CADDY study protocol

This draft has been prepared on the basis of advice from the Norwich CTU protocol review committee and consultation from our PPI advisory group and CADDY steering group.

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Study name:

Cognitive Function and Ageing Study II – Dementia Diagnosis Study (CADDY)

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Sponsor	NHS South Norfolk Clinical Commissioning Group
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Date	2 March 2016

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Glossary of abbreviations and terms

CADDY	Cognitive Function and Ageing Dementia Diagnosis Study
CADDY ID	Unique identifier to enable linkage of data whilst ensuring its anonymity
CAG	Confidentiality Advisory Group
CFAS	Cognitive Function and Ageing Study
'Clinical diagnosis' of dementia	A diagnosis of dementia made by primary or secondary care NHS practitioners, and recorded in GP notes.
CRF	Case Report Form
CTU	Clinical Trials Unit
GMS/AGECAT	Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy
HRA	Health Research Authority
Inspire	Organisation supporting patient and public involvement in Research
INVOLVE	NIHR-funded organisation supporting active public involvement in research
MMSE	Mini-mental state examination
MRC	Medical Research Council
PIS	Participant Information Sheet
PPI	Public and Patient Involvement
PPIRes	Organisation supporting patient and public involvement in Research
RQ	Research Question
'Study diagnosis' of dementia	A diagnosis of dementia made under the CFAS study based on an algorithm using data from a range of tests and interviews carried out by a trained study researchers.
Undiagnosed dementia	Undiagnosed dementia refers to dementia that is not recorded in a patient's medical records. For the purposes of this study a participant has 'undiagnosed dementia' if they have a study diagnosis but no clinical diagnosis.

Roles and responsibilities

CADDY steering committee roles (and expertise)

Frances	Bunn	Independent Chair
George	Savva	Chief/Principal Investigator (biostatistics and epidemiology)
Antony	Arthur	Co-Investigator (health services for older people)
Carol	Brayne	Co-Investigator (public health)
Tom	Dening	Co-Investigator (old age psychiatry)
Chris	Fox	Co-Investigator (old age psychiatry)
Fiona	Matthews	Co-Investigator (biostatistics and epidemiology)
Louise	Robinson	Co-Investigator (academic GP)
Blossom	Stephan	Co-Investigator (dementia epidemiology)
Judy	Henwood	Sponsor representative
Wendy	Hicks	Independent local commissioner
Gavin	Terry	Policy Section, Alzheimer's Society
Paul	Millac	Lay representative, Alzheimer's Society
Peter	Richmond	Lay representative, INSPIRE
Abigail	Dennington-Price	Lay representative, PPIRes
Clare	Aldus	Study Manger/Research Fellow

CADDY PPI Advisory group roles (PPI support group)

Peter	Richmond	Lay representative (PPI, INSPIRE)
Lesley	Evans	Lay representative (PPI, INSPIRE)
Amander	Wellings	Lay representative (PPI, INSPIRE)
Heather	Edwards	Lay representative (PPI, INSPIRE)
Julian	Ashton	Lay representative (PPI, INSPIRE)
Abigail	Dennington-Price	Lay representative (PPI, PPIRes)
June	Blythe	Lay representative (PPI, PPIRes)
Jennifer	Griffiths	Lay representative (PPI, PPIRes)
Helen	Jackson	Lay representative (PPI, PPIRes)
Penny	Vicary	Lay representative (PPI, PPIRes)
Wendy	Woods	Lay representative (PPI, PPIRes)
Paul	Millac	Lay representative (Alzheimer's Society)

CADDY Management Committee roles (and expertise)

George	Savva	Chief/Principal Investigator (biostatistics and epidemiology)
Antony	Arthur	Co-Investigator (CFAS II co-investigator care - of older people)
Carol	Brayne	Co-Investigator (CFAS II chief investigator - public health specialist)
Tom	Dening	Co-Investigator (CFAS II co-investigator - old age psychiatry)
Chris	Fox	Co-Investigator (Old age psychiatry)
Fiona	Matthews	Co-Investigator (CFAS II co-investigator - biostatistics)
Louise	Robinson	Co-Investigator (CFAS II co-investigator - academic GP)
Blossom	Stephan	Co-Investigator (biostatistics and epidemiology)
Clare	Symms	Sponsor
Erika	Sims	Clinical Trials Unit (Senior Clinical Trials Operations Manager)
Antony	Colles	Clinical Trials Unit (Senior Data Programmer)
Clare	Aldus	CADDY Study Manager
Linda	Barnes	CFAS II Study manager

1 Abstract:

Background

Between 600,000 and 800,000 people in England have dementia, yet only around 344,000 cases are recorded on dementia registers maintained by GPs. This means that a substantial proportion of people with dementia do not have a diagnosis (that is have 'undiagnosed dementia'), although estimates of dementia diagnosis rate are imprecise. Closing this 'diagnosis gap' is an NHS and Department of Health priority, but very little is known about the population with undiagnosed dementia. Few quantitative studies have explored the correlates of diagnosis and there is little direct evidence regarding the benefits of a diagnosis for people with dementia.

Aims:

This study is an extension of an existing dementia epidemiological study (the Cognitive Function and Ageing Study II), and is a data linkage study based data from CFAS II participants who had a CFAS II study diagnosis of dementia.

The aim of the CFAS II Dementia Diagnosis Study (CADDY) is to link existing CFAS II data with primary care records to estimate (i) the prevalence of undiagnosed dementia and its distribution among the older population of England (ii) to what extent diagnoses represent recorded knowledge of cognitive complaints and impairments (iii) the barriers to diagnosis and (iv) the clinical and psychosocial effects of diagnosis among people with dementia.

Summary of existing CFAS II study sample and assessments already conducted

CFAS II participants were sampled at random without respect to known cognitive impairment or dementia from Cambridgeshire, Nottingham and Newcastle. Around 7500 participants aged 65 years and older were recruited and assessed between 2008 and 2012.

CFAS II assessments included:

- A comprehensive cognitive assessment including mini-mental state examination (MMSE)
- Informant reports of psychiatric and medical comorbidity (including history and treatment) and functional impairment – hence a study diagnosis of dementia can be made.
- Behavioural and psychological assessment
- Social participation and contacts
- GMS/AGECAT dementia diagnosis: a widely used algorithmic dementia diagnosis, validated against Diagnostic and Statistical Manual (DSM) definitions and upon which many UK and global dementia prevalence estimates are currently based.

Methods of current study

No new contact with patients will take place.

CADDY participants will be selected only from CFAS II participants who gave consent to their medical record linkage and for their data to be used for long term including in the event of their incapacity and death.

We will select all such participants who had a study diagnosis of dementia (N approx. 460) and a number of those without dementia (with the non-dementia cases stratified toward those with a mild cognitive impairment who might also have a dementia diagnosis recorded in primary care).

From primary care records of the selected CFAS II participants we ask practice staff to extract:

- Fact and date of dementia diagnosis and first presence on practice dementia registers
- First mention of memory/cognitive impairment
- Fact, date and nature of referral to dementia services
- Fact and date of censoring events: death or leaving the practice.

Primary care data will be transmitted to a secure database at the University of East Anglia Clinical Trials Unit and will be de-identified and linked with the assessment data from CFAS II described above.

By combining the primary care data with assessment data we will answer questions including:

Primary Questions:

1.
    a. What was the prevalence of undiagnosed dementia (including sub-groups: dementia diagnosis suspected; GP aware of cognitive complaint/impairment; no record of any cognitive impairment) between 2008 and 2012?
    b. To what extent do general practice dementia registers mandated by the quality outcomes framework (QOF) reflect GPs knowledge of cognitive impairment among their patients?
    c. What is the size and what of are the characteristics of the group who did not receive a CFAS II study diagnosis of dementia but did have a dementia diagnosis recorded in primary care?
2. What are the associations between social and clinical characteristics of a person with dementia and their risk of being undiagnosed?
3. What is the incidence of new diagnosis among the population with undiagnosed dementia?

Secondary Question (if sufficient follow-up data among the undiagnosed):

4. How are clinical, psychosocial and healthcare utilisation trajectories over a two year follow-up period associated with diagnosis status among people with dementia?

2 Background and Introduction

Dementia

Dementia is a syndrome of progressive loss of cognitive and daily functional ability. It is caused by one or more of a number of underlying brain pathologies including Alzheimer's disease, cerebrovascular disease, Lewy Body disease and others. Memory impairment is a characteristic of Alzheimer's disease but other dementias may present with different patterns of cognitive impairment and non-cognitive symptoms including psychosis and behavioural disturbance. Dementia may also be preceded by changes in sensory function, mood, motor function and sleep many years before the characteristic cognitive and functional impairments become apparent.

Dementia has an enormous social and economic impact (1), and is a major cause of disability and death. There is usually no treatment for dementia that modifies the course of the underlying disease, but those who are diagnosed can receive symptomatic treatment, caregiver support, appropriately tailored healthcare services and the chance to plan for the future.

Prevalence of dementia and the number with a diagnosis in the UK

Estimating the number of people living with dementia is difficult. People with dementia are difficult to access for research, particularly the very old and frail, and dementia is difficult to diagnose, particularly in its early stages. Different operational definitions of dementia can lead to vastly different estimates of its prevalence (2). Recent evidence from the UK and other high income countries suggests a fall in age specific dementia prevalence (3–5). This means that older pan-European estimates of prevalence upon which UK prevalence had previously been based may now overestimate the true number of cases.

The proportion of people with dementia who have a formal diagnosis is known as the *diagnosis rate*. Current published dementia diagnosis rate estimates rely on dividing the number of diagnosed cases by the number of cases expected from prevalence estimates (6). The Health and Social Care Information Centre (HSCIC) reported that in 2013-2014 there were 344,000 people with a dementia diagnosis in England. This corresponds to an overall diagnosis rate (the proportion of people with

dementia who have a diagnosis) of just under 50%, but given the uncertainty around the prevalence of dementia the true figure might be somewhere between 44% and 57%. This represents a substantial increase from around 33% diagnosis in 2007 (7).

This estimate is useful as a national or regional indicator but is limited in a number of ways: First, it is not possible to disaggregate this by socioeconomic or clinical characteristics. Therefore it is not possible to currently say what the care needs of the undiagnosed population are likely to be compared to the population that are known to services. It is not possible to describe inequalities in access to diagnosis. Second, dementia prevalence estimates are unreliable when applied to small areas, and so diagnosis rates at the regional and especially the practice level are likely to be inaccurate. Third, by assuming all of those diagnosed with dementia actually have dementia the possibility of over-diagnosis is ignored.

Finally, in using routine records of recorded cases there is an implicit dichotomisation of individuals into those who are 'diagnosed' hence receiving support, and those who are 'undiagnosed' and so are unknown to services. This may not reflect the reality that many individuals are likely to be in a process of help seeking and diagnosis, or have a cognitive impairment that is known and managed but is not diagnosed. Two epidemiological studies have found that large proportions of the undiagnosed population were known to GPs as having a cognitive impairment or 'suspected dementia' and that at the times those studies were conducted this group was as large as those with a formal diagnosis (8,9).

Why do people with dementia remain undiagnosed?

The model for dementia diagnosis underlying this research draws on the experience of our research team, PPI, previous research into dementia diagnosis and research on inequality in diagnosis of other chronic diseases.

Dementia diagnosis relies on dementia being recognised by a patient, carer or family member who seeks help, or by a clinician making an opportunistic diagnosis. There are several likely barriers to seeking help, which include the belief that dementia symptoms are normal aspects of ageing, the ability to cope (for the time being), stigma, and lack of knowledge around dementia. In contrast, acute events such as hospitalisation or interaction with healthcare services, change in circumstances, behavioural disturbance, or concerned family can act as levers (10-13). Our conversations with the public in the development of this application have also revealed a fear of the consequences of diagnosis, and a determination among some family units to cope without outside interference until help-seeking becomes unavoidable.

GPs consistently attribute missed diagnosis to a lack of education and support for themselves and carers, their own concern about the availability of secondary or support services, financial and time constraints and difficulty in making the diagnosis or breaking bad news (14). Our discussions with carers of people with dementia and other stakeholders have raised the management of other health conditions as a distraction that meant cognitive impairments were not fully explored by medics, and the possibility that formal diagnoses are not made if they will impact upon care arrangements in which an individual is coping well.

Previous research has shown that age and gender are linked to diagnosis in dementia and other health conditions. Non-cognitive symptoms of dementia place a large burden on carers and are likely to lead to help-seeking, independently of memory loss and other cognitive symptoms. Qualitative studies and our PPI conversations suggest that not just the presence of a carer or family member but also other factors such as their awareness, knowledge and attitude are important. People living alone or with little social contact might be delayed in seeking help. The family history of the patient and the carer might influence awareness and help-seeking. Marital status is likely to affect help-seeking and this effect is likely to vary by gender. It is not known whether undiagnosed dementia is more common among those with lower education or in lower socioeconomic groups.

The current proposed analysis of CFAS II participants will test many of these hypotheses and will be the largest such study conducted to date. By linking epidemiological data to medical records this will

include more reliable and nuanced measures of diagnosis, will incorporate more detailed epidemiological assessment than previous studies and is directly applicable to England.

Expressed need for this research and policy context

Timely diagnosis of dementia is a current public and policy concern and resources are being directed toward improving dementia diagnosis rates. The Alzheimer's Society estimates the cost of dementia diagnosis in the UK to be around £85 million per year, of which £25 million is paid to GPs in the form of incentive schemes to increase diagnosis (1).

In England, policy on dementia diagnosis since 2009 has been defined by the National Dementia Strategy, more recently supplemented by the Prime Minister's Challenge on Dementia (15) and the 2013 G8 summit on dementia.

The National Dementia Strategy reported a diagnosis rate of 33% based on a 2007 National Audit Office report, and included an increased diagnosis rate among its key aims; recent announcements suggest a considerable increase to 48%. The Prime Minister's Challenge included a specific target to increase the national diagnosis rate to 66% before March 2015.

Local authorities and CCGs are tasked to improve dementia diagnosis rates where the number of patients diagnosed is significantly lower than the target based on number expected from prevalence data. Our work will inform the development of plans to improve diagnosis rates.

The James Lind Alliance priorities for dementia research include the impact of early diagnosis and the role of primary care to make diagnosis more effective; this was rated in the top 3 priorities (http://www.lindalliance.org/DementiaPSP.asp). Local commissioning groups, general practitioners and the Alzheimer's Society have expressed concern over the validity of comparing local dementia registers to national prevalence data to estimate diagnosis rates. Particular concerns are the possibility of over-diagnosis and the large number of people who are known to services but who are not diagnosed. Our work will estimate the number of people in both of these groups.

3 Aims and objectives

Our aim is to estimate the prevalence and distribution of dementia that is not known to primary care among the UK population aged 65 and older. This will reflect the quality and equality in access to dementia diagnosis and will have implications for the development and evaluation of strategies to improve access to timely dementia diagnosis.

We will compare diagnosis rates among subgroups of the older population defined by potential predictors of help seeking and diagnosis including age, sex, living arrangement, geography, socioeconomic status, comorbidity and clinical disease status. We will validate estimates of the dementia diagnosis rate that are based on primary care dementia registers. Our secondary aim is to explore the consequences of dementia diagnosis using longitudinal data.

We will use data from the MRC Cognitive Function and Ageing Study II (CFAS II), a recently recruited cohort study representative of the primary care population of England and which informs UK dementia prevalence estimates. CFAS II includes more than 600 individuals with a study diagnosis of dementia (~460 who have given consent for access to their primary care records). We will link and compare objectively and independently conducted dementia assessments ('study diagnoses') with records of cognitive complaints and dementia diagnoses found on primary care records ('clinical diagnoses'). We will use these linked data to address the following research questions:

Primary research questions:

RQ1a. What was the prevalence of undiagnosed dementia between 2008 and 2012? How many undiagnosed people with dementia had a GP record of cognitive complaint/impairment, how many had been referred to specialist services and how many had no record of any cognitive impairment.

RQ1b. To what extent do general practice dementia registers mandated by the quality outcomes framework (QOF) reflect GPs records of cognitive impairment among their patients? In other words, how many people with dementia are known to GPs as having a cognitive impairment but are not recorded on dementia registers.

RQ1c. What are the social and clinical characteristics of the group without a study diagnosis of dementia but with a dementia diagnosis?

RQ2. What are the associations between social and clinical characteristics of a person with dementia and their risk of being undiagnosed? Hence what are the independent predictors of help seeking and diagnosis among people within dementia?

RQ3. What is the incidence of new diagnosis among the population with undiagnosed dementia?

Secondary Question (if sufficient follow-up assessment data among the undiagnosed):

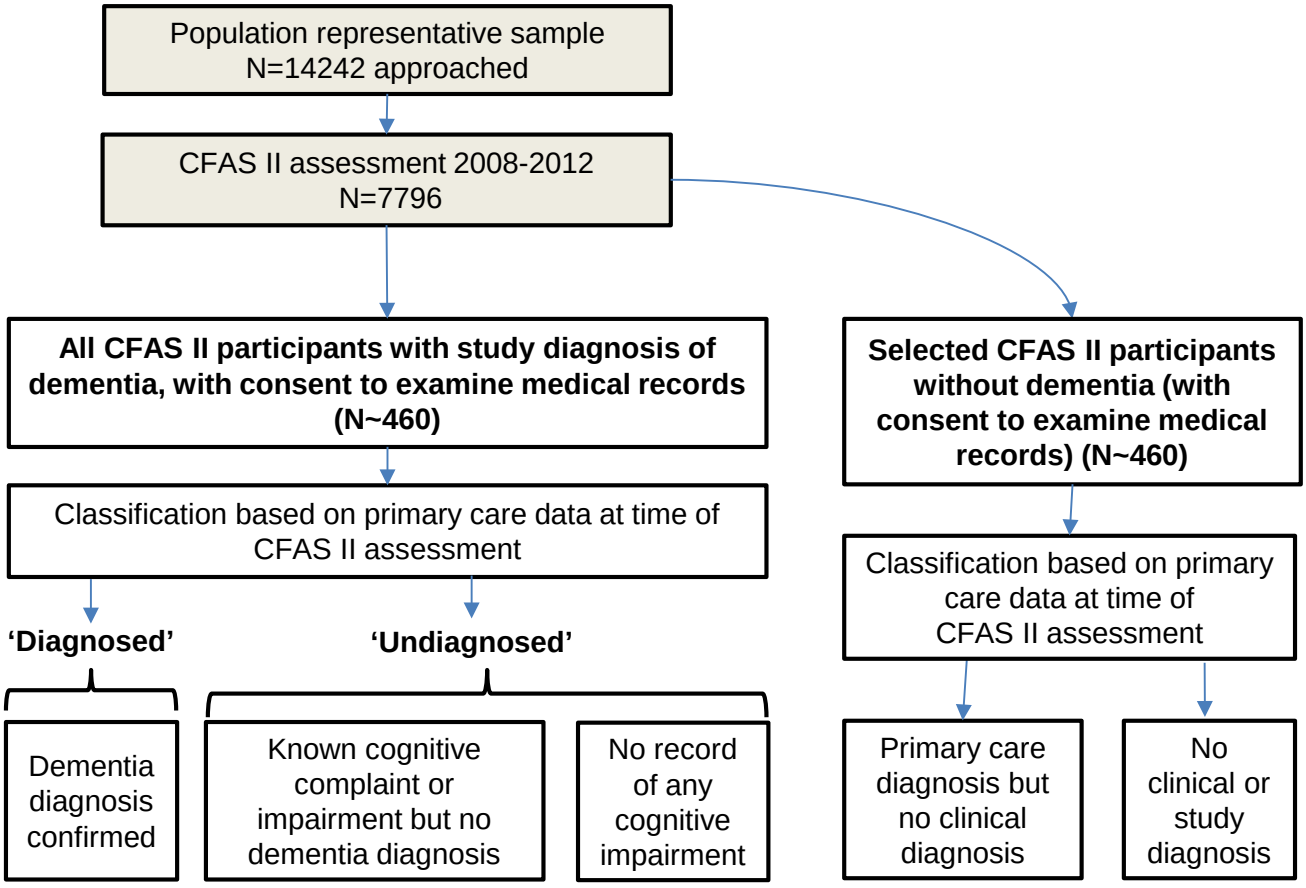
RQ4. How are clinical, psychosocial and healthcare utilisation trajectories over a two year follow-up period associated with diagnosis status among people with dementia? Hence we will provide an indication of the benefits and harms of diagnosis.

4 Study design and methods

4.1 Study design

This study will link medical records to an existing prospective cohort study. The participant flow diagram (see Figure 1) illustrates the relationship between the pre-existing CFAS II study (shaded boxes) and the planned data linkage and analysis (CADDY study; white boxes).

Figure 1. Participant flow



Objective 1: a) Prevalence of unknown or undiagnosed dementia. Estimate % diagnosed as a proportion of all participants with dementia. Estimate % with a diagnosis or cognitive complaint as a proportion of those with dementia.

b) Estimate % diagnosed as a proportion of those diagnosed or with a cognitive complaint.

Objective 2: Comparison of demographic, socio-economic, clinical, healthcare utilisation characteristics across groups

Objective 3: Estimation of rate of subsequent diagnosis among the undiagnosed

Objective 4: Comparison of future clinical, psychological and healthcare utilisation trajectories across groups

Objective 1c: Describe the group with a primary care diagnosis but without dementia according to CFAS II definition

4.2 Setting

CFAS II interviews were conducted in people's homes. Under the CADDY study we will extract primary care data (for which consent was provided at the time of CFAS II interview) and link these to interview data.

4.3 Participants

4.3.1 Inclusion Criteria:

- Existing participants of the Cognitive Function and Ageing Study 2 (CFAS II) (www.cfas.ac.uk).

- Consent given to link to medical records,
- Consent for data to be held long term and used for research purposes including in the event of the participant's incapacity or death.
- Study diagnosis of dementia (made using AGECAT algorithm equivalent to DSM diagnosis (16)) or selected participant without dementia (see section below)

4.3.2 Exclusion criteria

- No consent given for medical linkage
- No consent given for long term use
- Consent withdrawn at any point – any withdrawals will be forwarded to the CADDY team by the CFAS team in Cambridge.

4.4 Original CFAS II recruitment and consenting and assessment process

CFAS II participants were randomly selected from general practice lists in three centres: centre 1 was in rural Cambridgeshire including the villages around the city of Ely, and centres 2 and 3 were across the cities of Nottingham and Newcastle respectively.

Each centre recruited approximately 2500 participants aged 65 and older. Recruitment took place between 2009 and 2011. Sampling was stratified by age group to ensure equal numbers of those aged 65-74 and 75 and older. Primary care practices screened lists of selected samples to remove potential participants with a terminal illness. Eligible participants were sent a letter by their GP introducing the study. Participants were visited by a trained study interviewer.

Written consent was obtained for participation in CFAS II, and further consent was sought to use linked medical records, and for long term use of data. An example medical records consent form used is shown in the appendices of this protocol.

Where the participant did not have the capacity to personally consent, a proxy may have been used to consent for the main CFAS II study, but no attempt was made to consent for medical record linkage, and so these participants will not be included in CADDY.

4.5 Selection of CFAS II participants with a study diagnosis of dementia

All CFAS II participants meeting the inclusion criteria and with a study diagnosis of dementia will be included in CADDY. Preliminary analysis of the CFAS II data suggests there are approximately 460 participants with dementia that meet those criteria.

4.6 Selection of CFAS II participants without a study diagnosis of dementia (objective 1c only)

A sample of participants without dementia will be included. The selection will be weighted such that those with cognitive impairments not sufficient for a study dementia diagnosis are over-represented. This will enrich the sample towards those more likely to receive a false positive clinical dementia diagnosis or have mild cognitive impairment. (Population representation will be maintained in analysis for objective 1c through the use of weights reflecting this process).

Sampling weights will be calculated on the basis of previously collected cognitive test scores from the CFAS II assessments. Participants with lower cognition will be allocated a greater chance of being selected as a control.

4.7 Primary care data to be collected

For each participant we will request information from primary care records regarding the:

1. Date and nature of any clinical dementia diagnoses, using standard definitions, and the Read Code that is used to record the diagnosis.
2. Date of first mention of memory/cognitive impairment
3. Source of first mention of memory/cognitive impairment

4. Cognitive assessments offered in primary care, referrals to specialist dementia services and outcomes from diagnostic referrals
5. Date of leaving the practice

5 Data collection, management and analysis

5.1 Principles of data collection and management process

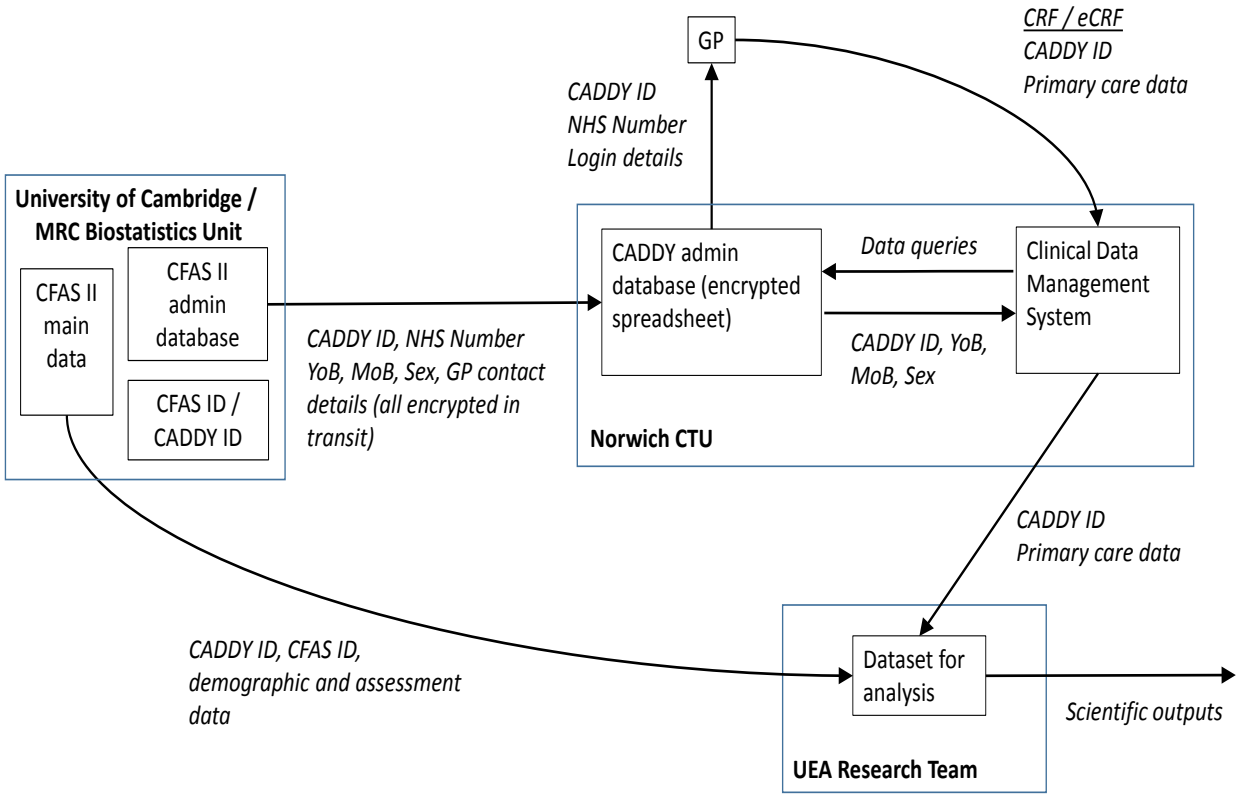
The data collection process is designed to protect patient confidentiality. Specifically:

1) Clinical diagnosis data will never be linked to NHS number on any database held outside of the GP practice;
2) NHS number or patient or practice contact information will never be linked to any CFAS interview or assessment data or study diagnosis;
3) NHS number or patient or practice contact information will never be linked to CFAS identifier outside of the existing administrative database held by the University of Cambridge;
4) No NHS number will be stored in an unencrypted form at Norwich CTU or the University of East Anglia;
5) Data will only be collected if participants had previously consented to medical record linkage and the wishes of patients who withdraw consent will be respected;
6) No new data will be requested directly from the participants.

5.2 Data management and storage

We will use an integrated data management system to ensure complete patient confidentiality, adhering to the principles described above. The storage, transfer and linkage of data is illustrated in the data flow diagram (Figure 2) and is described briefly below.

Figure 2. Data flow



Full details of all processes are described in the Norwich CTU Data Management Plan (DMP) for CADDY. This section should be read together with the 'process of primary care data collection below'.

Patient identifying information is currently held at the University of Cambridge by the CFAS II study team. This is held separately to the participant's interview and assessment data which is held by the Medical Research Council Biostatistics Unit. These databases are indexed by a CFAS ID number.

To support confidentiality two new databases and an encrypted spreadsheet linking CFAS II participant ID with a new CADDY ID are to be created by the study team.

The **CADDY Administrative Database** will hold participant NHS numbers, GP practice contact details, gender, month and year of birth, practice willingness to participate and preference for future communication. This database will be used by the study manager to identify patients to their GPs. This spreadsheet will be encrypted and held securely by Norwich CTU with access only for the study manager and CI.

The **CADDY Clinical Management Database** will hold the patient primary care data generated by GPs from participant records. The function of this database is to enable population of an electronic CRF that will be shown to participating GPs and to the study manager, to validate that data for the correct participant is entered into the database, to generate queries when inconsistent or incomplete data is detected and finally as a secure repository of primary care data. No personal identifiers will be held in this database.

The **CADDY Analysis Database** will comprise primary care data extracted from the Clinical Management Database, and will also hold demographic, assessment and interview data extracted from the CFAS II dataset. The primary function of this database is as a repository of linked data to be analysed. No personal identifiers will be held in this database. This database will be indexed by CFAS II ID.

5.2.1 Return of linked dataset to CFAS II for future use

Once the CADDY Clinical Management Database is finalised, the CADDY Admin Database will be destroyed. A copy of the CADDY Analysis Database indexed only by CFAS ID will be returned to the University of Cambridge and will be made available to researchers on request by approval of the CFAS Central Management Committee, following the process for data sharing (current at the time of application) that already covers linked mortality data.

5.3 Process of primary care data collection

5.3.1 Generation of CADDY ID

A new identifier (CADDY ID) will be used for all data within the CADDY data management system. This will be particularly important when transmitting primary care data in order to protect confidentiality. This ID will be generated by the CI and study manager in collaboration with the research team in Cambridge. A secure database linking CFAS ID with a CADDY ID will be held in Cambridge with the CFAS administrative database.

5.3.2 Transfer of identifying information from Cambridge to Norwich CTU to set up the CADDY databases

Administrative data including participant NHS number, GP practice details gender, month and year of birth will be transmitted in an encrypted form to the Norwich Clinical Trials Unit (CTU). This data will be used to set up the CADDY Administrative Database and the CADDY Clinical Management Database

5.3.3 Initial contact with GP and outline of data collection

The practice associated with each participant is the practice at which the participant was registered at the time of their most recent CFAS II interview.

Each practice will be initially contacted by telephone by the study manager. During this initial call we will (i) confirm the practice willingness and ability to participate, address any initial questions about the study and (ii) establish the practice preference for either paper or electronic communication of study information and data collection.

Study information packs will then be sent to each practice using their preferred method of communication. This will include a letter of introduction to the study, PIS and guidance notes for completion of the CRF. Dependant on practice preference the CRF will be supplied as a paper form or as a unique link to an electronic form hosted on the CADDY clinical management database.

5.3.4 Extraction and transmission of primary care data by the GP practice

Each practice will be independently and securely sent a key linking CADDY ID to NHS numbers for the participants who were registered with their practice. All practices have been working with the CFAS II study team since 2008 to provide access for recruitment to the CFAS II cohort. They will be reimbursed for their time to complete each form and each participating practice will receive a one-off set-up fee.

If the practice preference is for electronic communication then web access to an electronic CRF will be provided. Access will be through an active link to a CTU-maintained web-based interface. This will show the CADDY ID to the practice and enable practice staff to enter the requested information. This form will be linked to the clinical management database within the CTU. The NHS number will not be shown or transmitted with this information.

If the practice requests paper communication then a paper CRF will be generated for each participant who was registered at that practice at time of interview, using information held on the administrative database. The practice will complete the paper CRF and return this to the research team at the University of East Anglia who will enter data from the paper CRF into the electronic CRF using the same CTU-maintained website as described above.

5.3.5 Validation of records

The electronic CRF will validate the gender, month and year of birth of each participant against the details held in the admin database. If these do not match, the form will prompt the user to check they have the correct record.

The paper CRF will also include gender, month and year of birth and on entering the data, the study team will perform the same validation. Any inconsistency will prompt a phone call with the GP to resolve the discrepancy. If the incorrect record has been used then a new form will be generated and sent to the practice.

5.3.6 Support for practices in completing the form

A member of the research team will be available to address queries encountered by practice staff while completing the form, and clarifications will be raised on paper forms where incomplete, unclear or inconsistent information is supplied.

5.4 Pilot phase

A two month pilot phase will be undertaken to ensure the primary care data collection process is robust and to revise wording on the form, guidance, and data management procedures if necessary. We will use pilot data to test the robustness of our classification of participants along a dementia diagnosis pathway, and to modify this if necessary.

5.5 Data linkage

Once primary care data collection is complete we will extract them into the Analysis dataset database. Will will obtain the CFAS II data described below and link it to the primary care data. These linked data will be held together in the CADDY Analysis dataset database.

5.5.1 CFAS II data to be linked to the CADDY primary care record

The full CFAS II questionnaires are available at http://www.cfas.ac.uk/. In short, the data collected for each participant at each wave includes:

- Demographic information:
  - Living arrangement: Place of residence and household members,
  - Place of birth, ethnicity, time living in present area
- Employment and socio-economic status:
  - Current work, retirement age, nature of former work, nature of work of spouse
  - Educational attainment
- Social contact and participation:
  - Frequency of contact with friends and family, social activities
- Medication use:
  - All medications being used, either prescribed or bought over-the-counter
- Lifestyle:
  - History of smoking and drug abuse,
  - Current and history of drinking and alcohol abuse, alcoholism
- Symptoms of dementia:
  - Memory, psychotic episodes, mood changes, depression, wandering, abstract thinking, language, changes in personality and interests, concentration, changes in behaviour, sexual behaviour, incontinence
  - Informant and participant's awareness of participant's cognitive problems.
  - History and course to date of any identified cognitive impairment
  - Episodes of delirium.
- Comorbidity:
  - Previous diagnosis of: cancer, epilepsy, mood disorders, arthritis, peptic ulcers, sensory impairment, cardiovascular disease, diabetes, high blood pressure, stroke or transient ischemic attack, Parkinson's disease or tremor
- Disability and care needs:
  - Impairments in activities of daily living and instrumental activities in daily living, recent changes in impairments and mobility
  - Frequency and nature of informal help received
  - Healthcare contacts in the past four weeks, respite care used
  - Hospital visits in the past three months
- Other contextual information:
  - History of psychiatric conditions and dementia among first or second degree relatives.
  - History of head injury or illness, boxing, meningitis
  - Bereavement and distressing events

5.6 Data analysis plan:

5.6.1 Diagnosis outcome variables

Our main outcome variable is the presence or absence of a diagnosis of dementia recorded in primary care at the time of the CFAS II interview. However in order to understand the reality of the process of dementia diagnosis in this group we will also use the CADDY primary care data collected to classify participants according to the stage of the help-seeking and diagnostic process.

5.6.2 Predictor variables

In finalising our analysis plan we will carefully select variables to be tested as predictors of dementia diagnosis. These will be generated from the experiences of stakeholders, the qualitative and quantitative literature on dementia diagnosis, discussion of the usefulness and importance of specific predictors with the stakeholder group, and relevant theory of help seeking behaviour. At a minimum the following will be included given prior evidence of their importance: age, sex, living arrangement, dementia severity, area-level deprivation, educational attainment, and non-cognitive symptoms of

dementia. Potential predictors include co-morbidity, caregiver awareness, rural place of residence, deficits in memory and non-memory cognitive domains and others based on the data available.

5.6.3 Analysis for specific research questions

For each participant with a study diagnosis of dementia at CFAS baseline or follow-up interview, we will establish the clinical diagnosis classification (see above) on the date of the CFAS assessment where a study diagnosis was made (the index date). For all analyses study weights will be applied to correct for the initial stratification of the study sample and differential non-response.

The precise analysis plans will be finalised during year 1 in consultation with our study partners.

Question 1a. We will estimate the proportion of people with dementia in the population who fall into each category, hence we will estimate the overall 'diagnosis rate' in the population. For those with a study diagnosis but no recorded clinical diagnosis (expected approximately N=200), we will describe GP records of cognitive complaints or impairment and any referrals made. We will identify cases where a cognitive impairment or complaint is recorded by the GP but no formal clinical diagnosis exists. We will describe referrals to secondary care made for this group.

Question 1b. Using Read Codes we will estimate the proportion of known cases that would be recorded on practice dementia registers, hence how the dementia registers reflect GPs knowledge of dementia diagnoses.

Question 1c. We will estimate the prevalence of 'false positive' diagnoses in the population and produce statistics to describe the source of the diagnosis, the clinical and social characteristics of this group.

Question 2. We will describe the unknown and undiagnosed population in terms of social and clinical predictor variables, and we will use a multivariable regression model to test the independent correlates of diagnosis, help-seeking and GP awareness. We will describe the recent healthcare contacts among the undiagnosed and how this varies with dementia severity to explore where opportunities for diagnosis among those most at need are likely to arise. We will identify potential barriers to diagnosis once help has been sought. We will test for the presence of significant variations across practices accounting for patient characteristics using a random effects regression model.

Question 3. For those with no clinical diagnosis at the index date we will identify the timing of future help seeking or diagnosis over the subsequent years. Survival analysis will be used to estimate the median time to help seeking and diagnosis given baseline characteristics. We will estimate time to help seeking and diagnosis both from index date, and from caregiver's report of time since first symptoms among all participants with dementia.

By including calendar date as a time varying covariate, we will estimate how the rate of help-seeking and diagnosis varied before and after the introduction of the dementia DES, and provide an indication of which patient groups had been most effectively targeted by the service.

Question 4. For those with study diagnosis of dementia at baseline and whose informants provide interviews at follow up, we will test whether changes in functional ability, cognition, and health care utilisation (including institutionalisation for those living at home at baseline) over two years are linked to clinical diagnosis or GP awareness. Suitable regression models will be used with specific selection of outcome variables and their coding set by the steering group. Attrition weights will be used to correct for drop-out between waves. The feasibility of this aspect of the analysis will depend on the number of participants with good quality follow-up data and the distribution of the covariates.

Sample size calculations

Power calculations were conducted using Stata 13.0. All sample size calculations assume a target of 90% power and 5% size.

Given the existing relationship between the CFAS II study and practices we anticipate being able to ascertain diagnosis status on at least 400 of the approximately 460 for whom we have consent. If the

diagnosis rate is 40-60% then we will be able to estimate the diagnosis rate with a standard error of 2.5 percentage points. For exogenous binary covariates such as gender or marital status we will be able to detect a difference in diagnosis rates across groups of approximately 42% vs 59% (corresponding to relative risk of approximately 1.4) if the participants are well balanced across groups, or of 37% vs 64% (RR around 1.8) if the covariate has a 10% prevalence. For continuous covariates (including for example domains of cognitive impairment), we will be able to detect a difference of approximately 0.33 standard deviations between the diagnosed and undiagnosed groups.

If approximately 20% of cases are known to GPs but not present on dementia registers we will be able to estimate this proportion with a standard error of 2 percentage points. It will be more difficult to detect correlates of completely unknown dementia among those without a clinical diagnosis; in this case we will be able to detect a difference between continuous covariates of approximately 0.6 standard deviations.

5.7 Imputation of data for those who did not participate

For participants who did not consent to their medical records being used we will not collect or include linked data these participants in our main analysis. Either multiple imputation or weighting will be used to adjust for such missing data as is the standard approach to deal with such missing data. This will be finalised during the development of the full analysis plan.

Data analysis package

The data will be analysed using Stata version 14 or later.

6 Study administration and ethical issues

6.1 Day to day management of the study

Day to day management of the study will be coordinated by the study manager. A management group will meet monthly or an ad hoc basis if needed to resolve day to day issues.

6.2 Timelines

See study timelines for full details of the schedule for the research.

6.3 Safeguarding participants' interests

We will be clear to participating GPs that patient involvement in the study does not imply anything about their dementia status. We will link data only where consent was previously given by our participants at the time of interview, and will respect any subsequent withdrawal of consent.

The safeguarding of patient data is extremely important and we have taken steps to ensure that no data on dementia status or any interview or assessment data can be linked to patient identifying information. All keys used for linkage will be held in secure databases, either in the existing CFAS administrative database as is already done, or in an encrypted spreadsheet that will being held at Norwich Clinical Trials Unit.

Study data will only be available to members of the CADDY and CFAS research teams for permitted research and administrative activities. Requests from other researcher for access to pseudonymised study data for secondary analysis will be assessed by the CFAS II management committee on a case by case basis as per their current data sharing protocol at the time of application (http://www.cfas.ac.uk/cfas-ii/cfasii-data/)

6.4 Sponsorship

The sponsor for this study is NHS South Norfolk CCG. A representative of the sponsor is included in the study steering committee.

6.5 User involvement in the study design and in ongoing study development

In the development of this project we have held a discussion group meeting with people affected by dementia and the public, presented our plan to DeNDRoN Primary Care Clinical Studies Group PPI members, and engaged in structured correspondence with the PPI groups that will be involved in the study. We have discussed the proposed aims and design of the study and the experiences and attitudes of carers, people with dementia and the public toward dementia diagnosis.

These discussions have been important in informing the development of this proposal. The diversity of attitudes toward dementia diagnosis and the experiences of carers that have come to light have shaped our conceptualisation of the process of receiving a dementia diagnosis. Conversations so far have alerted us to potentially important predictors of diagnosis that we had not considered, or had hypothesised to act in a different direction to the expectation of the carers, in particular the role of close family and comorbidity. These contributions will continue to be important to the success of the project

Three PPI members will join our steering committee. One member each will be drawn from PPIRes, the *inspire* older people's panel, and the Alzheimer's Society Research Network Volunteers. Patient and Public Involvement in Research (PPIRes; http://nspccro.nihr.ac.uk/ppires) is a PPI group hosted by the South Norfolk Clinical Commissioning Group and focusses on research concerning primary care. INvolving Service users, Public and carers In Research (inspire) are hosted by the Norfolk and Suffolk Foundation Trust and focus on mental health and social care research. The Alzheimer's Society Research Network includes carers, former carers and people with dementia who have an interest in research. Members of each of these groups will provide a different perspective on the research. All PPI will be funded according to INVOLVE guidelines.

Up to ten PPI representatives will contribute to a PPI advisory group, which will meet twice during the study. These will be recruited from *inspire* and PPIRes members and reflect the views of the general older population, both with and without direct experience of dementia. The first session, held on 5 Feb 2016 focussed on concerns and beliefs regarding dementia diagnosis, the experience of dementia diagnosis and its consequences. We also discussed the CFAS II medical records consent and PPI advisors assured us that their understanding of this consent form would include the current proposed activity. The second session will respond to the main results of the study, to inform our dissemination activity; to ensure that we present our findings in a way that is correctly interpreted and to guide final stages of the analysis. Findings from these groups will be reported to the steering group by the PPI steering group representatives and the core research team.

In our PPI interactions to date we have discovered potentially technically challenging aspects to the study that might hinder full PPI participation if not addressed appropriately. The previous experience of our PPI advisors also suggests that members can feel isolated from research teams and unable to make meaningful contributions to data linkage and analysis projects of this type. To overcome this we will provide two training sessions for PPI members contributing to the study. These will focus on understanding the nature of the data sources, the challenges around the design of the analysis, how to correctly interpret the results of the analyses, and the strengths and limitations of the study. These sessions will be held in the weeks before steering meetings. We will supply documentation in good time and in plain English ahead of steering group meetings, welcoming and fully addressing questions at any stage and proactively identifying and discussing misconceptions where they arise. Short meetings with PPI representatives before steering group meetings will enable any final needs to be resolved so that they can be fully engaged with the study.

7 Dissemination and Outcome

Our dissemination plan is designed to reach all relevant stakeholders to inform the policy debate around dementia diagnosis and the design and implementation of plans to achieve timely diagnosis of dementia for all. The full dissemination plan will be designed by the research team with input from the steering group during the course of the study. This will include peer reviewed academic papers, conference presentations and presentations and outputs targeting stakeholder groups.

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9 Appendices

Appendix 1 Existing CFAS II medical records consent form that has been completed by participants (using the local study name in the Cambridgeshire centre)

CAMBRIDGESHIRE PROJECT FOR LATER LIFE II

Administrative Centre
Department of Public Health and Primary Care
Institute of Public Health
University of Cambridge
Forvie Site
Robinson Way
Cambridge CB2 2SR
Telephone: 01223 330312

Fax: 01223 330330

(Letterhead amended for each centre)

Consent Form for access to Medical Records

Project No……..

Name of Respondent……

The Cambridgeshire Project for Later Life II is a long term study into the health and well-being of the older population. In order to answer some of the research questions one of the research staff may need access to your family doctor's notes or other routine medical records.

Any information collected from these sources will be treated confidentially as per the Data Protection Act 1998.

We would also like to ask for your consent to flag your name at the Office of National Statistics (ONS) who would then record the date and cause of death of participants in the study, they would also inform us if someone on the study has left the National Health Service i.e. emigrated.

If you would agree please initial the boxes and then sign the form below.

I give my permission to the research staff working on the Cambridgeshire Project for Later Life II study inspecting GP and medical records that relate to me.	☐
I give my permission for any data I supply to the Cambridgeshire Project for Later Life Study II to be held for long-term storage for health related research purposes (even if I should become incapacitated or in the event of my death).	☐
I agree to Cambridgeshire Project for Later Life II study flagging my name at ONS.	☐

Signature of respondent……

Signature of Interviewer…… Date…….

Appendix 2 - Indicative Case Report Form showing the data that will be collected for the CADDY study.

CFAS II Dementia Diagnosis Study **CADDY Study ID:** XXX

1. Patient details *(please do not record any further identifying detail on this form)*

Male ☐ Female ☐ Month of Birth: ---------- Year of Birth: ----------

2. Dementia diagnosis *(see guidance)*

Dementia diagnosis (including any dementia subtype): Yes ☐ No ☐

If no please go to section 3

Date of dementia diagnosis: DD / MMM / YYYY

Read code used to record diagnosis (if available): ----------

Date of entry on practice dementia register: DD / MMM / YYYY

Pathway to diagnosis:

- Referral from GP following self-complaint ☐
- Referral from GP following family complaint ☐
- Referral following GP concern or GP initiated cognitive test ☐
- Cognitive complaint first noticed following acute admission or outpatient visit in secondary care ☐

Please tell us about any other pathway to diagnosis (Click here to enter text):

3. Memory or other cognitive complaints and tests *(see guidance)*

Please complete this section for all participants whether or not a dementia diagnosis is recorded in section 2

Any memory or other cognitive concern recorded? Yes ☐ No ☐
Date of first memory or other cognitive complaint: DD / MMM/YYYY

Concerns first raised by:

- Patient ☐
- Family member or supporter ☐
- General Practitioner ☐
- Other professional ☐

3. Memory or other cognitive complaints and tests continued *(see guidance)*

Name of cognitive test administered in primary care (if any): ----------

Date cognitive test carried out: DD / MMM / YYYY

4. Referral to specialist dementia services *(see guidance)*

Referral to specialist dementia services (e.g. memory clinic)? Yes ☐ No ☐

Type of specialist service? ----------

Date of first referral: DD / MMM / YYYY

Date outcome recorded: DD / MMM / YYYY

Outcome (diagnosis/findings) of referral to specialist service (click here to add text):

Read code (if available): ----------

5. Leaving the practice *(see guidance)*

Patient still registered at the practice? Yes ☐ No ☐

Date of death ☐ OR leaving the practice ☐ : DD / MMM / YYYY

6. Further detail *(see guidance)*

Job title of person completing the form: ----------

Please tell us any other relevant information (Click here to add text):

Thank you for taking the time to help us with our research.

[NIHR logo]

Appendix 3 – Indicative guidance notes to accompany Case Report Form.

Guidance Notes for case report form (CRF) or e-CRF completion

Please note: To protect patient confidentiality please do not include any identifying information on the form beyond what is specifically requested.

Before you start

The CFAS II Dementia Diagnosis Study (CADDY) case report form (CRF) can be completed *either* via our online database (e-CRF) *or* in hard copy (handwritten/word processed).

If you choose to complete the e-CRF via our online database you simply need to click the relevant link in the email which you will have received from our CADDYstudy@nhs.net email address.

Specific guidance for each part of the forms follows:

Section 1 – Patient Details

Please enter the patient gender and year and month of birth. This information will only be used to verify the patient.

Section 2 – Dementia Diagnosis.

If the patient has **ever** been diagnosed with dementia then mark 'Yes' and complete the rest of this section. If not then mark 'No' and move to the next section.

Please record the **earliest** date on which a diagnosis of dementia is recorded in the patient's records and the specific read code used to record this diagnosis. It would be helpful if dates were entered in DD/MMM/YYY format e.g. 01/Jan/2016. Please also enter the date at which the patient was first entered on the practice dementia register if applicable.

We are interested in how the process of dementia diagnosis was initiated, whether it was a referral from hospital, self or family concerns, your own concerns or other. Please indicate the pathway to diagnosis for the patient by marking the relevant box. If the specific pathway for the patient is not presented as a choice then please briefly describe the pathway for the patient (e.g. the practice nurse raised concerns).

Section 3 – Memory Complaints.

We are interested in when a cognitive concern was first raised for a patient, even if this did not lead to a diagnosis or referral. Please complete this section whether or not a dementia diagnosis is recorded in section 2 above.

If a memory or other cognitive concern is recorded for this patient (prior to dementia diagnosis or if no dementia diagnosis) then mark 'Yes' and complete the rest of this section. If not then mark 'No' and move to the next section.

Please record the **earliest** date on which a memory concern was raised and indicate the source of the concern. Please briefly describe the presenting symptom(s). These may include, for example, reports of repetitive behaviours, aggression, family conflict, missed appointments or confusion. If available please provide the read code.

If there is any record of a test for cognitive function in primary care then please enter the name of the test and the date on which the test was administered.

Section 4 – Referral to specialist dementia services

Please indicate whether the patient was referred to a specialist dementia service for diagnosis and, if so, please tell us which service this was (e.g. 'memory clinic') the date of the referral and the date on which the result was recorded.

Please briefly name or describe the diagnosis or findings provided by the specialist service or, if applicable, non-attendance at the specialist service. If available, please also provide the Read Code used to record this outcome.

Section 5 – Leaving the practice

Please mark 'Yes' or 'No' to indicate whether the patient is still registered at your practice.

If the patient is not still registered then please indicate whether the patient has died or has left the practice, and the date of death or leaving the practice if known.

Please enter your own job title.

If there is any other information that you feel is relevant, for example that the patient's records no longer exist then please enter this information in the space provided.

For further guidance please contact Clare Aldus at c.aldus@uea.ac.uk or telephone 01603 597057. Please return completed paper forms to Clare Aldus, School of Health Sciences, Edith Cavell Building, University of East Anglia, Norwich Research Park, Norfolk, NR4 7TJ

Thank you for your continuing support with the CFAS II Study, and for taking the time to assist with this research project.