NETSCC, HTA

2nd February 2011

HTA Clinical Trial Revised Proposal – CARE-DEM project 08/53/14 (Work packages 1 & 2, and Qualitative study)

1. Project title: Development and evaluation of the effectiveness and cost effectiveness of Collaborative cARE for people with DEMentia in primary care (the CARE-DEM project).

2 Planned investigations:

2.1 Research objectives

This study will develop and evaluate the feasibility of collaborative care for people with Dementia in primary care. It will create a training programme for primary care staff to enable them to undertake case managment with patients with dementia and their families (Work package 1). The feasibility of implementing the training programme will be tested in a pilot rehearsal trial (Work package 2), which will also allow effect sizes to be estimated for a definitive main trial. Qualitative methods will be used to study the development process and implentation in the field, to inform refinement of the training programme and introduction of the case management methods into routine practice.

If the intervention appears to be effective, we will seek further funding for Work package 3, a definitive main trial which will address the key research question:

What is the comparative clinical and cost-effectiveness of usual care augmented with enhanced case-management within a collaborative care model, compared to usual care, for people with dementia living independently in the community?

Primary objective: To evaluate the clinical and cost effectiveness of usual care augmented by collaborative care, compared to usual care, at reducing behavioural and psychological disorders in people with dementia in primary care.

Secondary objectives of this study:
1) To develop and pilot the feasibility of a UK model of collaborative care for dementia, led by a primary-care based case manager using evidence based care pathways (Work packages 1 & 2).
2) To provide a detailed description and analysis of the case management intervention, including a description of how it works in practice, and a toolkit for its replication should the intervention prove effective (Work package 2 & Qualitative study).
3) To explore the acceptability and value of a collaborative care model in dementia, delivered by a case manager, to people with dementia, their family carers and other dementia care professionals and services (Qualitative study).

Secondary objectives of the follow-on study (Work package 3)
4) To conduct a cost-utility analysis of usual care augmented by collaborative care management, compared to usual care, on NHS resource utilisation by people with dementia and their family carers. The outcome in this analysis would be change in quality-adjusted life years (QALYs) derived from the DEMQOL (using an algorithm currently being developed in a study by Banerjee, Brazier, Knapp and others, funded by the HTA) (Work package 3, definitive trial).

2.2 Existing research

Our ageing population and implications for NHS care: Life expectancy is increasing by two years per decade. Older people represent the fastest growing sector of our population. In the United Kingdom (UK), improving the health and social care of our ageing population is one of the key priority areas for health care policy [1 2]. Our ageing population will lead to an increase in age-related illnesses, such as dementia, and will present considerable challenges for healthcare providers in the future. This will be particularly so for primary and community services following the recommendations of the latest White Paper, *Our heath, our care, our say,* which stipulates that care for older people, and for those with long term conditions, should be delivered as close to their homes as possible [3].

Dementia; current impact and burden: Dementia is one of the main causes of disability in later life; in terms of Global Burden of Disease, it contributes 11.2% of all years lived with disability, higher than stroke (9.5%), musculoskeletal disorders (8.9%), heart disease (5%) and cancer (2.4%). One in 14 people aged over 65 has a form of dementia, rising to one in six of those over 85. In the UK, there are currently around 700,000 people with dementia but this is estimated to rise to 1 million by 2020 and 1.7 million by 2050, an increase of over 150% [4]. The total costs of caring for people with dementia in the UK have been estimated at between £17 and £18 billion a year[4], more than heart disease (£4 billion), stroke (£3 billion) and cancer (£2 billion). Currently around two thirds of people with dementia live in private households, with the majority of their care provided by family supporters and primary and community care teams [4].term care places available-er of longHowever the steady fall in the numb 024 for people with dementia, together with the rising numbers of older people generally, will lead to an increasing number of frail older people requiring complex care packages if they are to continue to live independently and hence postpone or avoid moving into institutional care.

Dementia care in the UK; existing provision and evidence: There is evidence that the standard of dementia care in the UK is in urgent need of improvement, with frequent failure to deliver services in a timely, integrated or cost effective manner to support people with dementia and their families to live independently for as long as possible [10]. Within primary care, general practitioners admit to difficulties both in dementia diagnosis and common areas of dementia management [10]. In the UK, dementia detection rates have been increased through the use of educational interventions in primary care but in terms of dementia care, alternative models of service delivery have not been explored. Research from outside the UK has revealed the potential of a collaborative care model for both the assessment [11] and care of people with dementia [7 12]**,** with demonstrated benefits in quality of life and other measures.

Case management and Collaborative Care: In mental health, case management, in which workers known as 'case managers' systematically follow up patients under regular supervision and usually provide both brief psychological therapy and medication management is a particular type of collaborative care [13]. Although the term case manager is used in health care, care manager is used within social care. The origins of collaborative care lay in concerns about the inadequacy of much current treatment for depression and developments in the field of chronic physical disorders. 'Collaborative care' has itself been variously defined to mean everything from collaboration between services, and 'shared care' to the more highly structured definition that is now becoming accepted internationally [14]. The components of a collaborative care model for depression are: A) ***multi-professional approach to patient care*** provided by a case manager working with the GP under supervision from specialist mental health medical and psychological therapies clinicians; B) ***a structured management plan*** of medication support and brief psychological therapy; C) ***scheduled patient follow-ups*** ; D) ***enhanced inter-professional***

communication patient-specific written feedback to GPs via electronic records and personal contact.

In earlier studies of depression, mental health professionals provided the enhanced staff input to primary care settings and undertook a care co-ordinator role [15, 16]. More recently, primary care nurses [17, 18] were used to fulfil the role of care co-ordinator. Most studies of collaborative care have been from the US. In the UK, one published study using practice nurses in the care co-ordinator role did not improve either patient antidepressant uptake or outcomes compared with usual GP care [18], but Chew-Graham et al [19] demonstrated an improvement in depression outcomes utilising the collaborative care approach and flexible psychological intervention delivered by a mental health nurse.
Christensen et al [20] in their systematic review of models of care for depression, suggested that components which were found to significantly predict improvement were the revision of professional roles, the provision of a case manager who provided direct feedback and delivered a psychological therapy, and an intervention that incorporated patient preferences into care.

Case management in dementia: Current national guidance on dementia care recommends the provision of coordinated health and social care, led by a single health or social care professional (care manager in social services but case manager in health care)[5]. This was also a key recommendation of recent reports on dementia care [10 21] and mirrors the views of people with dementia and their family carers . A US based trial (PREVENT) of such a collaborative care model, led by a nurse practitioner integrated in primary care [7], demonstrated significant improvements for both people with dementia (increased prescribing of cholinesterase and antidepressant drugs, fewer behavioural and psychological symptoms) and for their family carers (improved depression scores, higher carer satisfaction ratings). Our proposed intervention for dementia is derived from this US model [7]; however in the US trial, cost effectiveness of the intervention compared to usual care was not formally assessed and effects on institutionalisation could not be determined due to limited follow up, so we will address these questions. Challis and colleagues, [22], demonstrate the effectiveness of a model of intensive case management for people with dementia based in a community-based mental health service for older people. Our proposed case manager role will be carried out by primary care practitioners working in liaison with secondary care services.

National Dementia Strategy and Care Advisers: The recently published National Dementia Strategy (NDS) has recommended the introduction of a new role, dementia care advisers as best practice for people with dementia[23]. The focus of the dementia care advisor will be to provide information provision to people with dementia and signpost them to additional sources of help and support. The strategy clearly states that this new role would not be that of intensive case management, as currently carried out by community mental health teams or Admiral Nurses, or as in the intervention we propose to evaluate in this trial. It is unclear (given their proposed relationship to the third sector) how much authority dementia advisers will have within health and social care. Equally unclear is how much they will be able to go beyond signposting people with dementias, by responding directly to complex situations, especially where co-morbidities interact with dementia. There are grounds for thinking that a simple advisory service will not meet all the needs of people with dementia, particularly when these needs are complex and related to the interplay of complex co-morbidities and pre-existing social relationships.

Summary: The number of people with dementia is predicted to rise by 150% over the next 40 years. There is consistent evidence that the standard of dementia care in the UK is in urgent need of improvement, with frequent failure to deliver services in a timely, integrated or cost effective

manner to support people with dementia and their families to live independently for as long as possible. Current best practice guidance on dementia care recommends the provision of coordinated health and social care, led by a single health or social care professional (care manager)[5]. Such a collaborative care approach has shown promising benefits elsewhere; however there is a lack of UK-based research exploring the clinical and cost effectiveness of alternative models of service delivery in dementia care. This study will compare the impact of a collaborative care model in dementia against usual care in terms of both clinical and cost effectiveness.

2.3 Research Methods

This study will take place in general practice-based primary care in 3 centres; London and Kent in the South East of England and Newcastle in the North East of England. We will aim to engage whole Practice Based Commissioning localities and consortia, in order to limit the geographical areas across which case managers will work,

The target patient population is people, of any age, with a diagnosis of any type of dementia (confirmed by secondary care assessment) who are living independently in the community and who have a main informal carer (spouse, close relative or other informal care giver) who maintains regular contact.

Those undertaking the case management role will be already in post within a community-based organisation (either primary care team, Primary Care Trust (PCT) or Community Mental Health Team (CMHT) depending on existing local arrangements, interest and expertise. We anticipate that most of those interested in taking on the case manager role will be nurses of the level of experience found at band 7, working in district nursing, as CPNs or possibly as practice nurses. They will receive additional training (to be developed in workpackage 1 and tested in workpackage 2), provided through the Admiral Nurse training organisation 'For Dementia', with an induction period, periodic refresher days, experiential learning, mentoring and formal on-site supervision, via Admiral Nurses at the three planned study centres. Training will be delivered by a regional senior clinician from the project team and an Admiral Nurse, with other clinicians or allied medical professionals delivering specific training as required. In the PREVENT model training is over 8x2 hours sessions and it is anticipated that at least this amount of time will be necessary.

This project consists of the following work packages:

- Work package 1: Developing the intervention and customising care pathways from the PREVENT study
- Work package 2: Pilot (rehearsal) study
- Qualitative study, extending across work packages 1 & 2.

Funding will be sought for Work package 3 (the definitive main trial) if the pilot trial suggests that the intervention has an effect.

2.3.1 Workpackage 1.

The aim of workpackage 1 is to embed a collaborative care approach, based on case management methods and evidence basedcare pathways, in primary care to enable better management of common problems in dementia. A multi-professional care co-ordination approach to patient care will be provided by a case manager working with the patient's GP and liaising with specialist

mental health services, social services and third sector organisations as necessary. The practitioners with case manager roles will be located within primary care to coordinate care and liaise regularly with GPs, and will be supervised by Admiral Nurses. Training in collaborative care and case management techniques will be offered to district nurses, practice nurses, GPSIs or other existing primary care practitioners as determined by the local skill mix and local commissioning needs and intentions. Scheduled patient follow-ups will be included as part of the case management process, with the frequency and location of meetings being client-led. Enhanced inter-professional communication and liaison using patient-specific written feedback to GPs via electronic records as well as personal (face to face or telephone) contact will be an integral part of the case management method.

This workpackage will adapt and customise the care pathways used in the PREVENT study [7] for use in the NHS (http://iucar.iu.edu/research/behaviouralprotocols.html). It will draw on the experience that Admiral Nurses have in promoting collaborative care for people with dementia between general practice teams and specialist services, including an evaluated project in Kent [24], and current projects in Worcester and Southampton.

The case management methods will be based on those used in the US PREVENT trial but will be customised in the pilot phase of this trial for UK to reflect the following aspects of the UK health care policy and setting,:
i) The National Dementia Strategy's (NDS) commitment to training for professionals in dementia diagnosis and management;
ii) The NDS's commitment to the development of dementia advisors;
iii) The role of memory assessment units /memory clinics in confirming and conveying diagnoses and
iv) The current commissioning arrangements and the need for local services to reflect local need

A multidisciplinary expert group, including people with dementia and carers, will review the PREVENT care pathways, which will focus on management of the following topics: communication issues; behaviour problems (agitation, aggression); mobility; personal care; sleep; legal and financial issues; physical health; depression and anxiety; psychotic symptoms; carer interventions and medication support. This expert group will use an iterative technology development approach [25] to create modifications to the care pathways, which will then be reviewed and critiqued by a separate panel of practitioners, carers and people with dementia ('bench testing'), refined and 'field tested' in Workpackage 2.

The expert group will also develop learning resources and workplace training methods, based on adult learning principles (i.e.case-based & problem-solving), an approach which has proved effective in producing training materials for general practice that change clinical activity [26]. Admiral Nurses who will act as supervisors and mentors for practitioners undertaking case management work will participate in this development process, to ensure that co-design principles are applied [27].

The lead for this workpackage will be Iliffe, supported by Fox, Stephens & Manthorpe

2.3.2. Workpackage 2

This workpackage will consist of a rehearsal trial plus engagement of PCTs, Practice based Commissioning localities and consortia, individual practices and other relevant services and agencies in preparation for the main trial.

Prior to the full trial, we will conduct an 18 month rehearsal pilot study in four practices, two in the northern region, and one each in London and Kent. This pilot trial will check assumptions about practice and patient recruitment and retention, confirm the acceptability of brief intervention procedures and ensure the feasibility (data yield and quality) of proposed outcome measures. It will allow us, if necessary, to adjust our sample size calculation. Practices which take part in the rehearsal study will not participate in the main trial.

Practices will be asked to actively recruit patients over a three-month period. The major departure between the main trial and the pilot work is that study outcomes will only be collected at 6 months post intervention. The objective for the pilot phase is to ensure that case management skills and the collaborative care model will be easy to acquire and apply, and that they will become a form of 'soft technology' [28] that will be incorporated into routine practice. The difficulty with all new technologies in health care is that they may be hastily 'shoe-horned' into practice, and be abandoned once their introduction is technically completed. Co-design with end-users (both professional and patient users) [27] is essential to make skill packages and skill acquisition sufficiently flexible and adaptable to different disciplines and settings without diluting their impact on care.

The key success criteria for the pilot trial are if practices can recruit 11 patients into the study (depending on practice size), that 9 can be contacted at 6 months and that stakeholders find the intervention procedures acceptable and feasible within routine NHS practice. We will extrapolate rates of retention to 15 months based on retention at 6 months in this pilot, and trends thereafter in comparable studies. There will also be a nested qualitative study within this rehearsal study .

Qualitative study within workpackage 2

In order to describe and develop an understanding of the various *mechanisms* at work, and allow a look at of some of the *outcomes* of the intervention, an exploration of user and provider perspectives will be undertaken. This pilot study will investigate: i) The acceptability of the intervention (exploring the experience of the intervention and participants perceptions of its impact); and ii) The acceptability of participating within the study (exploring the process of recruitment, consent and participation within the research process).

We will employ in-depth interviews and focus groups in order to meet the objectives outlined above. In total, up to 20 individual interviews will be carried out with people with dementia (and their carers where appropriate) and case managers delivering the intervention across the four pilot practices in two different geographical sites (Newcaslte andNorth Tyneside in the North of England, and London and Kent in the South of England). Two focus groups, one from each goegrphical area, will be carried out bringing together the organisational framework in which this intervention is embedded (participants will be drawn from GPs, nurse managers, commissioners from social and health services) in each pilot site.

Working with local systems

Workpackage 2 will commence at the same time as Workpackage 1, to allow time for each of the site leads to begin detailed discussions and negotiations with PCTs, Practice based Commissioning localities and consortia, individual practices, Community Mental Health Teams, Councils with Social Services Responsibilities and third sector organisations in each site. These discussions will be needed to 1) identify individual practitioners who would be trained in collaborative care approaches and case management techniques 2) establish time commitments for these individuals and agree resources needed for their involvement 3) ensure that the project fits with local plans to implement the National Dementia Strategy and that local specialists and generalists are able to contribute to site management committees, and 4) map existing resources and services, for inclusion in site-specific training of case managers.

Progression to the main trial

The trial management committee, working with the leaders of Work Package 2, will set a range of criteria with respect to rates of eligibility, recruitment and retention. We need to show that we can implement the intervention, recruit and retain subjects and measure outcomes. We will set explicit criteria for rates of eligibility, recruitment and retention with explicit comparison of actual performance against these criteria and recommendations as to how the study would proceed. These are specified below together with the subsequent outcomes regarding the future progression of the trial. Data obtained from the qualitative interviews in Work Package 2 will also inform issues of feasibility and how the impact of the case management process can be improved in the main trial. Although it is unlikely that we will get a substantially greater effect than achieved in the US PREVENT study, it is possible that Work Package 2 will show such a benefit for the intervention that the main trial is unnecessary.

As noted above, the key success criteria for the pilot trial are if practices can recruit, on average, 11 patients into the study (depending on practice size), that 9 can be contacted at 6 months and that stakeholders find the intervention procedures acceptable and feasible within routine NHS practice.

Because of the sample size estimate for the definitive trial (Work package 3) which is pragmatically determined, rather than being based on a formal power calculation, it is unlikely that the difference in our primary outcome measure between the two arms of the pilot study will be statistically significant. However we can determine whether the observed difference is consistent with that specified in our sample size calculation. We could set this as a requirement to define one of the criteria for continuing from the pilot to the full scale trial.

This would be implemented using the following procedure. We would calculate the probability of obtaining the effect size observed in the pilot study, assuming that the true effect size is 0.4. If this probability is smaller than an agreed threshold then we would not continue to the main study. The choice of this threshold would be fairly low as we do not want too great a risk of rejecting a potentially effective intervention at this stage. Either 0.05 or 0.1 would seem sensible. The choice of threshold will be discussed with the Trial Steering Committee and Data Monitoring & Ethics Committee.

We will also ensure during the pilot study that what constitutes usual care is thoroughly documented and that we have identified any other relevant new service initiatives (see below). In terms of ways to improve loss to follow-up, we will document carefully and 'quantify' (simple

descriptive statistics) the reasons for loss to follow-up and identify potential strategies to overcome them (e.g. if people are lost because they move home we will ensure that we have mechanisms for tracing). We will also explore with key stakeholders, via the qualitative component of the Work Package 2, factors that would facilitate retention , and we will seek the advice of DENDRON's public and patient involvement (PPI) forum (Co-CI Iliffe is chair of DENDRON's PPI management committee)

We will supply an interim report to HTA on the pilot phase and, if justified by our findings, a bid for funding for progression to a full trial.

The leads for this workpackage will be Fox in Kent, Livingstone in London & Robinson in Newcastle, with the support of Coulton in Kent and the CTU in Newcastle.

Study outcome measures

Primary outcome measures: The primary outcome measure (on which the sample size calculations are based) for the trial will be the Neuropsychiatric Inventory (NPI)[1] measured at 15 months. This is a validated instrument with 12 domains, completed by carer interview, to assess the prevalence of BPSD in people with dementia. Cost-effectiveness of the intervention will be the other primary outcome, assessed from a societal perspective, based on comprehensively measured costs and outcomes measured using the NPI.

Secondary outcome measures (to be assessed at baseline*,and 6 months post-randomisation for the person with dementia and their carer will include:

Patient: Cognitive function via the Mini Mental State Examination [2](MMSE). Functional impairment via the Bristol Activities of Daily Living Scale[3]; Institutionalisation rates and Quality of life via the Qol-AD, a validated disease specific measure for dementia and DEMQOL, a generic measure from which it is possible to generate QALYs (quality of life adjusted health years (Smith et al 2007); societal weights will be applied.

Carer: Mood/depression via the GHQ-28[4], a 28-item questionnaire that gives a measure of a carer's general distress and strain and Quality of life (HSQ-12 and ii) EQ-5D, a generic measure to generate QALYs (quality of life adjusted health years; societal weights will be applied.**.**

Service use: The Client Service Receipt Inventory (CSRI)[5] captures service utilisation data for the carer and the patient (including institutionalisation, extra patient care during therapy), unpaid carer support and other aspects relevant to health economics. Rates and dates of entry into institutional care will be recorded.

[1] Cummings JL, Mega M, Gray K, Rosenberg-Thomas S , Carusi DA. The Neuropsychiatric Inventory: a comprehensive assessment of psychopathology in dementia. Neurol 1994; 44: 2308-2314

[2] Folstein MF, Folstein SE, McHugh PR. The "mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res 1975; 12: 189-198.

[3] Byrne LM, Wilson PM, Bucks RS, Hughes AO, Wilcock GK. The sensitivity to time of the Bristol Activities of Daily Living in Alzheimer's Disease. Int J of Ger Pscyh 2000; 15: 656-61

[4] Goldberg D. 1978. Manual of the General Health Questionnaire. NEFR-Nelson: Windsor.

[5] Beecham J, Knapp M (2001) Costing psychiatric interventions, in Thornicroft G (ed.) Measuring Mental Health Needs, Gaskell, London

Adverse events: Number of patient deaths and other adverse events like emergency admission to hospital.

Withdrawal from the trial: Those who withdraw from the trial including those who withdraw from the intervention only and those who withdraw from both the intervention and follow- up data collection will be recorded.

All outcome measures will be collected by interview which will be conducted in the patient/carer's homes. Karlawish et al [32] have indicated that home visits for assessment and follow-up are likely to increase willingness to participate in dementia trials.

Follow up: Six months after the initial baseline assessment, all participants will be followed-up by research staff unaware of their intervention status. Patients will initially be contacted by telephone and a follow home visit will be confirmed. In the main trial, a second follow-up of quantitative outcomes will also occur at 15 months.

At the 6 month follow-up point, a purposive sample of patients will be asked if they will participate in a longer face-to-face interview to explore their experiences in the trial in more depth (see 3.6.2 and 3.7.2).

Sample size estimation: We judge that we will be able to complete data collection on six patients per practice. This estimate is based on the following assumptions: an average general practice has a list size of 6000 patients, of whom 16% (960) are over 65, of whom 3% (28 patients) have a diagnosis of dementia (www.ic.nhs.uk/webfiles/publications/gpregpopulations2005). [Although prevalence rates of dementia in people 65 and over are quoted as 6% [35] ,in the UK less than half the people with dementia have a confirmed diagnosis [36.] Of these, 2/3 (19) will be living independently in the community [37].]. Taking the most conservative estimate of rates of consent amongst eligible patients from studies in similar populations [7, 19,38] we believe that we will be able to recruit 60% (11) of these patients. Assuming 18% mortality at 15 months and a loss to follow-up of 33% of those surviving we calculate that we will be able to obtain full outcome data on 6 patients per practice (cluster). Assuming an ICC of 0.04, in the definitive trial we will need to recruit and retain an average of 6 patients from each of 54 practices. Work package 2 will test these assumptions and inform estimates of the sample needed for a definitive trial.

The study will be adopted by the NIHR Dementias and Neurodegenerative Clinical Research Network (DeNDRoN). We will also seek the support of the local DeNDRoN network, Primary Care Research Network (PCRN), Mental Health Research Network (MHRN) at each of the research sites to maximise practice recruitment and ensure successful integration into primary care service delivery.

Qualitative studies

Workpackages 1 & 2 will have nested qualitative components. Qualitative methods play an important role within evaluation research and their value and importance have been recognised within a HTA monograph [41] In order to describe and develop an understanding of the *context* in which the CARE-DEM intervention is working, along with the *mechanisms* and *outcomes* of the intervention, a nested qualitative study alongside the main trial will be undertaken .

In workpackage 1 qualitative methods will be used to explore professional, patient and carers' perspectives on case management and the care pathways being customised for the trial. The emphasis within workpackage 2 will be on evaluating the acceptability of the intervention

developed for the main trial. Observation will take place during the training of case managers and when the intervention is being delivered in order to capture the practical aspects of delivering the intervention to these participants. Auditable fieldwork notes and research diaries of qualitative evaluation researchers will be produced.

The qualitative studies will use a critical realist perspective in which to explain the results of the CARE-DEM trial and how and why this complex intervention does or does not work from the perspectives of patient, carer, health professionals and commissioners. Realistic evaluation is based on the belief that the complex intervention proposed involves complex and holistic layers of reality and that 'outcomes are explained by the action of particular mechanisms in particular contexts' [42]. It will be used to understand, rather than simply describe, the content of the intervention and the process of its development within the context in which it is being practiced by exploring *context* (C), *mechanism* (M), *outcome* (O) relationships with the aim of identifying, articulating, testing and refining CMO configurations.

Within the rehearsal study (WP2) the qualitative evaluation will explore the acceptability of the intervention from three perspectives: the user (person with dementia and their informal carer where appropriate); practitioner (case manager, health and social care practitioners) and the organisation (providers and commissioners of old age and mental health services and social care). Methods of data collection employed to meet the above objectives include individual interviews, focus groups and participant observation.

Qualitative analysis: All data will be digitally recorded and transcribed verbatim. In line with Data Protection Legislation and Research Governance, all information pertaining to individuals will be anonymised. Data collection and analysis will occur concurrently to allow for issues which arise in earlier interviews to be explored in more depth in subsequent interviews and observations. Using all data transcripts, thematic analysis, based on the 'constant comparative method' will be employed [43,44]. Case studies of individual trial participants will be constructed to aid analysis. The validity of data interpretation will be ensured by independent coding and cross-checking by at least two members of the research team (CCG, LR and KB and qualitative researcher). Formal data analysis meetings will be held 10 times per year. A suitable software package (e.g. NVivo) will be used to facilitate the management of data analysis.

The qualitative component of the study will be led by Bond & Brittain and supported by Chew-Graham.

2.6. Economic evaluation : Health economic analysis will be a majpr component of the definitive trial, and this is reflected in the extra resources allocated to health economics in Work Package 2. Health and social care service use, medication data and (unpaid) carer inputs will be collected using an adapted version of the Client Service Receipt Inventory (CSRI). This instrument has recently been tailored and tested for use in studies of older people with dementia, particularly in the EVIDEM NIHR programme on which a number of the current applicants are engaged. It would be further tailored for the CARE-DEM trial. Unit costs will be taken from the PSSRU annual compendium and from individual service providers as necessary (particularly for individual hospitals, given the inherent unit cost variation between settings). New unit costs calculations will be needed for the case management methods (the collaborative care approach) developed in Work Package 1, although they will not be not calculated until Work Package 2.

A secondary economic evaluation will examine QALY gains for people with dementia. The QALY scores (with societal weights) will be generated from the DEMQOL using a conversion algorithm which is currently being generated in an HTA-funded study led by John Brazier and Sube Banerjee, to which Martin Knapp is contributing. Again, an incremental cost-effectiveness ratio and acceptability curve will be used as needed. The incremental values for QALY gains for these analyses can be guided by, for example, the implicit NICE threshold. Given the importance attached to cognition in most previous studies of dementia and its treatment, we will conduct a further secondary cost-effectiveness analysis based on changes in MMSE score.

For each of these analyses we will carry out the analysis first from a societal perspective, and then from a health and social care perspective. The main difference will be the exclusion of the costs of unpaid care and any out-of-pocket payments by carers. Payments by patients/users or families for services will need to be measured; whether or not they are treated as health and social care system costs is dependent on a number of things, including future policy as to the funding of long-term care. The study will examine the sensitivity of findings to different assumptions regarding such funding, and indeed to other key assumptions made in the analyses.

As far as the economics component of the trial is concerned, the pilot trial (WP2) will provide an opportunity to check the feasibility of data collection and to adjust the CSRI if necessary. It will also allow us to develop costs for the collaborative care model (which will still need to be calculated anew in the main trial (WP3)). It will not be possible to carry out a full cost-effectiveness analysis at this pilot stage to explore what might happen in the main trial because of the smaller sample size and shorter follow-up period.

2.7. Ethical arrangements: A favourable opinion has been obtained for Work package 1 from NW London Research Ethics Committee 1 (10/H0722/50**)**. This study does not fall within the scope of 'The Medicines for Human Use (Clinical Trials) Regulations 2004' as it is not a study of investigational medicinal products. Appropriate research governance approval will also be sought via the NIHR Coordinated System for gaining NHS Permissions. Site specific assessments will be sought for the participating practices as required.

Practice staff of the participating practices will use their electronic medical records to identify and invite people with dementia and their carers to take part in the study. Only the records of those who have given their consent will be interrogated for service utilisation for the economic analysis. An application will be made to obtain honorary contracts for the research assistants with PCTS to allow them to collect the qualitative data.

Risks and anticipated benefits for trial participants: There were no reports of adverse events during the PREVENT study [7]. The benefits of case management may be improved quality of life for both the person with dementia and their carer, and reduced incidence of behavioural and psychological symptoms.
Some people with dementia, and their carers, may find the data collection procedures, in particular qualitative interviews, tiring or distressing, especially if they are discussing mental health issues. We will ensure that the researchers collecting data are trained and supervised to manage this eventuality. Our experience suggests, however, that for many discussing such issues may be a positive experience.

Informing potential trial participants of possible benefits and known risks: In Work package 2 potentially eligible patients will be sent, by their GP, letters of invitation and patient

information leaflets. These have been designed with input from our patient advisory panel, inviting them to take part in the study. The invitation materials will include details of how to contact the research team, if they have any questions about the study. They will be asked to return an expression of interest form direct to the research team. This is a model we have used in previous studies, to minimise burden on busy general practice staff, while maintaining patient and carer confidentiality.

Those who express an interest will have their perception of the potential benefits and risks explored by research staff before written informed consent is accepted. Should information about benefits or risks become available from the trial, or from other studies, it will be communicated to all participants (including general practices) as speedily as possible in a special issue of the project's regular newsletter. At all points of contact it will be stressed that participation is voluntary and that they may withdraw from the study (they may withdraw from the intervention, but continue with data collection, if desired) at any time point, without this decision affecting their normal clinical care.

Obtaining informed consent from participants: NRES guidance on the content and format of patient information and consent form will be followed. We will also consult our PPI representatives to ensure these documents and other written materials are fit for purpose. Information about the study will be mailed to potential participants, their carers or a consultee by their usual General Practitioner. In accordance with the Mental Capacity Act 2005, the process of assessment of capacity to consent and securing consent will be regarded as an iterative process and will be reviewed at each stage. Once an individual has expressed an interest in participation, an appointment will be made for a member of the research team to visit them in their home. The purpose of this visit is to ensure that they have received and understood the study information and the implications of their involvement.

As many of the potential participants will have a degree of cognitive impairment, careful consideration needs to be given to the consent process. At each stage of involvement, the participant will be asked to give consent appropriate to their level of understanding, ranging from written informed consent to verbal or non−verbal communication of assent, of which account will be taken in determining willingness to participate. In accordance with the Mental Capacity Act 2005, nothing will be done to the person to which he or she appears to object, either verbally or via non-verbal means.

In addition, we need to make allowance for loss of mental capacity in a participant during the study. The consent form will include a statement to the effect that should the older person lose mental capacity during the study, they grant permission for the study team to contact a "named consultee" (who may be a next of kin but cannot be a paid carer) to revisit the consent process. If there are concerns about the potential participant's present level of capacity and ability to give informed consent, then a named consultee will be approached. If no family carer can be identified for this, a consultee can be nominated by the study team but they must have no other connection with the project. A detailed consent protocol and a consent checklist will be developed for the interviewer to follow so all aspects of the correct procedure have been followed in obtaining consent.

2.8 Proposed time period for management and retention of trial documentation: Data collection and transfer in this trial will comply with NRES and Caldicott guidelines and the Data Protection Act 1998. All data on participants will be anonymised and held on databases on free-standing computers in each centre. Patient information details will be separated from trial data

and stored with the consent forms. Trial data will be identified only by a unique code; the link between this code and patient identifiable material (which will be stored on secure, password protected computers) will be known only to a limited number of members of the research team. All study documentation will be held in secure offices, and the research team will operate to a signed code of confidentiality.
Transmission of identifiable data between the general practices, participants' homes and the University departments involved will be by secure e-mail, secure fax, registered post or via by a study team member. A clinical data management software package will be used for data entry and processing, allowing a full audit trail of any alterations made to the data post entry. Identifiable data will be kept for the duration of the trial and thereafter destroyed.
Long term storage: All study documentation will be archived and held for 10 years by the study sponsor.

2.9. Research Governance: Research governance approval will be sought relevant Primary Care Organisations. University College London is the sponsor for the full trial. On a day-to-day basis, sponsor-level activities will be carried out by the Newcastle Clinical Trials Unit (NCTU), with reporting lines to the study sponsor, who will ensure that all obligations have been adhered to. The study will be conducted in accordance with NCTU-wide and study-specific Standard Operating Procedures (SOPs) and Work Instructions.

All study-attached staff will be appropriately qualified and will be trained in those aspects of Good Clinical Practice (GCP) appropriate to their role in the study. Staff in participating general practices will be trained in the study protocol and in appropriate aspects of GCP (in particular, the informed consent process). The trial manager will undertake at least one monitoring visit to each participating practice to review that site's compliance with the study protocol and with principles of GCP; however, this is a relatively low risk study and we do not consider that 100% site data verification is mandated.

R and D approval will be sought from all Primary Care Organisations (PCOs) in which the general practices recruited to this study are located (via the Coordinated System for gaining NHS Permission (CSP)), and the study will be open to audit by the research governance teams in those PCOs (either as part of their 10% routine audit, or 'for cause').

We will follow *Research in the NHS - Human Resource (HR) Good Practice* in determining which members of the research team require an honorary research contract (providing those individuals with NHS indemnity in respect of negligent harm) and/or pre-engagement (CRB and Occupational Health) checks, and which simply require letters of access. Since this research spans multiple NHS organisations, we will seek research passports as appropriate. University professional liability insurance will further indemnify university employees in respect of liabilities arising from protocol design. General practitioners are independent contractors, rather than employees of PCOs, and they (and their staff) will be covered by their personal professional indemnity arrangements for negligent harm. We do not anticipate the Research Ethics Committee requiring us to have insurance in respect of non-negligent harm.

Independent oversight of the study will be provided by a Trial Steering Committee (TSC), with an independent Chairperson, other independent experts representing the major areas of interest (methodological and clinical), and two consumer representatives. A representative of the HTA programme will also be invited to attend. The standing membership of the TSC will also include the two Principal Investigators (Iliffe and Robinson), the trial statistician (Steen), Director of the Newcastle Trials Unit (McColl) and the trial manager. Other members of the research team will attend in person or via video/teleconference on an 'as needs' basis. The TSC will meet at the start and end of the pilot trial, twice in the first year of the main study and annually thereafter.

In order to monitor accumulating data on patient safety and treatment benefit an independent data monitoring and ethics committee (DMEC) will be established. The DMEC will act as an advisory body to the TSC, meeting twice for the feasibility study and 5 times over the course of the trial. Proposed DMEC membership will comprise an independent clinician, an independent statistician, and a consumer representative.

2.10. Project timetable and milestones: This is a two year study beginning 1.3.2011. The Gantt chart shows the distribution of tasks over the two year period.

3. Team expertise : The project team comprises collaboration between University College London, Kings College London, the London School of Economics, the charity For Dementia and the Universities of Kent, Manchester and Newcastle. The project will be co-led by Professor Iliffe (UCL) and Professor Robinson (Newcastle).

The multi disciplinary team members have experience in: primary care (SL, LR, CCG), old age psychiatry (GL, CF, CK), health economics (MK), social gerontology (JB, KB), academic nursing and dementia care (BS), social work and social care workforce planning (JM) clinical trial expertise (EM, JB, SI, GL, CK, CF, MK), statistical design (NS, SC) and qualitative methodologies (JB, LR, CCG, KB).

Together, the team provides internationally recognised expertise in trials methodology (including pragmatic and cluster randomised controlled trials), health care evaluation, health economics and qualitative research methodologies, involving older people, especially those with dementia.

SI,BS, JM, LR and CCG have also developed educational materials and service models for primary care professionals; importantly CCG has UK experience of the development, delivery and evaluation of collaborative care in other settings.

The development and feasibility testing of the intervention will be led by the London/Kent group and preparations for the definitive main trial will be undertaken by the Northern region group, through the UK CRC registered Newcastle Clinical Trials Unit. The qualitative study will be led by Newcastle, in collaboration with Manchester. The health economics evaluation will be lead by Professor Knapp, LSE.

People with dementia and their carers will be involved in the study at all levels, a leading role in this being taken by the carers of the charity For Dementia with the support of BS. JM is the academic co-applicant who will lead on patient and public involvement in the management of the study, interpretation of results and planning of dissemination.

Roles of team members: This is a complex study by a multidisciplinary team spread over a large area, and will need skilful management. CK, who is chair of the DENDRON Dementia Clinical Studies Group, will chair all project management meetings except for the TSC and DMEC. SI and LR will be joint Chief Investigators. The London/Kent group (CF, SC, BS, JM, SI) will undertake workpackage 1. As site leads, GL (London) CF (Kent) and LR (Northern region) will be responsible for practice recruitment, liaison with specialist teams and relevant trusts, managing site researchers, supervision of case managers. JB, CCG, KB will be responsible for supervision of qualitative research. GL and CK will provide clinical supervision from Old Age Psychiatry and expertise in dementia care and dementia clinical trials; EM, JB will provide expertise on design, analysis and trial management. The management hierarchy of the CARE-DEM study is shown on page 12.

4. Service User Involvement: This proposal arises from discussions within the DeNDRoN Primary Care and Dementia Clinical Study groups, both of which have patient and public involvement (PPI) representatives who have contributed to the discussion about the intervention and desirable outcomes. The user group that guides For Dementia will contribute members who will participate in the management of the trial at all levels, and BS will be responsible for liaison with this group. JM will be responsible for PPI involvement in the management of the trial, at trial steering committee, trial management and site management committee levels, and also in the PPI forum. A patient and public involvement forum will be established to allow individuals who do not wish to join the management committees to participate in debates about the development of the case management training, the content of the care pathways, the optimal ways to engage people with dementia and their carers in the trial, the interpretation of findings and the planning of dissemination. The invitation to join this forum will be extended to the Alzheimer's Society QRD group, the For Dementia carers' group, the Greater London Forum for Older People, and other relevant bodies (see the management diagram on page 12).

5. Justification of support:

This is a complex study that requires researchers with experience with different methodologies, from development of educational interventions, through trial design and implementation, to qualitative research. The mix of applicants, and the combination of different levels of skill is designed to both reflect the methodological needs of the proposed study and the need to increase research capacity. The wide geographical spread of the project, and its multi-disciplinary nature require research assistants in the South (London & Kent, covered by one RA) and the North East, also served by one RA. The South RA will work in both work packages, the Northe east RA only in work package 2

Staff costs
For **workpackage 1** we need to fund an iterative cycle of meetings with senior staff from different disciplines, and to include PPI representatives in a time-intensive product development process.

For **workpackage 2** Staff costs will include : Statistician: 5% Months 1-18;Data manager 40% WTE for first 4 months (database set up) and last 3 months (pulling out data for analysis and archiving), 10% WTE for remainder of this workpackage; Trial manager: (towards top of non-discretionary points Grade F), 30%, to begin the detailed design of the definitive trial as well as manage the feasibility trial (Workpackage 2) ; Senior trial manager: 5% for work package 1 and 10% for work package 2, to support trial management and the design of the definitive trial .

Travel to practices:

In Work Package 2 practices expressing interest in the trial will need to be recruited at an initial visit, Prior to this the study team will need to engage with PCTs, Practice Based Commissioning Boards and consortia, and CMHTs to gain support for the study. In our experience this can take more than one visit. These costs are included under the heading *'Travel for recruitment of practices'*.

Qualitative research

For the qualitative component KB will commit 5% of her time in both work packages. JB will commit 5% of his time to support KB in the first 2 years of the study. The budget for the qualitative component will include fieldwork travel; carer reimbursement, travel expenses, room hire and refreshments for focus groups.

In Work Package 2 there will be up to 40 interviews across the study sites, plus three focus groups of up to 12 people each. There will, therefore, be up to 76 encounters attracting travel costs.

The travel costs for Work Package 2 are included under the heading *'Travel for qualitative interviewing at each site'*, and *'Travel costs for focus groups'*.

Management travel costs

We anticipate 15 person trips in total for **TSC meetings** (5 independent members to 2 meetings at a 'per meeting per person cost' of approx £161).. These costs are included under the headings *'Travel by TSC members'*

Conference travel. We anticipate presenting methodological issues and quantitative and qualitative results at national conferences during the lifetime of the study.. These presentations are central to our scientific dissemination plan, and because research staff will be actively involved in them, will contribute to research capacity building in an underdeveloped research domain. These costs are included under the heading *'Conference travel'*.

Travel for **project team meetings**. Because this is a complex study on three sites, with two Work Packages to manage, we are planning to have up to four project management team meetings a year, alternating between Newcastle & London, plus separate Work-Package meetings as needed.

Equipment & consumable costs

Computers etc: Because of the high level of mobility required of research staff we will need to collect data electronically on site and download it to a secure, stand-alone workstation at the trial management centre in Newcastle.

Printing: Using institution algorithms we estimate the total printing costs for all questionnaires to be £2,853 over the two years, to include production of 9 instruments that will be used with all participants, plus all other standardized trial documents (letters and information sheets to practices and other organisations, letters and information sheets to participants, protocols etc.)

General office consumables: These have been calculated at £854 per person per year and are shown as 'Office Consumables' in London & Kent, and 'IHS project costs' in Newcastle

Training costs: The training (to be developed in work package 1 and tested in work package 2), will be provided through the Admiral Nurse training organisation 'For Dementia', with an induction period, periodic refresher days, experiential learning, mentoring and formal on-site supervision, via Admiral Nurses at planned study sites. Training will be delivered by a regional senior clinician from the project team and an Admiral Nurse, with other clinicians or allied medical professionals delivering specific training as required. In the PREVENT model training

requires eight 2-hour sessions and it is anticipated that at least this amount of time will be necessary. We have budgeted £5,201 for this, to allow training to occur at each site.

Recruitment costs: We have budgeted £511 for recruitment of two RAs and a data manager,. This amounts to £170 per appointment. Since University HR department make studies carry the costs of advertising and interviewees' travel, this sum is needed.

ISRCTN registration is paid centrally by HTA and is not included in the proposal's budget.

NHS extra treatment and support costs:

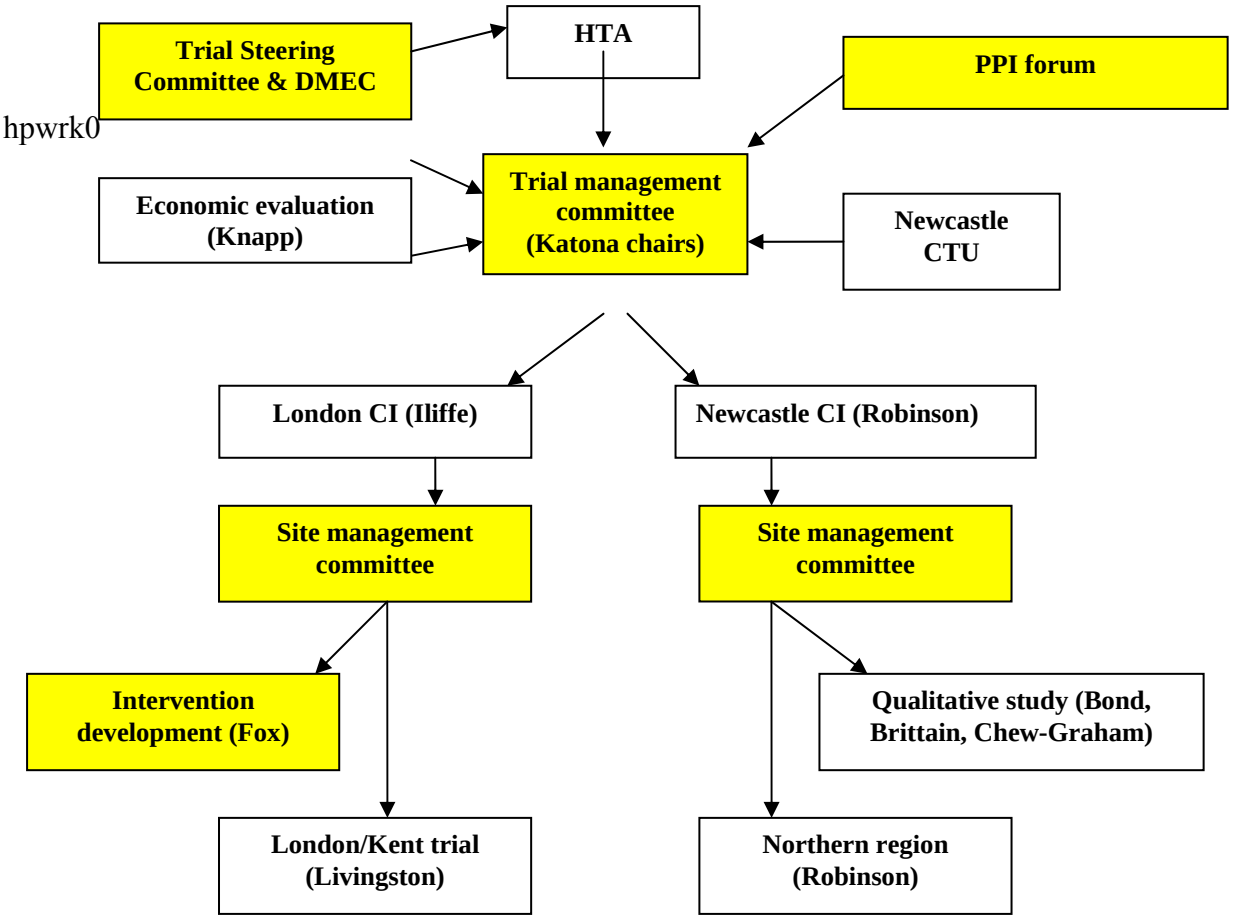
Discussions with PCTs and other Trusts are underway at the three intervention sites to establish agreed NHS costs.

NHS support costs will be needed to release NHS staff for training in work package 2, and we have estimated these costs based on the PREVENT study's commitment of eight sessions of two hours each. We estimate that database searches and patient engagement will be funded at £500 per practice, with a £5 fee for every patient consented and another £5 for every participant retained in the trial. These costs may vary between CLRNs.

Extra treatment costs for NHS staff who undertake case management work as part of the trial will not become apparent until after workpackage 1 has identified the amount of training needed and the amount of time necessary for the intervention. This is likely to vary from site to site, depending on the disciplines and experience of potential case managers. We have, therefore, estimated these extra treatment costs, in discussion with North of Tyne PCT.

6. CARE-DEM management structure

Boxes with yellow fill show where involvement of patient and public representatives in the management of the study occurs.



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9. Gantt chart

Quarter	1	2	3	4	5	6	7	8
	Year 1				Year 2			
Work package 1: Developing the intervention								
Recruit research associates								
Expert group meets monthly								
Prototype intervention developed								
Bench testing								
Work package 2: rehearsal study								
Ethics, Recruit sites, R&D governance								
Discussions with PCTs, PBC organisations, CSSR, 3rd sector								
Recruit interviewers								
Training practitioners								
Field testing								
Qualitative study								
Analysis, further modification of intervention								
Preparation of funding submission for Work package 3								