GREAT

Goal-oriented Cognitive Rehabilitation in Early-stage Alzheimer's and Related Dementias: Multi-centre Single-blind Randomised Controlled Trial

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Contents

Research objectives

In this trial we aim to obtain definitive evidence about whether goal-oriented cognitive rehabilitation (CR) is a clinically-effective and cost-effective intervention for people with early-stage Alzheimer's disease, vascular or mixed dementia and their carers. The following specific objectives will be addressed:

1. To compare the effectiveness of goal-oriented CR with that of treatment as usual with regard to: (a) improving self-reported and carer-rated goal performance in areas identified as causing concern by people with early-stage dementia; (b) improving quality of life, self-efficacy, mood and cognition of people with early-stage dementia; (c) reducing stress levels and ameliorating quality of life for carers of participants with early-stage dementia.

2. To estimate the incremental cost-effectiveness of goal-oriented CR compared to treatment as usual.

3. To examine how the goal-oriented CR approach can most effectively be integrated into routine NHS provision, to develop a pragmatic approach that can be directly applied within standard NHS services, and to develop materials to support the implementation of this approach within the NHS following trial completion.

Background

There is a greater need than ever before to identify effective and beneficial interventions for people with early-stage dementia. There are thought to be over 750,000 people with dementia in the UK, a figure that is expected to have doubled by 2040 [1, 2]. Current policy targets include ensuring early diagnosis and good quality early intervention for all, and supporting people with dementia in living as full and active a life as possible [1]. Early diagnosis of dementia creates an opportunity to equip patients and carers to manage the disease effectively and to live well with dementia [3]. In this context early intervention offers the possibility of reducing or delaying the progression of functional disability, depression or behavioural difficulties, helping to maintain independence, supporting management of co-morbidity and hence avoiding or reducing hospitalisation, maintaining quality of life, and ultimately delaying institutionalisation. At present, however, the chances of accessing early psychosocial intervention following a diagnosis of dementia are low, and research evidence regarding the efficacy of early psychosocial interventions remains limited. Research priorities set out by the Ministerial Advisory Group on Dementia Research (MAGDR) in 2011 indicate a need to evaluate the effect of psychosocial interventions for people with dementia living in the community, including those based on 're-ablement', and to identify ways of improving quality of life for people with dementia and their carers.

Relatively little attention has been given to developing psychosocial early intervention approaches aimed at helping people to live well with dementia. Traditionally, efforts have focused instead on attempting to address the underlying impairments in memory and other

cognitive functions which are a defining feature of early-stage dementia. A number of research studies have examined the potential of cognitive training to benefit people with dementia. Cognitive training involves repeated, structured practice on tasks targeting specific cognitive domains, such as working memory or attention. Evidence is mixed, with some studies reporting modest benefits and others reporting no benefits, but a Cochrane systematic review [4] found no evidence for significant benefits. Even where improvements on cognitive tasks assessing trained domains are reported, there is no evidence that these generalise to other areas, have any impact in the real-life context, or offer any benefits as regards engagement in everyday activities [5]. That is to say, these approaches, which target underlying impairment, albeit with limited success, fail to reduce functional disability. Yet there is evidence for preservation of some degree of cognitive and neural plasticity in early-stage dementia [6], and it should be possible to harness this potential to deliver beneficial intervention effects. According to neuropsychological models of memory [7], while some cognitive functions (e.g. long-term episodic recall) are significantly impaired in early-stage Alzheimer's disease, others are relatively spared (e.g. procedural memory for skills, routines and actions, semantic knowledge, and implicit memory) [8], and people with early-stage dementia are capable of some new verbal and behavioural learning [9], although they are likely to require extra support to achieve it [10]. Consequently, there are possibilities for behaviour change to occur.

Conceptualising dementia within the framework of a disability model [11, 12] highlights the distinction between the underlying impairment, resulting from pathological changes, and the resulting limitations on engaging in activity (disability) and restrictions on social participation (handicap). Activity limitation and participation restriction are not solely determined by the degree of impairment, but are subject to a range of personal, social and environmental influences. Negative influences can contribute to the development and maintenance of 'excess' disability [13], where the extent of functional disablement is greater than would be predicted by the degree of impairment; an example would be where an individual loses confidence, gives up previously-enjoyed activities, and becomes socially withdrawn and depressed in reaction to receiving the diagnosis of dementia, with consequent effects on cognitive and functional ability. This is similar to Kitwood's description of the way in which a negative, unsupportive social environment can undermine well-being for people with dementia [14]. Equally, positive influences can support optimal functioning and overcome some of the potential impact of impairment, enabling people to live well with dementia. A focus on addressing barriers to activity and participation, and encouraging adaptive behaviours, can therefore be expected to produce benefits for people with dementia and their family members.

Interventions that aim to reduce functional disability by targeting activity and participation, drawing on retained strengths to support adaptive behaviour, are typically described as forms of rehabilitation. Rehabilitation interventions aim to 'enable people who are disabled by injury or disease to achieve their optimum physical, psychological [and] social well-being'

[15]. The rehabilitation of people who have cognitive, as opposed to purely physical, impairments is termed 'cognitive rehabilitation' (CR) [16]. Although rehabilitation is most often associated with non-progressive conditions such as brain injury, it is equally applicable to people with chronic and progressive conditions. There is considerable evidence for the efficacy of cognitive rehabilitation with a range of clinical groups [17]. Rehabilitation interventions are generally highly individualised, as clients have a diverse range of impairments, needs, circumstances and preferences. Central to the practice of rehabilitation is the identification of realistic and personally-meaningful individual rehabilitation goals for each client, and the development of tailored interventions to address these. Goal-based approaches have been applied in numerous conditions, including brain injury [18, 19], stroke [20], neurological illness [21], physical disability [22] and chronic pain [23, 24], as well as with frail older people [25]. Goals are, wherever possible, negotiated collaboratively between client and therapist. Such interventions may be regarded as inherently person-centred.

It has been suggested that rehabilitation provides a useful overarching conceptual framework for the care and support of people with dementia and for the design of interventions to meet their needs [26]. A few early examples of interventions that addressed meaningful individual goals relating to self-care or activity participation supported the possible utility of this approach [27, 28]. Hence feasibility studies were undertaken to explore the application of cognitive rehabilitation to help people with early-stage dementia and their families manage the impact of the condition.

Feasibility studies

A series of feasibility studies using single-case experimental designs or small-group pre/post comparisons demonstrated that it was possible to identify meaningful personal goals and use evidence-based restorative or compensatory rehabilitation methods [29, 30] to bring about behaviour change in these areas for people with early-stage dementia [31-34]. Restorative approaches build on retained abilities and use a range of instructional or prompting techniques to promote new learning or relearning, whether of information, habits or strategies; examples include the application of the spaced retrieval method to support retention of information [35]. Compensatory methods use a range of aids and adaptations to support functioning and overcome limitations resulting from cognitive impairments; examples include the use of memory books to support engagement in conversation [36]. Rehabilitation interventions for people with dementia need to offer practical benefits in daily life. In the context of cognitive impairment it is particularly challenging to ensure that learning and behavioural change generalises from one setting to another; to circumvent this obstacle, the interventions in our small-scale studies were carried out in the person's everyday setting, rather than in the clinic. The behavioural changes observed, although focused on specific targeted goals, led to wider benefits in everyday life; for example, learning names of other participants in a social club helped to maintain attendance and participation and reduced the risk of social isolation [31], and

using a memory aid to reduce repetitive questioning reduced carer frustration and tensions between the participant and carer [32]. There was also some evidence for generalisation of the problem-solving approach to other everyday situations and challenges [32, 33]. Gains were maintained for several months post-intervention, and one longer-term study demonstrated maintenance of gains up to three years post-intervention [37]. Further studies investigated the efficacy and applicability of specific memory rehabilitation techniques, such as errorless learning and spaced retrieval methods [38-40]. These findings were augmented by reports from other research groups [41, 42]. A Cochrane systematic review found no randomised controlled trials of cognitive rehabilitation [4]. The findings from the feasibility studies, therefore, formed the basis for developing an intervention protocol that could be tested in a pilot randomised controlled trial [34].

The design of trials to evaluate the efficacy of rehabilitation interventions must take into account the fact that rehabilitation typically focuses on the attainment of highly individual goals that are functionally, socially and contextually relevant [43]. When evaluating service or program outcomes in rehabilitation settings, goal attainment scaling has been used to identify goals and rate progress on a standardised scale [18, 25, 43, 44]. However, where the focus is on treatment outcomes for the individual client, as opposed to overall efficacy of a multidisciplinary or multi-component program, goal-setting and goal achievement are more readily evaluated by means of client-centred approaches in which the client plays a central role in a collaborative goal-setting process, and the client's perceptions of change serve as the primary outcome measure. The most widely-used example of this approach is provided by the Canadian Occupational Performance Measure (COPM) [45], which offers a structured format for eliciting individual goals and a standardised means of rating goal performance and satisfaction with performance. There is evidence for the reliability, construct validity, sensitivity and responsiveness of this measure as well as for its clinical utility [20, 46-51]. When using this measure in research, it is possible to elicit goals and performance ratings at baseline and to have participants in both treatment and control groups re-rate goal performance at follow-up. Where clients have cognitive impairments, it is helpful to supplement self-ratings with independent ratings made by professionals or caregivers for comparison purposes [20, 50]. The goal-oriented approach accords with person-centred values in dementia care, allowing the person with dementia to engage in an intervention that is specifically tailored to his/her own needs and preferences, while also providing for a standardised group-level comparison. Therefore, for the pilot trial, the intervention was focused on the identification and attainment of individual goals, and perceived goal performance, rated using the COPM, was selected as the primary outcome.

Pilot RCT

A pilot trial of individual, goal-oriented CR, funded by the Alzheimer's Society and published in the American Journal of Geriatric Psychiatry, was conducted in North Wales from 2005 – 2009 [52]. This was a single-site, single-blind RCT comparing CR to (a) relaxation therapy (RT), which involved equivalent therapist time and attention, and was expected to be

pleasurable for participants without addressing the areas targeted in CR, and (b) treatment as usual (TAU). All participants received acetylcholinesterase-inhibiting (AChEI) medication and routine out-patient monitoring, and had access to the range of voluntary sector services available at the time in the area. The primary outcome was goal performance and satisfaction with performance.

Participants were 69 individuals (41 women, 28 men; mean age 77.78 years, s.d. 6.32, range 56-89; mean years of education 10.64, s.d. 1.67, range 8 – 17) recruited from NHS Memory Clinics, with an ICD-10 diagnosis of early-stage Alzheimer's disease (56) or mixed Alzheimer's and vascular dementia (13), and a mean MMSE score of 23 (s.d. 3.02, range 18 – 30). All were receiving a stable dose of AChEI medication (46 donepezil, 18 reminyl, 4 rivastigmine). Forty-four participants had carers who contributed. Of these 44 carers (26 female; 38 provided details of their age; mean age 69.89 years, s.d. 12.55, range 33-88), 32 were spouses/partners, 9 were adult children, 1 was a sibling, and 2 were other kin, and 40 lived with the person with dementia.

Following initial assessment, participants were randomised by computer algorithm, independently operated by the clinical trials unit (NWORTH CTU), to one of the three conditions (CR n = 23, RT n = 24, TAU n = 22); there were no differences between the groups on baseline measures. In the CR condition, participants received a one-hour home visit from the therapist once a week for 8 weeks. They engaged in an individualised intervention, conducted in the home setting, which addressed personally meaningful, practical goals related to management of everyday activities, using evidence-based rehabilitation methods and techniques as described above. This was supported by (a) advice on improving use of practical aids and strategies; (b) instruction in, and practice of, techniques for learning new information; (c) practice in maintaining attention and concentration; and (d) instruction in, and practice of, stress management techniques. Participants were encouraged to work on goals, and practice strategies, between sessions. Carers, where available, were invited to join the last 15 minutes of each session to support between-session implementation. In the RT condition, participants received a one-hour home visit from the therapist weekly for 8 weeks and engaged in an equivalent degree of between-session practice to the CR group. Following a structured treatment protocol, RT participants were taught progressive muscle relaxation and breathing exercises and were encouraged to implement these whenever they experienced anxiety. TAU participants had no contact with the research team between initial and post-intervention assessment. Post-intervention assessment, conducted by a blinded researcher, took place after 8 weeks, and a further follow up was conducted 6 months later.

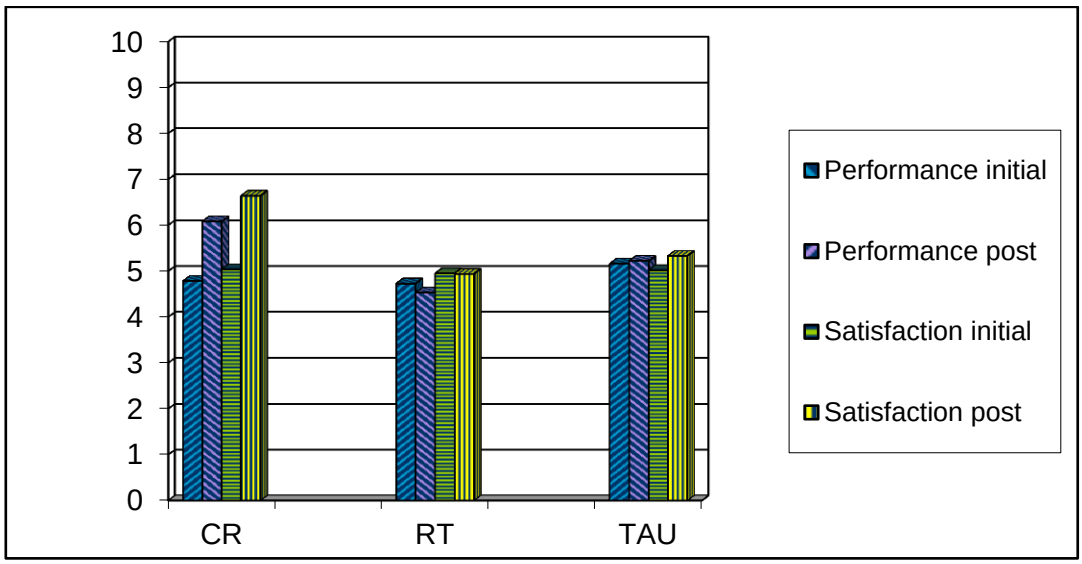
At baseline, all participants identified up to 5 goals each (mean 3.15, s.d. 1.04) relating to aspects of everyday functioning and activity which they would like to manage better. Goals were identified in a collaborative process using the structured interview format of the Canadian Occupational Performance Measure (COPM) [45], which facilitates the identification of specific, measurable, achievable and realistic goals, and elicits participant

ratings of performance and satisfaction for the identified goals. For participants in the CR group only, details of these goals were provided to the therapist, and one, or in some cases two, goals were then identified as therapy targets and addressed during therapy using evidence-based rehabilitation and behaviour change methods. The goals targeted in therapy were very practical, and related to everyday memory (e.g. remembering what happened yesterday, remembering names of people at a keep fit class), concentration (e.g. remembering what one was doing after being distracted), resuming or maintaining skills and activities (e.g. crocheting a cardigan following a written pattern), learning new skills (e.g. using the computer to email a friend; learning to use a mobile phone), or organisation (e.g. improving use of a calendar as a reminder of non-routine events).

Following intervention, goal performance and satisfaction ratings improved for the CR group and showed no change in the other two groups (see Figure 1). Analysis of covariance indicated a significant effect of CR on performance ($F2,58 = 7.880$, $p < 0.001$) and satisfaction ($F2,58 = 8.270$, $p < 0.001$). For both measures, CR differed significantly to both RT and TAU (performance: 1.459 ± 0.936 for RT and 1.128 ± 0.989 for TAU; satisfaction: 1.686 ± 1.041 for RT and 1.193 ± 1.090 for TAU). For the CR group, achievement of therapy goals was corroborated in three ways through within-group analyses [53]. First, participants rated performance and satisfaction with performance for each goal targeted, recording significant increases (performance: $t\ 25 = -3.742$, $p < .001$; satisfaction: $t25 = -4.877$, $p < .001$). Second, a separate therapist rating of goal performance was made at the start and end of therapy; this reflected significant improvements ($t\ 25 = -8.027$, $p < .001$). Third, a simplified goal attainment scaling procedure was used, whereby for each therapy goal behavioural indicators of full and partial attainment were established by the research team at the start of therapy and each goal was rated accordingly at the end of therapy. This classified 12 (46%) of goals as fully implemented, 13 (50%) as partially implemented, and 1 (4%) as not implemented. It was noted that many of the partially- implemented goals would likely have been fully achieved given a little more time.

Secondary outcomes were evaluated in terms of effect sizes (Cohen's d) for the CR group compared to the pooled control (RT and TAU) groups, as no differences were observed between the two control groups on any measure. Outcomes examined for the person with dementia were quality of life, mood and cognition (effect sizes are shown in Table 1). CR produced benefits in all three areas, and quality of life continued to improve at 6 month follow up. It should be noted that for the most part mood was within the normal range at baseline and hence scope for improvement was limited. For carers, CR reduced stress and improved psychological well-being, and quality of life (effect sizes are shown in Table 1), and in some cases these were maintained or continued to improve at follow-up.

Figure 1. Effects of intervention on goal performance and satisfaction (COPM ratings) for participants in each condition: significant improvements for CR and no change for RT or TAU



The CR intervention was acceptable to, and well-received by, participants and carers. Across all three groups, the attrition rate between randomisation and post-intervention assessment was 7%; 5 individuals discontinued due to physical illness (1), death (1), incorrect diagnosis (1) and self-withdrawal (2). Attrition between post-intervention assessment and 6 month follow up was 12%; 8 individuals were lost to follow up due to death (2), moving out of area (3) and self-withdrawal (3). Thus, the overall rate of elective self-withdrawal for the trial was only 7% (2 each from CR and RT, and 1 from NT).

This pilot trial demonstrated that participants with early-stage dementia can identify personally-meaningful goals relating to managing everyday activities, and, with a modest amount of support from a therapist, make significant progress towards implementing these. Goal performance constituted a sensitive and specific measure of change. As performance and satisfaction ratings were closely associated, performance ratings should suffice in future work. The addition of carer ratings of performance would be informative. The trial provided valuable experience in collaborative identification of specific, measurable, achievable and realistic goals [53]. Results suggested that a slightly longer intervention may be advisable in order to fully establish and consolidate gains. The trial showed that CR can bring benefits with regard to cognition, well-being and quality of life for the person with dementia, as well as the well-being and quality of life of the carer. The lack of observed differences between the two control groups (RT and TAU) suggested that in a definitive trial TAU could be adopted as an appropriate comparison condition for CR. Findings from the pilot provided information about intervention parameters, outcomes and effect sizes that has informed the design of the proposed multi-site trial presented below.

Table 1. Effect sizes (Cohen's d) on secondary outcome measures obtained in the pilot trial for the CR group compared to the pooled RT and TAU groups

Measure	Post-intervention	6 month follow-up
PARTICIPANTS WITH DEMENTIA		
Quality of life (QoL-AD)	0.24	0.29
Depression (HADS)	0.26	0.13
Anxiety (HADS)	0.21	0.11
Memory (RBMT)	0.37	0.08
Verbal fluency (FAS)	0.29	-
Sustained attention (TEA elevator counting)	0.76	-
Auditory selective attention (TEA ECD)	0.53	-
Visual selective attention (TEA map search 1 min)	0.11	-
Everyday problem-solving (ILS)	0.21	-
CARERS		
Stress (RSS)	0.54	0.27
Psychological well-being (GHQ)	0.51	0.11
Quality of life - social relationships (WHOQoL)	0.34	0.49
Quality of life – psychological (WHOQoL)	0.11	0.55
Quality of life – physical health (WHOQoL)	0.69	0.38
Quality of life – environment (WHOQoL)	0.46	0.08

Methods

This is a multi-centre single-blind randomised controlled trial (RCT) comparing cognitive rehabilitation (CR) to treatment as usual (TAU) for people with early-stage Alzheimer's, vascular or mixed dementia, with outcomes assessed at 3 and 9 months post randomisation. Participants will be recruited from memory clinics, old age mental health services, and GP practices. CR will be delivered in participants' homes, with a carer involved where possible. The study will be conducted in eight centres[1]: North-East England (Newcastle site), North-West England (Manchester site), South-West England (Bath site), West Midlands

[1] The initial plan was for the study to be conducted in six centres: North-West England (Manchester site), South-West England (Bath site), West Midlands (Birmingham site), London (London site), South Wales (Cardiff site), and North Wales (Bangor site). Two additional sites, North-East England (Newcastle site) and South-East England (Kent site), were added in 2015.

(Birmingham site), London (London site), South-East England (Kent site), South Wales (Cardiff site), and North Wales (Bangor site). At each centre, a part-time therapist (with an appropriate professional background, e.g. occupational therapy or psychology) will conduct the interventions, and a research assistant, blind to group allocation, will carry out assessments at baseline and at 3 and 9 months post-randomisation.

The cognitive rehabilitation intervention

CR is an individualized approach for people with dementia (PwD) aimed at managing or reducing functional disability, and maximising engagement and social participation. PwD and their carers work together with a health professional over a number of sessions to identify personally-relevant goals and devise and implement strategies for achieving these. CR will be delivered in 10 individual sessions over 3 months, followed by 4 maintenance sessions over 6 months. Carers will be involved in part of each session where possible. Involvement of a carer helps to ensure that skills are maintained and applied to novel situations, and facilitates communication about how current or possible future difficulties might be managed.

Over the course of the 10 weekly sessions, participants with dementia will work in collaboration with the therapist to address personal rehabilitation goals. Drawing on the goals identified at baseline assessment, up to three behavioural goals will be operationalised, and strategies for addressing these will be devised and implemented. Goals will be introduced one at a time, in a flexible manner depending on rate of progress. Following introduction and modelling of strategies and skills during the therapy sessions, the participant and carer will work on the selected goal between sessions following an agreed schedule of activities. Progress with each goal will be reviewed and the strategies adopted will be adjusted as necessary on a weekly basis. Performance for each goal will be independently rated at the outset and in week 10 by the participant, carer and therapist. Work on goals will be supplemented by the following components, which will be systematically introduced across the 10 sessions: 1. Introduction of, and practice in applying, a solution-focused problem-solving approach by following a short sequence of steps to specify and test possible solutions. 2. Introduction of anxiety management strategies, building on participants' existing strengths and preferences in this area, and practice in strategy use and application. 3. Monitoring of activity levels, leading to plans for increasing engagement in meaningful and enjoyable activity, and implementation of these plans. 4. Practice in strategies for maintaining or improving attention and concentration. 5. A review of compensatory strategy use (e.g. calendars, diaries, reminder systems), and development and implementation of plans for improving strategy use, which might include increasing the efficiency of existing strategies and introduction of new strategies. 6. A review of current use of restorative strategies for retaining new information or improving recall, and practice in key strategies (mnemonics, semantic association, spaced retrieval), enabling participants to identify a preferred strategy and apply this in everyday situations. 7. For the carer, discussion of carer well-being and strategies for managing stress. 8. Identification of

additional sources of support and help, and encouragement to access these. The four maintenance sessions will focus on supporting maintenance of gains and encouraging continued goal performance and strategy use. A session-by-session protocol for the CR intervention is summarised in Table 2.

The effects of the CR intervention will be compared to treatment as usual (TAU). In the pilot, CR was compared with TAU and with an attention placebo condition (relaxation therapy). There was no evidence of a difference between the two control groups, which suggests that TAU can serve as an appropriate comparator. For the CR group, the CR will be provided in addition to TAU, while the control group will receive only TAU and will have no contact with the research team between assessments. TAU will consist of acetylcholinesterase-inhibiting medication where prescribed, and any other services normally provided apart from specific programmes of cognitive rehabilitation or other cognition-focused intervention. TAU may include, for example, routine monitoring by the Memory Clinic, information provision, attendance at drop-in groups or support groups, or carer participation in support groups. Service receipt during the intervention period, including dementia-specific services, monitoring, and interventions provided by Memory Clinics, will be documented for all participants. All participants will be free to access services such as those offered by the Alzheimer's Society, and the extent of this will be recorded.

Participant selection

Participants will be recruited from memory clinics, old age mental health services and GP practices, and will have been diagnosed with early-stage Alzheimer's disease (AD), vascular dementia, or mixed AD and vascular dementia. For each participant, a carer (a family member or close friend who is either co-resident or in regular contact) will also be involved.

Inclusion criteria:

1. The participant must have been assigned an ICD-10 diagnosis of Alzheimer's disease (AD), vascular dementia, or mixed AD and vascular dementia. AD accounts for 62% of dementia diagnoses, and vascular dementia for 17%, with mixed AD and vascular dementia accounting for a further 10% [2]. These categories together capture 89% of those diagnosed with dementia. There is no reason to assume that people with rarer sub-types of dementia, including dementia with Lewy bodies (4%), fronto-temporal dementia (2%), and Parkinson's dementia (2%), could not benefit from CR, but these forms of dementia have specific features that would require a distinct approach. For this reason, and because numbers are likely to be too small to allow for sub-group analysis, we are not proposing to include these groups in the current trial.

2. The participant must be in the early stages of dementia, as indicated by an MMSE score of 18 or above. This is to ensure that participants recruited to the trial have a level of cognitive functioning that is sufficient to allow them to complete the selected outcome measures without undue difficulty for the duration of their participation in the study. Use of a cut-off

point, while inevitably somewhat arbitrary, provides protection for people who may be overly burdened by the assessments. The selected cut-off of a score of 18 on the MMSE is frequently used in research studies and worked well in the pilot trial. We have not placed any upper limit on the MMSE score, since it can be expected that a small proportion of people meeting diagnostic criteria for dementia will have high MMSE scores [54].

3. If taking acetylcholinesterase inhibitors, the participant must have been receiving a stable dose for one month prior to trial entry, and there should be no intention to change the dose over the period of participation in the study unless clinically indicated. This is to ensure that intervention effects are not confounded by changes in medication status.

4. The participant must have a carer who is willing to participate. While having a carer is not an essential prerequisite for receiving a CR intervention, it is important for the purposes of research to obtain an informant perspective on the effects of the intervention, and in this trial carers will be asked to provide an independent rating of goal performance. It is also important to determine the effects of the intervention on carer well-being; positive effects on the carer are likely to bring added benefits in the longer-term for the person with dementia.

5. The participant must be able to give informed consent. People in the early stages of dementia are normally expected to have capacity to consent to participation. When recruiting participants, the research team will use a checklist to ensure that all relevant information is considered and that the participant is able to give informed consent. While CR principles may be applied at any stage of dementia, the intervention to be tested here involves engaging the person with dementia in a collaborative process of identifying and addressing personally-meaningful goals, and therefore the participant needs to be able to understand this and to make a positive choice to take part.

Exclusion criteria:

1. Participants will be excluded if they have a prior history of stroke (i.e. history or neuroimaging evidence of cortical infarct or haemorrhage resulting in persisting and significant focal physical disability, such as hemiplegia), brain injury or other significant neurological condition. Such conditions would be expected to affect cognitive, behavioural and emotional functioning, and people who have one of these conditions prior to developing dementia would have additional rehabilitation needs. While such individuals might benefit from CR, their inclusion would represent a potential confounding factor.

2. Participants will be excluded if they are unable to speak English. This criterion is applied for practical reasons, because the standardised outcome measures we plan to use are only available in English. No official data are available to indicate what proportion of the UK population cannot speak English; while it is estimated that about 3% of the population use a language other than English at home, with over 100 different languages represented (source: The National Centre for Languages), many of the individuals concerned also speak

English. The time and costs involved in translating standardised measures and providing interpreters for assessment and therapy sessions would be substantial, and is beyond the scope of the present proposal. However, we predict that very few individuals would be excluded from participation due to inability to communicate in English.

Ethical considerations

Based on previous findings, participants randomised to receive CR may be expected to derive some benefits in terms of managing everyday activities and general well-being. Their caregivers may also be expected to show reduced stress and improved well-being. Availability of evidence from a definitive trial may be expected to have a positive influence on the future provision of interventions to support people with early-stage dementia and their carers. Previous findings also suggest that participants randomised to TAU are expected to show little or no change; thus, they will not be harmed by this allocation. As the trial will provide the first evidence from a large-scale trial regarding the benefits of CR, it cannot at this stage be considered unethical to withhold this treatment from the control group, and the control group will still have access to the care typically provided by memory clinics and GPs, and to voluntary sector services.

There are no known risks associated with CR. It is possible that some participants may find it challenging to confront their difficulties, but the therapist will provide support as they engage in this process, and the intervention protocol incorporates attention to managing emotional reactions. Neither the feasibility studies nor the pilot trial have suggested that this represents a significant risk to participants. The research team will be trained to be alert to any concerns about participants' well-being. If there are serious concerns about a participant, these will be referred, wherever possible with the permission of the individual concerned and the carer, to the clinician responsible for the participant's care.

Participants with early-stage dementia, and carers, will be fully informed prior to entry into the trial about the intervention and about the current state of knowledge regarding possible benefits and risks, and this information will be updated if additional evidence becomes available during the course of their participation.

Table 2. Cognitive rehabilitation intervention protocol comprising 10 weekly sessions followed by 4 maintenance sessions spread over 6 months[1]

Session	Participant with dementia	Carer	Between sessions
1	Orientation to the intervention and explanation of between-session tasks; goal 1selection and rating; anxiety management strategies; activity monitoring exercise	Orientation and explanation; goal 1 rating; anxiety management; activity monitoring	Monitor current activities using diary sheet; practise anxiety management strategies
2	Review of activity monitoring and plans for increasing activities; introduction of solution-focused problem-solving approach; intervention plan for goal 1; anxiety management	Problem-solving; goal 1 intervention; plans for increasing activities	Agreed tasks for goal 1; practice anxiety management strategies; develop plans for increasing activities; practice solution-focused approach
3	Progress review for goal 1; progress review for increasing activities; review of adaptations and compensatory strategy use; anxiety management	Progress review; review of adaptations and compensatory strategy use; increasing activities	Agreed tasks for goal 1; practice anxiety management strategies; implement plans for increasing activities
4	Progress review for goal 1; progress review for increasing activities; goal selection and rating - goal 2; plan to improve compensatory strategy use	Progress review; goal 2[1] rating; plan to improve compensatory strategy use	Agreed tasks for goal 1; implement changes to compensatory strategies
5	Progress review for goal 1; progress review for compensatory strategy use; intervention plan for goal 2; strategies for improving attention and concentration	Progress review; goal 2 intervention; strategies for improving attention and concentration	Agreed tasks for goals 1 and 2; changes to compensatory strategies; practice maintaining attention and concentration
6	Progress review for goals 1 and 2; progress review for compensatory strategy use; goal selection and rating - goal 3; improving attention and concentration	Progress review; goal 3[1] rating; carer well-being	Agreed tasks for goals 1 and 2; practice in maintaining attention and concentration
7	Progress review for goals 1 and 2; intervention plan for goal 3; restorative strategies for taking in new information	Progress review; restorative strategies; carer well-being	Agreed tasks for goals 1, 2 and 3; practice of restorative strategies
8	Progress review for goals 1, 2 and 3; practice with restorative strategies	Progress review; application of restorative strategies	Agreed tasks for goals 1, 2 and 3; practise restorative strategies
9	Progress review for goals 1, 2 and 3; practice with restorative strategies; preparation for ending weekly sessions	Progress review; discuss other sources of help and support	Agreed tasks for goals 1, 2 and 3; practice of restorative strategies; investigate other sources of support
10	Progress review for goals 1, 2 and 3; review of strategy use for anxiety management, attention and concentration strategies, compensatory strategies and restorative strategies; re-rating of goal performance	Progress review; re-rating of goal performance; review other sources of help and support	Review written information provided about strategies; monitor progress; where appropriate access other sources of support
M1	Re-orientation to problem-solving approach; review of progress with goals; review of strategy use	Problem-solving approach; progress review	Review information given; monitor progress

M2	Problem-solving; review of progress with goals; review of strategy use	Problem-solving; progress review	Review information given; monitor progress
M3	Problem-solving; review of progress with goals; review of strategy use	Problem-solving; progress review	Review information given; monitor progress
M4	Review of progress; goal ratings; reminder of problem solving approach and strategies; goodbyes	Progress review; goal ratings; future orientation; goodbyes	N/a

[1)] Exact timing of introduction of goals 2 and 3 may vary depending on progress with earlier goal(s)

Informed consent will be obtained from all participants and carers. People with early-stage dementia are expected to have capacity to consent to participation. DeNDRoN and NISCHR will support participant identification and recruitment. Initial identification of participants will be made by NIHR Comprehensive Local Research Network (CLRN) and Mental Health Research Network (MHRN) staff in England and National Institute of Social Care and Health Research Clinical Research Collaboration (NISCHR CRC) staff in Wales. Participants will be contacted by or on behalf of the clinician responsible for their care and invited to respond directly to the research team to express an interest in finding out more about the study. Interested participants and carers will then be contacted by telephone by the local research assistant, who will provide additional information and send out written details. This will be followed by a further telephone call; for those interested in finding out more, a meeting will be arranged at which the research assistant will explain the study, answer any questions they may have, re-check eligibility, and ensure that the person with dementia has capacity to consent. Consent from the participant and the carer will be taken at, or following, this visit. While this provides an initial mandate for entry to the trial and commencement of trial procedures, consent is an ongoing process, and this is crucial for psychosocial interventions where participants' active engagement is required. Therefore, research assistants and therapists will be trained to monitor ongoing consent, and to respond appropriately to any indication of a possible withdrawal of consent. As participants will be in the early stages of dementia, loss of capacity to consent during the course of participation is expected to be infrequent. However, on entry to the trial participants will be asked whether, should they lose capacity to consent, they are willing to continue to be included in the trial and to have their data used.

Personally-identifiable information will be retained only until publication of the trial report unless the participant has consented to retention of details for potential further follow up, while anonymised data will be retained for five years after publication unless a longer period is required by the Research Ethics Committee or other regulatory authorities. Consent forms will be retained for 25 years following trial closure.

The governance and management of the study will be undertaken within the Department of Health Research Governance Framework for Health and Social Care (2nd edition, 2005). This will ensure the highest standards of clinical research, covering scientific quality, ethical standards, and all related management issues. The trial will adhere to the North Wales Organisation for Randomised Trials in Health (NWORTH) Clinical Trials Unit (CTU) Standard

Operating Procedures (SOPs; http://www.bangor.ac.uk/imscar/nworth/spec services. php?menu=3&catid=2236&subid=0) for all trial and data management, statistical and regulatory matters. This is not a clinical trial of an investigational medical product (CTIMP) and therefore it does not come under the provisions of the Medicines for Human Use (Clinical Trials) Regulations (2004).

All research staff and therapists will undergo training in Good Clinical Practice with regard to the conduct of clinical trials. Trial-specific training requirements will be addressed throughout the study period and regularly reviewed so as to ensure fidelity of the intervention, and consistency of recruitment strategies, intervention and data collection. Orientation and project-specific training will be provided for CLRN, MHRN and NISCHR CRC staff.

Sample size

Power calculations and attrition rates are based on findings from the pilot trial. We wish to confirm the finding that the primary effectiveness outcome of goal performance as measured by Canadian Occupational Performance Measure (COPM) was improved in the treatment group [45]. The difference observed in the pilot was large (standardised effect > 1 at post-intervention assessment). However, we also wish to detect any effect sizes in the order of 0.38 for important secondary outcomes, as we judge that this will give confirmation of effects which are large enough to have substantive clinical benefits. For the proposed study, intervention length has been increased and now includes a maintenance phase in order to further strengthen demonstrable effect sizes in secondary outcomes. We have elected to be conservative in all aspects of our estimate of power, and we have made a larger estimation of potential attrition than the <20% observed in that study, based on the 27% rate observed in the REMCARE trial [55]. To achieve 80% power to detect a medium effect size of 0.38, with alpha 0.05, using a random effects model, in primary and secondary outcomes, we will need 175 PwD, with their carers, to complete the trial in each arm. Attrition was 20% at 6 months in the pilot, but it is possible that this could be higher in a longer multi-centre trial, given that we are working with an older and often frail population, who may have co-morbid physical illnesses as well as dementia, and whose social circumstances may in some cases be unstable. Therefore we adopted an attrition rate of 27% for purposes of sample size calculation, although in practice we will put in place measures to minimise drop out and aim to keep this at or below 20%, thus increasing the effective sample size. Adjusting for potential attrition, we aim to randomise 480 PwD, each with a carer. To meet this target, we calculate that each centre will need to recruit 3 participants per month over 27 months. Experience suggests that 1 in 3 of the PwD identified as eligible and invited to participate will be successfully recruited; thus, each month, 9 potentially-eligible participants will need to be approached in each centre. The centres see on average 25 (North-West, South-West), 33 (North Wales), 40 (South Wales) and >50 (London, West Midlands) potentially-eligible new referrals each month. In addition, each centre has between 300 and 1500 recently-diagnosed individuals on its books whose

records can be screened for eligibility, and some centres have access to participant databases containing details of PwD who are interested in research participation (North Thames in London, North Wales). This indicates that recruitment targets can be regarded as feasible. Feedback on the outline proposal suggested that consideration be given to possible clustering around practitioner experience. There will be one practitioner involved at each centre, and we will test for differences between sites in the analysis. If there is a change of practitioner at one or more centres during the course of the trial we will also test for practitioner effects.

Outcome measures

(a) Primary outcome measure

Bangor Goal-Setting Interview. The Bangor Goal-Setting Interview is an adapted version of the *Canadian Occupational Performance Measure* (COPM) [45]. The COPM is a structured interview in which respondents are asked to identify areas of their daily activities that are difficult to do to their own satisfaction, and in which they would like to see improvements, and important problem areas are collaboratively agreed between the participant and the assessor and formulated as goals. In this study, all participants will identify three goals and rate these at baseline, 3 month and 9 month assessments. For each goal, performance and satisfaction are separately rated on a 1 – 10 scale (1 = unable to perform/not satisfied; 10 = fully able to perform/extremely satisfied) and mean levels of performance and satisfaction are calculated by summing the individual goal ratings and dividing by the number of goals. The goal performance rating will serve as the primary outcome measure. The COPM has good test-retest reliability over a one-week period, >.80 in studies with different clinical groups [45]. For example, test-retest reliability of .89 for performance ratings and .88 for satisfaction ratings has been reported with stroke patients [20]. Validity has been assessed in relation to a range of measures and findings generally support the validity of the COPM [45]. A number of studies provide evidence for the reliability, construct validity, sensitivity and responsiveness of this measure as well as for its clinical utility [20, 46-51]. Carer ratings will be included as recommended for participants with cognitive impairment, [50].

(b) Secondary outcome measures for participants with dementia (in order of priority)

DEMQOL [56]. DEMQOL has been designed to assess health-related quality of life of people with dementia across the full range of severity and subtypes, and shows high internal consistency (Cronbach's alpha 0.87) and good test-retest reliability (ICC 0.76) in people with mild to moderate dementia. It consists of a 28-item interviewer-administered questionnaire for the person with dementia, and a 31-item interviewer-administered questionnaire on which the caregiver provides proxy ratings. These may be used together or separately. In this study, only self-ratings by the person with dementia will be taken. An algorithm has been developed to generate quality-adjusted life year (QALY) scores from DEMQOL scores for use in economic evaluation [57].

Generalized Self-Efficacy Scale (GSES) [58]. The 10-item Generalized Self-Efficacy Scale (GSES) was created to assess a general sense of perceived self-efficacy, the potential to influence one's situation through one's own actions. Responses are made on a 4-point scale. Responses to all 10 items are summed to yield the final composite score with a range from 10 to 40. Cronbach's alphas range from .76 to .90 [59].

Hospital Anxiety and Depression Scale (HADS) [60]. The HADS contains 14 items forming two subscales: anxiety and depression. Each item is rated on a four-point scale, giving maximum scores of 21 for anxiety and for depression. Scores of 11 or more on either subscale are considered to be a significant 'case' of psychological morbidity, with scores of 8–10 classified as 'borderline' and 0–7 'normal'. The HADS has been employed and validated in studies of people with dementia and carers [61, 62].

Brief cognitive assessment battery. This will consist of brief tests of memory, attention and executive function, suitable for people with early-stage dementia, each taking less than 5 minutes to administer:

(a) Memory: Rivermead Behavioural Memory Test (RBMT) [63], story recall sub-test. The RBMT is a well-established ecologically-valid test of everyday memory. In the story recall task the researcher reads out a short story, similar to a brief report of a newsworthy event in a daily newspaper, and the participant is asked for immediate and delayed (after 20 min) recall of the content. Recall is scored following a standard protocol (inter-rater reliability > 0.9) with a maximum possible score of 21 for the immediate and for the delayed component. Four equivalent versions are available to permit reassessment without the risk of practice effects; practice effects are not anticipated with test-retest intervals of 3 and 6 months, but as a precaution a different version will be used at each time-point. Raw scores will be used in the analysis as they provide a greater range than the condensed standardised profile score that is used in calculation of the overall RBMT score.

(b) Attention: Test of Everyday Attention (TEA) [64], elevator counting and elevator counting with distraction subtests. The TEA is a well-established ecologically-valid test of everyday attention, with subtests assessing different components of attention. The elevator counting subtest assesses sustained attention. Participants are required to count a short string of monotonous tones and give the total number. Seven strings are presented, and the total score is the number of strings correctly counted. The elevator counting with distraction subtest assesses auditory selective attention. Further strings of tones are presented, this time also including distractor (high-pitched) tones that are not to be counted. The total score is the number of strings correctly counted. Three equivalent versions of each subtest are available to permit reassessment without the risk of practice effects; as above, practice effects are not anticipated but as a precaution a different version will be used at each time-point.

(c) Executive function: Letter fluency sub-test of the Delis-Kaplan Executive Function System (D-KEFS) [65]. D-KEFS consists of a set of standardised tests of executive function. The verbal letter fluency task evaluates the executive sub-domains of initiation, response generation and inhibition [66] as well as drawing on semantic memory and language ability. In this task, the participant is asked to list as many words as possible beginning with a specific letter of the alphabet in a one-minute period, excluding proper nouns and repetitions. Three letters, F, A and S, are used. The total number of correct responses to the three letters is used in analysis. This task has been extensively examined in people with early-stage dementia [67]. Evidence suggests that even in healthy participants there are no practice effects for most components of this task even at test-retest intervals of less than two weeks; there are minimal practice effects for the switching component with test-retest intervals of less than two weeks, but not with longer intervals.

(c) Secondary outcome measures for the carer (in order of priority)

Relatives' Stress Scale (RSS) [68]. The RSS is a 15-item dementia-specific measure of caregiver stress with items rated on a 5-point Likert scale and summed. A higher overall score indicates higher levels of caregiving-specific stress.

EuroQOL (EQ5D) [69] The EQ-5D is a standardised measure of health status and health outcome, applicable to a wide range of health conditions. In the first section, the respondent is asked to select one of three options for each of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each dimension, the three response options are coded on a 3 point scale from 1 (no problems) to 3 (unable to perform/extreme problem). This yields a descriptive profile (e.g. 11232) across the five dimensions. The second part of the measure is a visual analogue scale for self-rating of health-related quality of life ('your health state today'). This measure is included because the EQ5D score will be used to generate QALY scores using societal weights.

WHO Quality of Life – BREF (WHOQOL-BREF) [70]. The WHOQOL-BREF is a 26-item scale assessing perceived quality of life, giving scores in four domains: environment, social relationships, psychological and physical health.

(d) Service utilisation

Client Services Receipt Inventory (CSRI) [71].

The CSRI provides a template that can be adapted to the needs of each specific study. Respondents are asked about their use of health care services for a period preceding baseline assessment and during the study period. The questions cover contact with a range of health and social care professionals, prescription of medications, hospital appointments and stays, participation in local authority funded activities such as day centres, participation in activities run by voluntary organisations, and the contribution of informal carers. Questions to examine the nature and extent of any dementia-specific treatment received from the Memory Clinic will be included.

(e) Demographic and background information for the person with dementia and carer.

Details such as gender, age, relationship between person with dementia and carer and whether they live together, age of onset of dementia, educational level, social class, and co-morbidities will be collected. This will allow us to examine effects of demographic and social variables on treatment efficacy.

(f) Process measures for the CR group

For the cognitive rehabilitation group, process measures will be taken to provide convergent evidence about change in goal performance. In-session parallel ratings of goal performance by participant, carer and therapist will be made when each goal is introduced and in session 10. A simplified goal attainment scaling procedure [43] will be applied, as described for the pilot trial; clearly-specified behavioural indicators of full and partial goal achievement will be established when each goal is introduced, and progress according to these criteria will be rated by the therapist following session 10 and again following session 14. Establishment of goal attainment criteria, and ratings of attainment, will be extensively addressed in the therapists' supervision sessions. The therapy process will be supported by the Pool Activity Level (PAL) instrument, which is a valid and reliable tool for assessing level of ability for activity of daily living skill training and for activity planning and is recommended in the National Clinical Practice Guideline for Dementia (NICE, 2006). The instrument also profiling tools for interpreting the assessment in order to plan and deliver effective, enabling care and support [72]. The Checklist contains nine domains of function which are each described in the four performance levels. The therapist will complete the Checklist in interview with the carer. The resulting profile will support the therapist to apply a standard process for assessing, planning, implementing and recording interventions that enable the participant to achieve personally meaningful goals using a cognitive rehabilitation approach.

(g) Therapist adherence to protocol

Therapist adherence to the treatment protocol will be monitored through therapy logs and structured supervision sessions. Therapists will receive monthly telephone supervision and face-to-face supervision meetings will be held every three months. Therapy logs reporting session content (with participant details anonymised) will be submitted to the supervisor for scrutiny prior to supervision sessions.

(h) Treatment compliance

Treatment compliance will be indexed by the number of sessions completed for each participant.

(i) Qualitative analysis

Quantitative data on the efficacy of CR for people with early stage dementia will be complemented by a qualitative sub-study exploring the way in which the intervention was experienced by the participants in the treatment group (See Appendix 1).

Procedure

At each centre, once participants have given informed consent, they will be visited by the research assistant who will conduct the baseline assessment. Following this assessment, the research assistant will trigger randomisation. Results of the randomisation will be sent to the therapist, who will telephone the participant and the carer to explain the next steps. Participants allocated to CR will receive 10 weekly visits from the therapist over a three-month period. The therapist will trigger the post-intervention assessment for all participants. The research assistant will visit each participant to conduct the assessment. Following the post-intervention assessment, participants in the CR group will receive 4 maintenance sessions with the therapist over a six month period. The research assistant will visit all participants six months after the post-intervention assessment to carry out the final, six-month follow up assessment. All primary and secondary outcome measures, and service utilisation measures, will be administered at each assessment point.

After consent and baseline assessment, participants will be individually randomised. Randomisation to GREAT will be achieved by secure web access to the remote randomisation centre, NWORTH CTU, at Bangor University. This system will be set up, maintained and monitored independently of the trial statistician or other trial staff. The randomisation will be performed by dynamic allocation [73] to protect against subversion while ensuring that the trial maintains good balance to the allocation ratio of 1:1 both within each stratification variable and across the trial. Participants will be stratified by centre, gender, age (under 75 *vs.* 75 and above), and MMSE score (under 24 *vs.* 24 and above). For validation purposes, additional information will be taken including the participant's trial number, initials, and date of birth, and details of the person requesting the randomisation.

This is a single-blind trial. The researchers taking the measures will be blind to allocation, as will the data analysts. The importance of maintaining blinding will be emphasised in the training for both research assistants and therapists. As the participants are not blind to their treatment, at post-intervention and follow-up assessments participants will be specifically asked not to comment on the nature of their involvement in the study and not to reveal to the researcher whether or not they were visited by the therapist. Following each assessment, the blinded researcher will note to which condition s/he thought the participant had been allocated and how certain s/he was of the allocation. Sensitivity analyses will be performed to determine whether this knowledge affected participant scores. If there is evidence to suggest that consequential bias is present, the analysis will be adjusted to counteract this effect.

Other protection from bias will include the method of allocation to groups. The randomisation will be performed independently of the data analysis team by the CTU using a dynamic, stratified, web-based system designed to protect from bias by the unpredictability of the algorithm and the security of the web-based program. Blinding will be maintained by automatic generation of randomisation codes and distribution via e-mail direct to the therapists responsible for implementing the treatment. Further bias protection will come from a "treatment as allocated" analysis which will be the principal analysis performed on both primary and secondary outcomes. Treatment compliance measures will be restricted to inclusion in secondary analyses. We will monitor all sites closely to ensure that we identify and correct any causes of drop out which could lead to systematic bias.

We will collect basic anonymised demographic data and reasons for not progressing to trial participation for all those people identified as warranting screening and invitation to the trial but declining to be screened or to participate. This data will be reported on a CONSORT diagram, together with information on the amount and nature of missing data, to enable readers to assess bias arising from recruitment or acceptability issues within the trial.

Statistical analysis

Demographic and baseline data will be fully described and all outcome data will be analysed and reported. Significance will be assumed to be 5% throughout, and 95% confidence intervals will be quoted. All data will be anonymised and coded so that data collection and statistical analysis are blind to treatment allocation. The code will be broken only after the primary analysis has been completed. A fully pre-specified analysis plan will be prepared prior to the data being released to analysts. The analysis will be performed on a "Treatment as Allocated" principle to ensure protection against unintended bias. The data will be fully imputed in line with the pre-defined statistical analysis plan, based on the assumption that data are missing at random, to minimise data loss due to missing values or time points. Sensitivity analyses (best case/worst case) will be performed to assess the influence of differing imputation assumptions and to ensure that assumptions made are robust and unbiased. These will include a complete case analysis and a range of different imputation strategies. If these analyses were to yield any evidence that data were not missing at random, we would extend the sensitivity analyses to examine the effect of the non-random missing data. All trial reporting will be CONSORT-compliant [74].

For each outcome measure, at both post-intervention and follow-up, three analyses will be presented, the first two being unadjusted and adjusted treatment-as-allocated analyses and the third a treatment received analysis:

1. An unadjusted two-sample t-test by allocation group.

2. An analysis of covariance with baseline score and stratification variables as the covariates and allocated group as the condition factor. Between-group effect sizes with confidence intervals will be calculated using Cohen's d. Centre will be added as a random factor, and if

the number of practitioners is greater than the number of centres, practitioner will replace centre as the random factor.

3. A repeat of analysis 2 with treatment compliance factored in.

If CR is shown to be effective, additional forward stepping regression modelling will be undertaken to identify factors important in maximising the observed effects. Factors that will be investigated will include diagnostic category, medication status, educational level, social class, caregiver relationship to the person with dementia (spouse, adult child, other) and whether or not the carer is residing with the person with dementia.

For the cost-effectiveness analysis (CEA), service utilisation and carer input data will be collected using the CSRI. Unit costs will be attached to service use measures (from national reference costs, the PSSRU compendium [75], or calculated anew), CR costed in liaison with providers, and carer inputs valued using opportunity and replacement cost options. The CEA will look at changes over 9 months from each of two perspectives (health & social care; societal) in four analyses: cost of achieving an incremental change in COPM; cost of achieving incremental changes in self-efficacy for participants with dementia; cost of achieving incremental QALY gains for participants with dementia; cost of achieving incremental QALY gains for carers. Incremental cost-effectiveness ratios will be computed as required and acceptability curves plotted for a range of willingness-to-pay values. Net-benefit regressions will make it possible to control for site, baseline outcome measures (where appropriate) and baseline costs, as well as gender, age and MMSE score. Sensitivity analyses will be conducted to test for different assumptions in the attachment of costs. We will also estimate the investment costs and net costs to the NHS and the social care system of making CR available nationally.

Research governance

The research will be sponsored by the University of Exeter[2], and will be subject to routine internal audit through the University's standard research monitoring policies. The University has well-established policies, protocols and systems for finance, health and safety, human resources and other management areas that will regulate the study. The University of Exeter will provide appropriate indemnity for negligent harm. The fully accredited Clinical Trials Unit at Bangor University (NWORTH) has a comprehensive set of Standard Operating Procedures (SOPs) for the management of clinical trials and best practice will be employed throughout to ensure this project is managed to the highest possible standard. NWORTH routinely audits its trials to ensure adherence to good practice and to its operating procedures. The NWORTH Quality Assurance Officer will be available to guide the project in

[2] The sponsorship transferred from Bangor University to the University of Exeter on the 1st March 2015.

all aspects of quality management and regulatory issues. NWORTH will supply appropriate templates to assist in developing the Trial Master File (TMF).

Safety reporting

Whilst participation in this trial is unlikely to cause any safety issues, it is important that rigorous and complete safety monitoring is maintained throughout (NWORTH 3.07, SOP for monitoring clinical trials). This will be managed through a trial-specific safety SOP which will be closely aligned to the relevant NWORTH SOP (NWORTH 4.03, SOP for safety monitoring including pharmacovigilance). The procedures for safety reporting will be fully articulated in the trial protocol. Safety data will be routinely reported to the trial Data Monitoring and Ethics Committee (DMEC), and any suspected unexplained adverse reactions (SUSARs) noted will be reported to both the DMEC and the trial sponsor within established timeframes (NWORTH 4.06, SOP for implementation of urgent safety measures).

Trial Management

A *Trial Steering Committee* (TSC), consisting of an independent chair, two academic clinicians, two service user representatives, principal investigator, trial statistician and trial manager, will meet six-monthly. Other members of the trial team, e.g. local PIs, will be invited as non-voting members. HTA observers will be invited to all meetings. The TSC will oversee the running of the trial on behalf of the sponsor and funder and will have the overall responsibility for the continuation or termination of the trial. The role of the TSC will be to ensure that the trial is conducted in accordance with the principles of Good Clinical Practice and the relevant regulations, and to provide advice on all aspects of the trial. The trial protocol and any subsequent amendments will be agreed by the TSC. The TSC will report to the Trial Management Group (TMG), the sponsor and the funder. A *Data Monitoring and Ethics Committee* (DMEC), consisting of an independent chair, an independent statistician, and an experienced academic clinician, will meet six-monthly. The DMEC will be able to advise changes to the conduct of the study or to stop recruitment if the risks of continuing are considered to outweigh the benefits. It will be responsible for considering any newly-published research data which might affect the trial and any additional information that should be passed on to participants. The trial statistician will be available to answer any questions and to provide blinded and, if requested, unblinded trial data for interim analysis. The DMEC will receive regular safety reports from the TMG. The DMEC will report to and make recommendations to the TSC. The investigators will meet quarterly in a *Trial Management Group* (TMG) mainly by teleconference, but face-to-face at least yearly, to ensure the effective strategic management and oversight of the project. Individuals responsible for the day-to-day running of the trial, including the trial manager, statistician and collaborating clinicians, will be invited as necessary. The TMG's role will be to monitor all aspects of the trial's conduct and progress and adherence to the protocol. It will take appropriate action to safeguard participants, and ensure the overall quality of the trial. The TMG will report to the DMEC and TSC. A *Trial Researchers' Management Group*

(RMG) will manage day-to-day research issues both at the centres and within the Exeter team. This quarterly meeting, usually held by teleconference, but face-to-face once a year, will be chaired by the Chief Investigator and will include representation from the CTU and from each centre. The RMG will report to the TMG.

Deliverability

We have worked closely with DeNDRoN during the development of the proposal to establish a realistic assessment of deliverability. An experienced local PI will lead the study at each centre, and targets have been discussed and agreed with the local PI and the relevant NIHR CLRN or MHRN (England) or NISCHR CRC (Wales) team. The length of the recruitment period for the trial has been determined in order to ensure that recruitment rates are feasible. The proposed sample size requires each centre to recruit at the rate of 3 participants per month for 27 months. This is considered achievable by all centres and networks. Recruitment strategy has been discussed and agreed with all centres and networks. The issue of potentially competing studies will be monitored carefully. Only one study that could be perceived as potentially competing has been identified by local networks. This is the HTA-funded iCST study; however, that study will be recruiting people with lower MMSE scores, and recruitment is due to complete by May 2013. GREAT is a pragmatic trial and therefore participation would not preclude involvement in other clinical trials *per se*, unless those trials involved cognition-focused intervention. However, participant burden and inclusion/exclusion criteria in other, fastidious trials may preclude such dual participation. Each local PI will review any situation where there may be a conflict of recruitment pathways between trials to ensure that all potential participants are offered the most suitable option based on closest fit to eligibility criteria and participant preference. Attrition rates have been discussed above; we have adopted a conservative estimate of 27% attrition over the whole course of the trial. While it is possible that actual attrition rates may be somewhat lower than this, it is very unlikely they would exceed this level. In planning the trial we have carefully considered the resources, expertise and facilities needed at each site

Implementation of the intervention within the NHS

The CR approach offers a practical means of engaging people with dementia and carers in an early intervention process that aims to reduce functional disability and maximise engagement and participation, contributing to the possibility of living well with dementia. This approach can readily be offered by memory clinics in the period following diagnosis. Several UK memory services have already expressed interest in implementing CR. CR is also becoming acknowledged internationally; for example, it has recently been authorised for insurance reimbursement in Belgium, and has been conducted with the aid of trained volunteers in Canada. People with dementia have themselves begun to advocate for a rehabilitation approach [76]. The proposed trial will provide the necessary evidence base to extend these developments.

We will build on the experience gained at each site to demonstrate how the CR approach can most effectively be integrated into NHS provision. For each site, we will work closely with local services to identify staff who could be involved in delivering CR interventions and ways in which work practices could be adjusted to support this; for example, in some multidisciplinary teams CR might be incorporated alongside routine monitoring, while in others an appropriate staff member might shift the balance of work between assessment and intervention. Once recruitment for the trial comes to an end, we will offer training, firstly for whole teams in order that they understand the approach, and secondly for staff who would be specifically engaged in delivering CR interventions. Trial therapists will be involved wherever possible in delivering this training. Training will be supplemented by consultation and advice to ensure that services are able to develop a pragmatic means of integrating the approach within their own practice in a way that fits with local circumstances. Thus at the end of the trial we expect to have established demonstration services implementing the approach within each of our eight centres. Each service will be encouraged to evaluate the implementation and benefits of adopting this approach. This process will be supported by the development of written materials that can aid implementation. We will prepare a handbook for services wishing to implement the CR approach, and a manual for therapists wishing to use the approach with their clients. The former will explain the approach and its role in early intervention, and describe the ways in which services could incorporate the approach into their work. The latter will provide a detailed guide for health service staff engaged in direct client work with people with early-stage dementia and their carers.

CR is a collaborative method, requiring the active engagement of the person with dementia and, where appropriate, the carer, and it provides a vehicle for fostering self-management and problem-solving skills in dealing with the challenges that dementia brings. Some people with dementia, and carers, may be able to adopt the approach as a form of self-help, with only limited support from a therapist. Others may be equipped by a period of therapeutic intervention to engage further in effective self-help. We will develop a self-management guide for people with dementia and carers, which can support efforts at self-help and supplement or extend the therapeutic work undertaken by health service staff. We will also prepare a lay information sheet, which will be made available to people with dementia, carers, and the general public through publication on the Alzheimer's Society website. We will consult widely to ensure that all procedures and materials can be clearly understood by people from a range of ethnic and educational backgrounds.

Once the demonstration services are in place and written materials prepared, the investigators and the trial steering committee will work with experts in publication, training and marketing within the Alzheimer's Society, and with experts in knowledge translation, to identify effective methods targeting both NHS health professionals and people affected by dementia. We will explore the most appropriate means of making the written materials

prepared for services, health professionals, and people with dementia and carers widely available.

Project timetable and milestones

A CONSORT-style flow chart for the trial is shown in Figure 2 below. Project milestones and target completion dates are listed in Table 3 (p. 29). An overview of timescales is given in Figure 3 (p. 30).

Figure 2. GREAT trial CONSORT-style flow chart

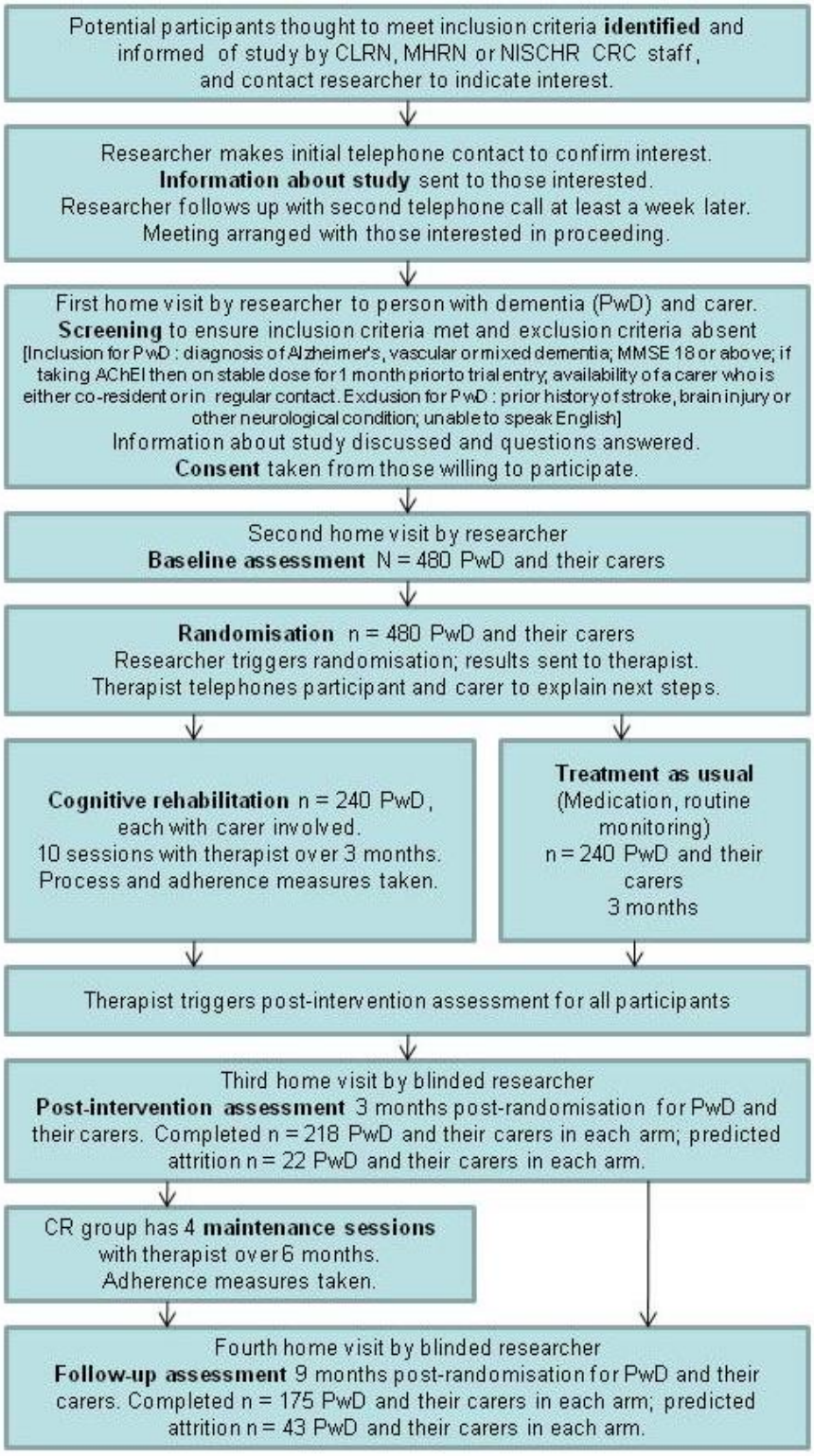
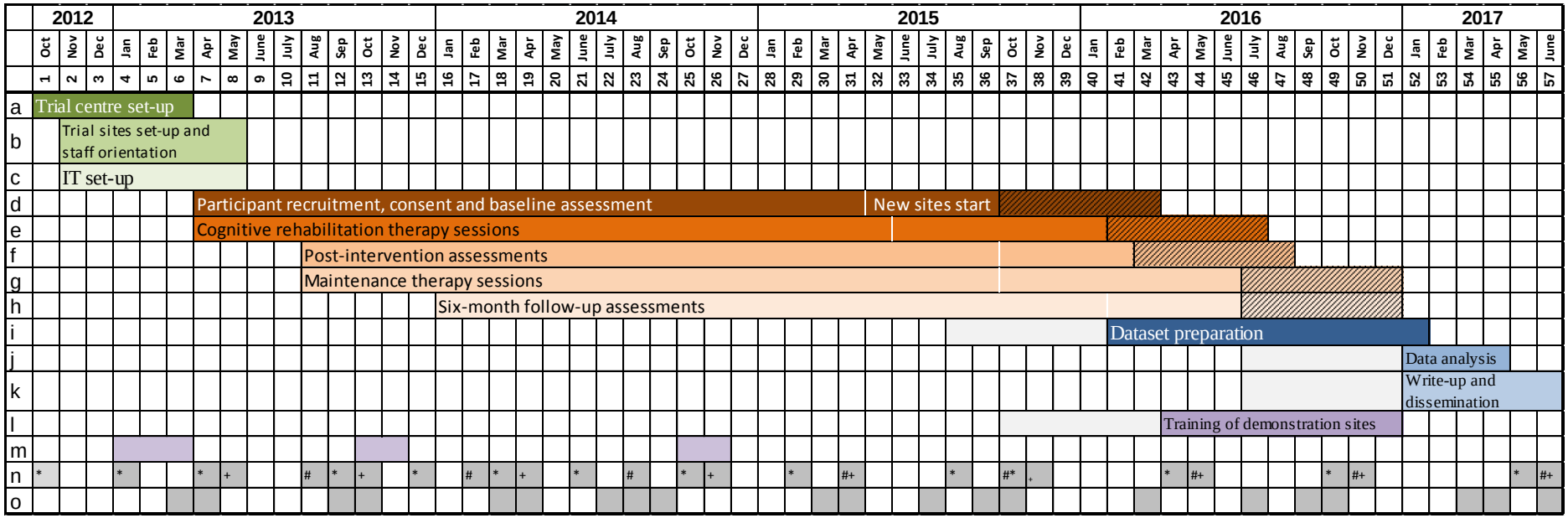


Table 3. Project milestones and target completion dates

Year	Project milestone	Completed by	Actual date (end of):
Prior to start	Excess treatment costs obtained	Start date	Sep 12
	Ethical approval, site-specific approval, R&D permissions	Start date	Sep 13
	Trial manager recruited	Start date	Sep 12
	Bangor research assistant recruited	Start date	Sep 12
Year 1	Trial manager and Bangor research assistant in post	Month 1	Oct 12
	Macro system set up for data entry and analysis	Month 2	Nov 12
	Handbook for therapists and research assistants written	Month 2	Nov 12
	Trial site research assistants recruited and in post	Month 3	Dec 12
	Equipment purchased (computers, measures)	Month 3	Dec 12
	Prepare trial protocol for publication	Month 3	Dec 12
	Therapists recruited and in post	Month 4	Jan 13
	Initial training for research assistants	Month 6	Mar 13
	Initial training for therapists	Month 6	Mar 13
	Orientation and training for LRN/NISCHR staff	Month 6	Mar 13
	Trial management set-up completed	Month 6	Mar 13
	Supervision schedule for therapists and RAs in place	Month 6	Mar 13
	Participant recruitment in progress in North Wales	Month 7	Apr 13
	Baseline assessments begin	Month 7	Apr 13
	Trial site set-up completed	Month 8	May 13
	IT set-up completed	Month 8	May 13
	Therapy sessions begin for CR group	Month 8	May 13
	Participant recruitment in progress at all six centres	Month 9	Jun 13
	Post-intervention assessments begin	Month 11	Aug 13
	Maintenance sessions begin for CR group	Month 11	Aug 13
	Trial protocol accepted for publication	Month 11	Aug 13
Year 2	Training for LRN/NISCHR staff	Month 14	Nov 13
	Training for therapists and research assistants	Month 14	Nov 13
	Six-month follow up assessments begin	Month 16	Jan 14
	Detailed analysis plan and publication strategy developed	Month 20	May 14
Year 3	New site research assistants and therapist recruited and in post	Month 32	Apr 15
	Initial training for new sites	Month 32	Apr 15
	Participant recruitment in progress at new sites	Month 33	May 15
	Therapy sessions begin for CR group at new sites	Month 34	Jun 15
	Training for LRN/NISCHR staff	Month 36	Sep 16
	Training for therapists and research assistants	Month 36	Sep 16
	Post-intervention assessments begin at new sites	Month 37	Oct 15
	Maintenance sessions begin for CR group at new sites	Month 37	Oct 15
	Six-month follow up assessments begin at new sites	Month 41	Feb 16
	Dataset preparation begins	Month 41	Feb 16
	Participant recruitment completed	Month 42	Mar 16
	Baseline assessments completed	Month 42	Mar 16
	First draft of handbook, manual and self-help guide prepared	Month 42	Mar 16
Year 4	Training of local demonstration services begins	Month 43	Apr 16
	Plan in place for making CR materials widely available	Month 45	Jun 16
	Therapy sessions completed for CR group	Month 46	Jul 16
	Post-intervention assessments completed	Month 47	Aug 16
Year 5	Maintenance therapy sessions completed	Month 52	Dec 16
	Six-month follow up assessments completed	Month 51	Dec 16
	Training of demonstration sites completed	Month 51	Dec 16
	Site closure and archiving completed	Month 51	Jan 17
	Dataset preparation completed	Month 52	Jan 17
	Data analysis begins	Month 52	Jan 17
	Write-up of findings begins	Month 52	Jan 17
	Data analysis completed	Month 55	Apr 17
	Write-up of findings completed	Month 57	Jun 17
	Handbook, manual, self-help guide and information sheet available	Month 57	Jun 17
After end of trial	Journal articles published	Beginning of year 6	Mar 18
	Findings disseminated to academic and practitioner audiences	Beginning of year 6	Mar 18
	NHS implementation supported	Ongoing	Ongoing

Figure 3. Overview of project timescales: months 1 - 57



Key

extension

originally planned

a. Trial centre set-up
b. Trial site set-up and staff orientation
c. IT set-up
d. Participant recruitment, consent and baseline assessment
e. Cognitive rehabilitation therapy sessions
f. Post-intervention assessments
g. Maintenance therapy sessions
h. Six-month follow up assessments
i. Dataset preparation
j. Data analysis
k. Write-up and dissemination
l. Training of demonstration sites
m. Training sessions for project staff
n. Key meetings (* = Trial Management Group and Trial Researchers' Management Group; + = Trial Steering Committee; # = Data Monitoring and Ethics Committee)
o. Reporting (HTA, Data Monitoring and Ethics Committee, Research Ethics Committee)

Expertise

The team will be led by Professor Linda Clare, a clinical psychologist, who developed the cognitive rehabilitation approach for people with early-stage dementia and led the pilot trial. She will be responsible for trial management, for the intervention protocol, and for reporting and dissemination of findings. An experienced academic clinician with expertise in researching psychosocial interventions and a background in clinical psychology, old age psychiatry, neuropsychiatry or geriatric medicine will provide project leadership at each site, supervise the day-to-day work of the research assistants, and contribute to dissemination and local NHS implementation: Dr Tony Bayer (South Wales), Professor Alistair Burns (North-West), Professor Roy Jones (South-West), Professor Michael Kopelman (London), Dr Jan Oyebode (West Midlands) and Professor Bob Woods (North Wales). Mrs Jackie Pool, an occupational therapist, specialist consultant and experienced trainer, will provide expertise in applying rehabilitation in dementia care and in therapist training and supervision, and will work together with Professor Clare and Dr Oyebode on these areas. Dr Oyebode and Professor Clare will provide specialist monthly telephone supervision for the research assistants, focused on the process of identifying and setting goals with participants (months 4 – 33). Professor Martin Knapp (London School of Economics) will contribute expertise in health economic evaluation. Expertise in trial design and data management and analysis will be provided by the Associate Director of NWORTH - the Bangor Trials Unit. Dr Anne Corbett of the KCL will represent the patient and carer perspective and contribute expertise in relation to patient and public involvement and dissemination of findings. The Alzheimer's Society will be a partner in the project, supporting patient and public engagement and dissemination. The investigators will meet monthly, mainly by teleconference, but at least yearly face-to-face, to ensure the effective management of the project.

Service users

Service users have been involved in the feasibility and pilot stages of the research leading to this proposal. The pilot trial benefitted greatly from the involvement of Alzheimer's Society Research Network Volunteers. The Research Network is a group of people with dementia, carers and former carers who are trained and experienced in research process and design. The Network volunteers developed a very positive view of the approach used in this study; for example, one commended 'the ability of your approach to deal with the very individual concerns that people with dementia have and in such a person- friendly manner. [It is] very supportive, very specific to each person.' (Victoria Morgan, Research Network Volunteer). The findings of the pilot trial were presented at a recent conference of the Alzheimer's Society Research Network, and when asked later in small-group workshops run by Society staff what kind of research the Society should be promoting, the volunteers responded that they wanted to see more research of this kind. During the development of this proposal we again sought, and took into account, the views of Alzheimer's Society Research Network Volunteers and of service users contributing to the DeNDRoN Patient and Public Involvement (PPI) programme. PPI for the proposed trial will be provided through a

partnership with the Alzheimer's Society, reflected in the inclusion of Dr Anne Corbett as a co-applicant; this will ensure that service users are fully involved with the design, delivery and dissemination of the research. Service users will be consulted at each stage of the trial to ensure optimal tailoring of study protocols and procedures. To ensure that PPI is integrated throughout the study, two service user representatives will sit on the Trial Steering Committee. The Alzheimer's Society Research Network will also contribute to dissemination activities towards the end of the study, ensuring that outcomes are communicated to lay audiences and policy-makers.

Project staff

A full-time trial manager will be appointed, based in Exeter. An experienced therapist (NHS Band 6, point 5 – 7, except in Bangor where the appointment will be on NHS Band 7 point 5 with the expectation that this therapist will take a leadership role in supporting the other trial therapists) will be appointed at each of the eight centres at 0.6 full-time equivalent (FTE) to conduct the intervention. A research assistant (University Grade 6) will be appointed at each centre to carry out assessments, enter data, and undertake other project-related administrative tasks. The research assistants will be appointed at 0.6 FTE except in Bangor, where the position will be full-time in order to provide extra support to the Chief Investigator and trial manager.

Dissemination strategy

Findings will be disseminated to academic audiences through publications in academic journals and presentations at academic conferences (e.g. the Alzheimer's Association International Conference, British Neuropsychology Society, International Neuropsychological Society, British Society of Gerontology, Gerontological Society of America, International Association of Gerontology and Geriatrics, etc). Dissemination to practitioners will focus on articles in practitioner-oriented publications (e.g. Journal of Dementia Care) and presentations at practitioner-oriented conferences (e.g. UK Dementia Congress, Memory Clinic conferences, DeNDRoN and NEURODEM conferences, Alzheimer's Society conferences) and training events organised by relevant professional groups (e.g. British Psychological Society Division of Neuropsychology). Dissemination to people affected by dementia (service users and carers) and voluntary sector workers will be achieved using printed and web-based materials through various routes including DeNDRoN and NEURODEM, Dementia Services Development Centres, and relevant voluntary sector organisations (including, but not restricted to, the Alzheimer's Society). DeNDRoN and NEURODEM will also provide routes through which the findings may be brought to the attention of policy-makers. The close involvement of the Alzheimer's Society in this study offers access to specialist expertise in marketing, publications and training, which will allow the investigators to benefit from expert advice that will help to optimise the dissemination strategy.

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Appendix 1. Description of the qualitative component for GREAT v2 20/01/2014

Qualitative exploration of the experience of goal-oriented cognitive rehabilitation for people with early stage dementia and carers

Quantitative data on the efficacy of CR for people with early stage dementia will be complemented by a qualitative sub-study exploring the way in which the intervention was experienced by the participants in the treatment group. At four research sites (Bangor, Bath, Cardiff, and Manchester) up to 40 participants completing the intervention, and their carers, will be interviewed to gain insight into the way in which they experienced the therapy, and what aspects of the therapy were found particularly challenging or helpful. In-depth understanding of the subjective experience of the intervention for study participants may be helpful in understanding the process of therapy and will provide further information about the efficacy of the CR in early stage dementia. It will enable the study participants to contribute their views and experiences to evaluation of the treatment.

Research questions (objectives)

The key research questions for the qualitative analysis are as follows:

1. How did participants and carers experience the intervention? What were their overall perceptions, how useful did they find it, and what did they feel about the degree of effort required.
2. What impact, if any, did the participants and carers feel the intervention had on their everyday life?

Methods of data collection

Every participant at the participating sites completing the course of CR during 2014/2015, together with the carer, will be invited to discuss the experience of receiving the intervention in an interview. The invitation will be given at the penultimate session (session 13) and supplementary Participant Information Sheet will be provided. At the final session (session 14) the therapist will establish whether the participant and carer are willing to be interviewed and if so will record informed consent. The interviews will take place after the final follow-up assessment to avoid any possible bias resulting from having discussed the experience of therapy with the interviewer. Interviews will be conducted by a researcher who is not part of the study delivery team to ensure that participants and carers feel they can speak freely. Participants and carers willing to be interviewed will be contacted by the interviewer to arrange a date and time for the interview. The interviews are expected to take place in participants homes, but participants and carers will be offered the option to be interviewed on the university/NHS premises if they wish. Participants and carers will be interviewed separately. When meeting with the researcher they will have the opportunity to raise any questions they may have about the interview, and consent will be re-established prior to conducting and audio-recording the interview.

The interview will follow a semi-structured interview schedule, and will take form of a conversation in which the interviewer will encourage the participants and carers to talk freely about their experience of the intervention. Participants and carers will be asked if they would like to receive and comment on a summary of the findings from the qualitative study.

Plan of analysis and plan for synthesis of qualitative and quantitative findings

All interviews will be audio-recorded, transcribed verbatim and anonymised. Thematic analysis starting from a realist position and based on an inductive approach will be used to identify and explore patterns of meaning within the data in order to identify themes that capture something important in relation to the research question [1]. The analytic process will adhere to the methodological steps outlined by [2], and will be conducted separately for person with dementia and carer interviews. QSR NVivo 8 software will be used to organise and manage the data. Initially, for each set of interviews, two researchers will read and re-read the first five transcripts to familiarise themselves with the data and will then identify and code (briefly summarise and characterise) units of meaning within each transcript. Codes will be listed separately, reviewed, and organised into meaningful groups representing initial themes for each interview. The resulting lists of themes will be compared and discussed by the two researchers until consensus is reached about content and organisation, after which each researcher will re-code the transcripts and inter-coder reliability will be assessed [3-5]. The remaining transcripts within the set will then be analysed in the same way by a single researcher. Once all transcripts in the set have been analysed, the lists of themes for each participant will be compiled into an overall list, and related themes will be clustered together and the clusters ordered into group-level themes and sub-themes , with the two researchers working together to integrate these into an overall thematic map. All transcripts will then be recoded in line with the thematic map, with inter-coder reliability being established in the same way as was done at the previous stage, and representative extracts will be identified that illustrate each theme and sub-theme. A draft account will be prepared and the credibility and trustworthiness of the resulting account [6] will be supported by inviting comments from those interviewees who expressed willingness to comment on the findings. The study therapists and researchers will also be invited to consider the extent to which the account resonates with their experience of interacting with the participants. The responses will be taken into consideration when finalising the account of the qualitative findings. The findings will be summarised in the main trial report in order to augment the quantitative findings and, if appropriate, will be used to support the process of implementing the intervention in NHS contexts that is envisaged to take place in the final stages of the study.

Management arrangements

The qualitative researcher will be supervised by the CI and Trial Manager. The researcher will liaise closely with the therapist and where necessary the local PI. Progress of the

qualitative sub-study will be reported to and overseen by the Trial Management Group and Trial Steering Committee. Ethics

Timescale for the qualitative component within the overall study

Interviews will be conducted during 2014. Analysis will take place during 2014 – 2015 and will be completed by the end of 2015.

Resources required (to be covered from project underspend)

Travel costs for the researcher to visit participants - £1600. Expenses for 40 x 100 mile round trips at £0.40 per mile, estimated based on expected location of participants.

Transcription costs - £3,200. Transcription costs for 40 interviews at a fee of £80 per hour of interview material.

Available resources which can be accessed at no extra cost to the project

- Researcher time to conduct the interviews – we have a researcher available who can carry out the interviews during 2014 at no cost to the project
- Researcher time to conduct the analysis – this will be undertaken by project team members at no extra cost to the project
- Audio-recording equipment (digital voice recorder and lapel microphone)
- QSR NVivo 8 software

The required resources (£4,800) can be covered from the GREAT budget because the Trial Steering Committee and Data Monitoring and Ethics Committee elected to hold most of their meetings as teleconferences rather than engaging in the face-to-face meetings we had budgeted for. This resulted in savings in excess of £4,800 (representing travel and subsistence costs estimated at £180 per meeting for 11 people).

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