venue to be booked

3.2.4 21 September ‘10

10:00 – 12:00

Cruciform Building (UCL), Gower St, Room B.01

Attendees: Craig Ritchie (CR)(Chair), Kalpa Kharicha (KK), Arlinda Cerga-Pashoja (AP), David Lowery (DL), Fiona Waters (FW), Sylvia Gupta (SG).

Apologies: James Warner (JW), Steve Iliffe (SI), Clare Leonard (CL), Mark Griffin (MG), Lyn Strother (LS), Natalie Fox (NF).

Did not attend: Sue Ricketts (SR)

James Lee (JL) is no longer required to attend these meetings

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- **Welcome & Introductions**
- CR welcomed and thanked attendees

- **Previous Minutes**
- CR took the group through the minutes of the previous meeting point by point. Previous minutes represented an accurate reflection of the meeting and were agreed by the group.

a. Previous Actions

- **DeNDRoN**: CR has emailed Dr Cath Mummery to clarify Evidem's position with DeNDRoN. DL met with DeNDRoN manager and enquired about DeNDRoN's support to Evidem-E. In the meeting it was agreed that we will receive support from DeNDRoN, and the Evidem studies will be included in its brochure.
- **Recruitment:** AP has provided NF with information regarding packs sent to teams and patients. AP and DL attended the monthly meeting with NF and admiral nurses. The meeting went generally well, although some of the nurse leads seemed somewhat resistant to recruiting for the study.
- **NF, JW and CR have emailed all trust OA clinicians about trial importance and recruitment.** This seems to have raised awareness and

there has been an increase in referrals as a result.

- **WLMHT:** AP contacted the R&D department and updated the CSRI accordingly to include the WLMHT site. AP has also been issued with a Letter of Access for WLMHT.
- **Registry**: AP has contacted Lisa and recruitment for the trial from the registry has commenced.
- **Databases:** AP has set up a new database in Epi-data, with MG's help.
- **Timeline:** CR's target of having recruited a total of 16 participants in the trial by September 2010 has been met. We have recruited 19 people so far.
- **Adverse Events**: AP has emailed the adverse events letter to CR**.**

- **Recruitment:**

AP updated the group on accruals, expressions of interest and recruitment rates. AP also feedback about different networks that have been supporting recruitment for Evidem-E:

- **North London Mental Health Research Hub** has been supporting recruitment through two CSO's: Amy Murphy and Antoinette McNulty. They have been actively meeting with OA teams in both CNWL and WLMHT, supporting the teams identifying eligible candidates and sending information packs to those eligible.

  FW said that the CSOs have visited her team and she believes way of recruitment works very well.
- **Demreg:** AP has been sending invitations to people in the registry. CR explained to the group what Demreg is. CR raised his concern about people in the registry being contacted more than once through our different recruitment paths: from AP and from the CSOs. **Action: AP and CSOs to make sure to use Demreg to exclude people that have been already invited into the study. CSOs need to have research passports for both CNWL and WLMHT.**

- **Living with Dementia and self-referrals.** Our publication in Living with Dementia magazine arose interest about the trial and we received self-referrals as a result, although most of them came from out of our geographical catchment area. SG suggested we consider posting on Talking Point Forum, which is part of Alzheimer's Society website. **Action: DL to contact Catherine Watt from the Alzheimer Society and to prepare material for publication on the forum.**

- **Reporting and Dissemination**
  - **Newsletter:** Content and frequency was discussed. It was agreed to produce it twice annually. CR suggested we ask people who have finished the trial about their experience in it. DL suggested we introduce the Steering Group members in our next newsletter.
  - **Evidem-E Output strategy**: DL discussed the themes for publications. CR enquired if there is a Cochrane review for BPSD and exercise and asked if would consider one.
  - **Focus Group**: DL and AP reported the attempt to run a few focus groups with professionals in order to explore barriers to recruitment and ways how to overcome the above. Although the groups did not happen as planned, we managed to hold one group and gathered some important views from clinicians. DL has prepared a draft, which we aim to publish as a letter in the International Journal of Geriatrics.

- **What is it like to be a control participant?**

  Two participants have expressed dissatisfaction about being allocated in the control arm of the trial. AP and DL have amended the scripts to emphasize the probability of being allocated in the control arm. CR asked if could investigate motivation for participation in research prospectively, as people enter the trial and at the end of it.

  DL explained that one participant on the control arm has asked to come out

of the trial then re-enter it in order to receive the intervention. The group agreed that this would affect study's rigidity and we can not take this approach. CR asked if we could offer exercise intervention at the end of the trial to people in the control group. DL explained that financial constraints do not allow us to provide intervention individually, but we may be able to provide a group approach. On the other hand, we are not sure if the intervention is beneficial and it would be presumptuous to offer intervention while we are still trialing this.

- **Time line**

  DL has recalculated target numbers. We need to recruit 10 dyads a month, which puts us in a tight time schedule. KK advised that we take into account that the overall program ends in July 2013 and we need to contribute to its final report.

  KK asked if we can recruit from primary care. CR thought recruiting from primary care can be both time and effort consuming and most of the people diagnosed with dementia in primary care are being seen in secondary care as well.

- **AOB**

  - SG emphasized the importance that different dementia subtypes react differently to interventions. People also deteriorate at different rates and experience different symptoms. SG asked how does the study account for this. CR explained that Evidem-E is a big trial with a large sample size, which should account for such differences. AP talked about the tools we use to capture data such as NPI, qualitative interviews and diaries. SG also asked about the effect of medication, and how we monitor this. AP explained that we monitor medication at baseline, week 6 and week 12 into the trial. The group suggested we also monitor it at week 26. **Action: AP to send SG copies of the NPI and the diary. AP to add medication at 26-**

week interview.

- DL enquired if the present Steering Group membership is working. **Action: CR to contact Natalie Fox and Sue Ricketts to clarify their future involvement with the group.**

- **date of next meeting**
  14 December 2010, 10:00-12:00, Greater London House, Boardroom.

3.2.5 14 December '10

10:00-12:00

Greater London House, Boardroom

Attendees: Craig Ritchie (CR)(Chair), Kalpa Kharicha (KK), Lyn Strother (LS), Clare Leonard (CL), Arlinda Cerga-Pashoja (AP), David Lowery (DL), Fiona Waters (FW)

Apologies: James Warner (JW), Steve Iliffe (SI), Mark Griffin (MG), Natalie Fox (NF), Sylvia Gupta (SG).

- **Welcome & Introductions**
- CR welcomed and thanked attendees

- **Previous Minutes**
- CR took the group through the minutes of the previous meeting point by point. Previous minutes represented an accurate reflection of the meeting and were agreed by the group.

a. Previous Actions

- AP had advised the MHRN CSO's to make sure there are no duplicate invitations to the study, thus avoiding overburdening people. CSO's have valid research passports for both CNWL and WLMH.
- DL has contacted Catherine Watt from the Alzheimer Society and published material on the web-based Talking Point Forum.
- AP has sent SG copies of the NPI and the diary.
- AP has added medication info at 26-week interview.

- **Recruitment**

  - AP updated the group on recruitment numbers, expressions of interest and recruitment rates: 38 participants recruited so far, 2 – waiting to be randomized, 22 - not eligible, 70 - declined participation. DP presented

a chart of projected and achieved recruitment figures. Currently we are on target.

AP and DL feedback about different networks that are supporting recruitment for Evidem-E:

- **NHS Clinicians:** Amy Murphy and Antoinette McNulty from MHR have been recruiting actively from CNWL and WLMH. There has been an increase in recruitment figures, however there is a risk these figures may start falling again with the exhaustion of the present resources. **Action: AP to send NF recruitment information broken down per each CNWL team.**

  AP has received a list of 111 people with dementia from Dr Regan (WLMHT) and has been sending information packs to everyone on the list.

  James Warner is negotiating with CNWL in order to generate a central list of everyone in the trust with a diagnosis of dementia.

- **Care and nursing homes**: A few independent care homes have expressed an interest to participate in the Evidem-E study. However, there is a concern over contamination of intervention and especially regarding the control group in such settings. The group suggested we should pursuit recruitment with the care homes, but should proceed slowly and carefully, i.e. just a couple of participants at a time.

- **East London Mental Health Trust:** We may expand our recruitment to ELMHT. Rahul Bhattacharya who is a member of the study team is exploring with the trust the opportunity to set up a research site for Evidem-e within the trust.

- **DeNDRoN:** As mentioned previously we are very grateful to the CSOs from MHRN for their invaluable support with recruitment. This support is to end and is being presently transferred to Jonathan Anderson a CSO from Dendron. Jonathan will provide support for Evidem-E recruitment for two day a week. He is presently setting up IRAS application to include Barnet Enfield and Haringey NHS Trust as a patient identification site.

- **Demreg:** AP has sent invitation packs to 88 people on Demreg. Unfortunately the reponse has been disappointing: **3-recruited, 3-not eligible, 10-declined, 72-did not reply**. CR explained that Sarah Gregory will be helping to populate the registry from CNWL and demreg numbers should increase. CR asked if it would be difficult for AP to manage recruitment single-handed. This has not been a problem so far, we'll monitor progress.

- **Self referrals :** FW inquired about Talking Point publication and whether it raised to interest and self-referrals. DL said that he has posted a blog but no one has made any comments about it. LS suggested that the blog may need rewording and volunteered to contribute to this. **Action: DL to revise Talking Point blog.**

- **Reporting and Dissemination**

  - **Newsletter** was circulated and amendments were suggested in relation to a typo.

  - **Focus Group** write up has been accepted as a letter to the editor, by the International Journal of Geriatric Psychiatry.

- **SAPC:** AP is presenting at the Society for Academic Primary Care conference in Madingley, Cambridge. The presentation is about Evidem-E recruitment challenges.

- **BPSD review paper** will be submitted soon for publication

- **Qualitative work**
  - AP presented topic guides for interviews with control and intervention participants, and raised the question: when should we start gathering the qualitative data. Considering AP is blinded to group allocation, she can only gather such data from participants she is already de-blinded. CR asked if we are excluding participants we get deblinded from. The answer is No. Considering this is a single blind, pragmatic trial we expected for deblinding to happen. AP gave examples of cases when she has been deblinded.
  - FW suggested if the qualitative interviews can be done by someone else, not AP, on the telephone. **Action: The group suggested this methodological issue needs to be raised with the trial management group.**
- **Date of next meeting**

  18 March, 15:00-17:00

  Boardroom B
  Greater London House,
  Hampstead Road
  London NW1 7QY

3.2.6 18 March '11

15:00-17:00

Boardroom B, Greater London House, Hampstead Road, London NW1 7QY

Attendees: Craig Ritchie (CR)(Chair), Steve Iliffe (SI), Clare Leonard (CL), Arlinda Cerga-Pashoja (AP), David Lowery (DL),

Apologies: James Warner (JW), Kalpa Kharicha (KK), Natalie Fox (NF), Lyn Strother (LS), Sylvia Gupta (SG), Fiona Waters (FW).

- **Previous Minutes**
- CR took the group through the minutes of the previous meeting point by point. **Amendments: In page 2, paragraph 6 change LS to SG.**

a. Previous Actions

- AP has sent NF recruitment information broken down per each CNWL team.
- DL has revised the Talking Point blog according to SG suggestions.

- **Recruitment**

  - AP updated the group on recruitment numbers, expressions of interest and recruitment rates: **48 participants recruited so far, 27 - not eligible, 108 - declined participation**. A chart of projected and achieved recruitment figures was presented. Currently we are lagging behind the revised target numbers.

    AP and DL feedback about different networks that are supporting recruitment for Evidem-E:

  - **NHS Clinicians:**

- **CNW**L- JW will identify patients to invite to the study from his workload and start sending invitation packs to his patients.

- **WLMHT**- AP has been visiting Brentford Lodge and several recruitments have happened as a result. DL said that from his discussions with Sujoy Mukherjee, he suggested to visit other memory clinics in WLMH. **Action: AP to arrange to meet with Sujoy.**

- **East London Mental Health Trust:** Agreements are with John Green to be signed. Preliminary advisory sessions for awareness raising with clinical teams are scheduled for early April. KK and DL to organize these sessions.

- **DeNDRoN: Barnet Enfield and Haringey NHS Trust have been added as patient identification site.**

- **Demreg: Barnet Enfield and Haringey NHS Trust have been added as patient identification site. Recruitment from WLMHT is going very well.**

- **Self referrals:** DL has revised the Talking Point blog but it has not raised any interests as yet.

- **Housing 21:** is an organisation that provides care, health and housing services for the elderly. Can we recruit from Housing 21? It was agreed that we can visit tenants' meetings and discuss our study with tenants. Any referrals as a result with be considered as self-referrals. **Action: DL to attend visits at Housing 21 homes**.

- Evidem-ED: SI agreed that people who finish their participation with

Evidem-ED can be invited to Evidem-E. This will be done during their final interview that Ingela is presently conducting. SI said that there are about 70 people that may be approached**. Action: SI to clarify with Ingela.**

- **GP's:** SI asked if we can recruit from the primary care and work through issues that may arise ethically and practically. Evidem-ED has worked with 20 GP practices and they have agreements in place for these practices. **Action: SI to discuss with Priya regarding involving GP surgeries in Evidem-E recruitment.**

- **Press**: SI asked if we can advertise to the press. DL explained that he has been approached by BBC One about being interviewed in regards to exercise and dementia subject.

- CR asked whether there was any possibility for the study to be extended. Unfortunately, this is not possible.

- **Reporting and Dissemination**

  - **Summer School:** CNWL has committed to hold an event mainly for CNWL staff on Friday 7 October. It is planned that this year Evidem themed events will be delivered to Band 7 clinicians.

  - **Dementia Care Congress:** DL asked about ideas regarding our presentation at the Dementia Care Congress. CL suggested to set up several scenarios such as getting people to walk up and down the room, give them multiple tasks to carry out etc.

AOB: Fiona Waters has left her position with CNWL and is no longer able

to participate in this group.

- **Date of next meeting**

  6 October 2011

  12:00-14:00

  Room 3

  Greater London House, Hampstead Road, London NW1 7QY

3.2.7 6 October '11

Boardroom B, Greater London House, Hampstead Road, London NW1 7QY

Attendees: Craig Ritchie (CR)(Chair), Steve Iliffe (SI), James Warner (JW), Clare Leonard (CL), Arlinda Cerga-Pashoja (AP), Sylvia Gupta (SG)

Apologies: Kalpa Kharicha (KK), Lyn Strother (LS), David Lowery (DL), Alison Gordon (AG)

- **Previous Minutes**

- CR took the group through the minutes of the previous meeting point by point.

a. Previous Actions

- AP has tried to arrange to meet with Sujoy Mukherjee, PI for WLMH, but has been unsuccessful.
- DL has visited the Housing 21 homes and we've recruited a few participants as a result.
- SI confirmed that Evidem-ED follow-ups are about to conclude and we shouldn't be expecting many more referrals from it.

- **Extension of Evidem-E**

The trial has been granted a non-cost extension from NIHR for six months. Therefore we will be recruiting until June 2012. CR advised that we should inform Dendron as well as the Ethics Committee about the extension. **Action: AP and DL to inform the above bodies about the**

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trial extension.

JW explained that trial's dropout rate has been 10%, which is lower than the 20% predicted rate used when power calculations were carried out. JW said that when using the actual dropout rate the recruitment target is 120 dyads. JW asked the group if we should keep recruiting beyond 120. CR said that as there is no risk involved we should carry on recruiting until we meet the initial target of 146 dyads or until the recruitment end date.

- **Recruitment**

  - AP updated the group on recruitment numbers, expressions of interest and recruitment rates: **80 participants recruited, 44 - not eligible, 137 - declined participation**. A chart of projected and achieved recruitment figures was presented.

  - **NHS Clinicians:**

  - **CNWL**- JW has asked his PA to send invitation packs to his patients. AP has not received any interest so far. **Action: JW to ask Sheila how many packs have been sent out.**

  - **WLMHT**- Unfortunately, AP has not been able to contact Sujoy Mukherjee or arrange visits to his memory clinic. However, referrals from Brentford Lodge have been coming regularly, especially from Demreg.

  - **East London Mental Health Trust:** Recruitment at this site is going very slow. We have only recruited one dyad from this site.

- **Demreg: Luton has been added as patient identification site. Recruitment to start soon.**

- **Housing 21:** DL has attended a few homes in the scheme and five dyads have been recruited as a result.

- **Evidem-ED:** Four dyads have been recruited from Evidem-ED. Ingela said that we shouldn't expect any new referrals.

- **Reporting and Dissemination**

  - **Summer School:** CNWL has committed to hold an event mainly for CNWL staff on Friday 7 October. It is planned that this year Evidem themed events will be delivered to Band 7 clinicians, who will then cascade the information to their teams.

  - **Dementia Care Congress:** DL is presenting a session called*: Providing People with Dementia and their Carers with Tools to improve their levels of Physical Activity*.

  - **Chartered Society of Physiotherapy Annual Congress "Liverpool":** DL and JL are co-presenting the pilot video kit in a session called: *Physical Activity as a tool for improving outcomes for people with dementia: current clinical guidelines, research recommendations and gaps in our knowledge.*

  - **Gerontological Society of America Conference:** Our abstract has been accepted for presentation at The Gerontological Society of America's 64th Annual Scientific Meeting. The title of the session is*:*

Factors Affecting Clinician Engagement in Recruitment for Dementia Trials.

- AP has successfully converted from MPhil to PhD status.

- CR stated that the trial's dissemination strategy is very impressive.

- **Date of next meeting**

15 March 2012
12:00-14:00

3.2.8 15 March '12

12:00-14:00

Alexander Fleming, Stephenson House, 75 Hampstead Road, London NW1 2PL

Attendees: Craig Ritchie (CR)(Chair), Clare Leonard (CL), Arlinda Cerga-Pashoja (AP), Gill Sargeant (GS), Jane Wilcock (JWC)

Apologies: Steve Iliffe (SI), James Warner (JW)

Previous Minutes

CR took the group through the minutes of the previous meeting point by point.

Recruitment (AP)

Update on recruitment rates. CR said that WLMH will have a last drive to recruit as many participants as possible. Claudia Wald, consultant at Westminster Memory Service is very keen to recruit.

J WC enquired about who is classified as 'self-referred'. AP and DL explained they include participants from Housing-21 and Memory Cafés.

Reporting & Dissemination (DL)

Video toolkit and Alzheimer's Society bid (DL)

DL talked about his presentation at Dementia Care Congress where the video tool kit was piloted. This received good support from Congress participants. Useful suggestions to modifying it were also made. This work turned into an application for Alzheimer's dissemination grant, which we're waiting to hear about.

SG members suggested the video can be disseminated through the Alzheimer's Society website, DVD's on request, YouTube, AgeUK, Demreg newsletter etc.

JWC asked if there will be any feedback from those viewing the video. CR

suggested sending a card with the DVD, which people can tick and return to study team, or if the video is being played online to have a box popping out with a short feedback form.

CR said that we may disseminate at memory clinics, but may need to wait until the outcomes are clear.
GS said that she can put us in touch with AgeUK communication team.

James Lee's dissertation

James Lee is attending his final BSc year and has proposed to utilize some of the physical data (Blood pressure). CR advised that this may compromise data integrity (blinding). It was agreed that JL will utilize the before and after data of the intervention group only. His findings will be submitted in the interim report.

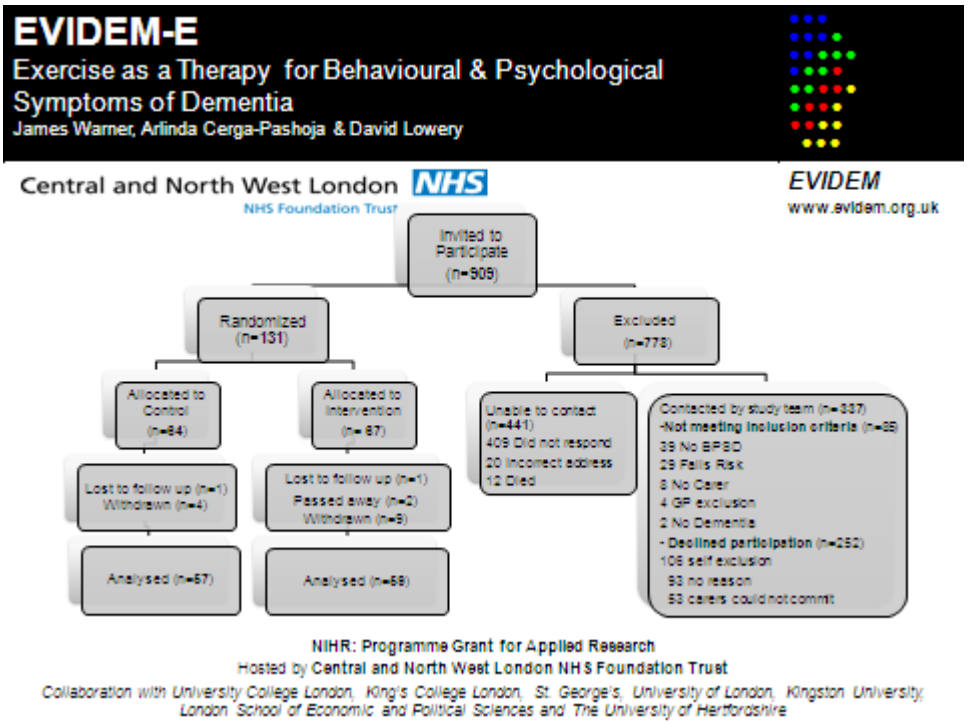
Alzheimer Disease International Conference

We presented a poster on the Alzheimer Disease International Conference last week. The poster raised interest.

Adverse events

An incident has been reported to JL, who reported to DL. The incident was classified as not related to the trial and the participants have agreed to contribute their data in the follow ups.

3.2.9 17 December '12



Control Group			Intervention Group		
N 64		Demographics	N 67		
Age (mean)	*78 (58-99; sd. 7.4)*		Age (mean)	*79 (64-97; sd. 6.8)*	
Gender	*M 25 (39.1%), F 39 (60.9%)*		Gender	*M 32 (47.8%), F 35 (52.2%)*	
Ethnicity:	*White 50 (78.1%)* *Asian 9 (14.1%)* *Black 3 (4.7%)* *Other 2 (3.1%)*		Ethnicity:	*White 56 (83.6%)* *Asian 5 (7.5%)* *Black 5 (7.5%)* *Other 1 (1.5%)*	
Marital Status	*married 45 (71.4%)* *widowed 15 (23.8%)* *single 1 (1.6%)* *divorced 2 (3.2%)*		Marital Status	*married 46 (68.6%)* *widowed 18 (26.9%)* *single 3 (4.5%)* *divorced 0*	
FRAT score	*0-score 12 (18.8%)* *1-score 16 (25%)* *2-score 36 (56.3%)*		FRAT score	*0-score 14 (20.9%)* *1-score 26 (38.8%)* *2-score 27 (40.3%)*	
Living	*home 57 (89.1%), care home 7 (10.9%)*		Living	*home 59 (88.1%), care home 8 (11.9%)*	
Years of Education (mean)	*11.92, (0-36), sd. 5.9*		Years of Education (mean)	*12.1, (6-23), sd. 4.1*	

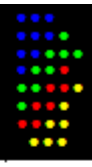
Control Group N 64			Intervention Group N 67		
MMSE (mean)	*14.9, range 0-29, sd. 8.7*		MMSE (mean)	*16.3, range 0-30, sd. 7.4*	
Severity	*mild*	*26 (40.6%)*	Severity	*mild*	*26 (40%)*
	moderate	*19 (27.7%)*		*moderate*	*23 (35.4%)*
	marked	*19 (27.7%)*		*marked*	*16 (24.6%)*
Dementia Subtype:	*Alzheimer's*	*38 (64.4%)*	Dementia Subtype:	*Alzheimer's*	*44 (67.7%)*
	Unspecified	*6 (10.2%)*		*Unspecified*	*7 (10.8%)*
	Vascular	*6 (10.2%)*		*Vascular*	*4 (6.2%)*
	Mixed	*3 (5.1%)*		*Mixed*	*4 (6.2%)*
	Lewy body	*3 (5.1%)*		*Lewy body*	*2 (3.1%)*
	Fronto-temporal	*1 (1.7%)*		*Fronto-temporal*	*3 (4.6%)*
	Other	*2 (3.3%)*		*Other*	*1 (1.4%)*
Year of Diagnosis	*≤2 years*	*38 (62.3%)*	Year of Diagnosis	*≤2 years*	*35 (54.7%)*
	3-5 years	*18 (29.5%)*		*3-5 years*	*24 (37.5%)*
	6-9 years	*5 (8.2%)*		*6-9 years*	*5 (7.8%)*
Physical Conditions	*none*	*22 (34.9%)*	Physical Conditions	*none*	*28 (41.8%)*
	one	*23 (36.5%)*		*one*	*26 (38.8%)*
	two	*9 (14.3%)*		*two*	*6 (9%)*
	three	*7 (11.1%)*		*three*	*5 (7.5%)*
	four	*1 (1.6%)*		*four*	*2 (3%)*
	five	*1(1.6%)*		*five*	*0*
NPI(mean)	*30.6, range 4-80, sd. 16.8*		NPI(mean)	*30.6, range 4-76, sd. 18.6*	
Demqol-Proxy (mean)	*97.3, range 59-117, sd. 14.1*		Demqol-Proxy (mean)	*99.8, range 58-122, sd. 13.1*	
HR	*68*		HR	*66*	
BP	*127/70*		BP	*129/70*	

Carer Characteristics			
Control Group N 64		Intervention Group N 67	
Age(mean)	*60. 9, range 22-88, sd. 17*	Age(mean)	*65.4, range 27-89, sd. 14.9*
Gender	*M 25 (39.1%), F 39 (60.9%)*	Gender	*M 17 (25.4%), F 50 (74.6%)*
FRAT score	*0-score 46 (71.9%)* *1-score 13 (20.3%)* *2-score 5 (7.8%)*	FRAT score	*0-score 40 (59.7%)* *1-score 21 (31.3%)* *2-score 6 (9%)*
Relationship:	*partner 35 (54.7%)* *child 21 (32.8%)* *relative 5 (7.8%)* *paid 3 (4.7%)* *friend 0*	Relationship:	*partner 42 (62.7%)* *child 17 (25.4%)* *relative 2 (3%)* *paid 5 (7.5%)* *friend 1 (1.5%)*
GHQ	*cases 17 (27%), non-cases 46 (73%)*	GHQ	*cases 19 (28.4%), non-cases 48 (71.6%)*
ZBI	*cases 10 (16.1%), non-cases 52 (83.9%)*	ZBI	*cases 15 (23.1%), non-cases 50 (76.9%)*
NPI	*mean 11.9, range 0-39, sd. 8.1*	NPI	*mean 11.8, range 0-38, sd. 8.9*
HR	*70*	HR	*69*
BP	*127/73*	BP	*122/71*

EVIDEM-E

Exercise as a Therapy for Behavioural & Psychological Symptoms of Dementia

James Warner, Arlinda Cerga-Pashoja & David Lowery



Central and North West London NHS
NHS Foundation Trust

EVIDEM
www.evidem.org.uk

Main analysis

NPI	Control	Intervention	Significance
Mean	25.6±16.6	23.9±20.6	P=0.61
Change (≤3)	33/64 (57.9%)	39/67 (66.1%)	P=0.36

Not significant

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