<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Young Onset Dementia Assessment Study (YODA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chief Investigator</strong></td>
<td>Dr Christopher Kipps</td>
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<tr>
<td><strong>Co-investigators</strong></td>
<td>Dr Christopher Kipps, Dr John Spreadbury, Dr Boyd Ghosh, Dr John Spreadbury, Fiona Chaabane, Elaine Hayward, Angus Prosser</td>
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<tr>
<td><strong>Research type</strong></td>
<td>Primary Research - Observational, prospective, multi-centre study without experimental treatment</td>
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<tr>
<td><strong>Start date</strong></td>
<td>31/10/2014</td>
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<tr>
<td><strong>End date</strong></td>
<td>31/12/2017</td>
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<tr>
<td><strong>Cost</strong></td>
<td>£197,137</td>
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Dr Chris Kipps and his team are conducting a research study looking at how to improve the way doctors spot the signs of dementia in younger people (often called YODA Younger Onset Dementia Assessment study), and at the impact that diagnosis of dementia can have on people, their family and friends. The hope is that we can find better ways of spotting the symptoms of dementia earlier and improve the care people get when they are diagnosed.

It is estimated that over 15,000 people in the United Kingdom suffer from dementia where the onset occurs before the age of 65. In some estimates the figures are three times this figure (Dementia UK, 2007). In this age-group, while Alzheimer's disease remains a common cause of dementia, it often presents in unusual and diagnostically challenging ways. There is little data on the financial and social impact of these diagnoses in a younger population, how individual syndromes may influence this, and how this relates to delay in diagnosis.

This study aims to:

a) Improve the understanding of the changes in the brains of sufferers and how the disease develops
b) To promote the development of evidence-based guidelines to inform clinical decision-making and improve health outcomes for participants
c) To provide a platform to support the design and conduct of clinical trials
d) To maximize the use of routinely collected clinical data to optimize future use of such information
Protocol

Young Onset Dementia Assessment Study (YODA)
Version 1.9
27/02/2015
<table>
<thead>
<tr>
<th><strong>Study Title</strong></th>
<th>Young Onset Dementia Assessment Study (YoDA)</th>
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</thead>
<tbody>
<tr>
<td><strong>Study Design</strong></td>
<td>Observational, prospective, multi-centre study without experimental treatment</td>
</tr>
<tr>
<td><strong>Sponsor</strong></td>
<td>University Hospital Southampton NHS Foundation Trust</td>
</tr>
<tr>
<td><strong>Study Centres</strong></td>
<td>University Hospitals Southampton NHS Foundation Trust, Hampshire Hospitals Foundation Trust Oxford Radcliffe Hospitals NHS Trust, The Walton Centre NHS Foundation Trust, Brighton and Sussex University NHS Foundation Trust</td>
</tr>
</tbody>
</table>
| **Study Objectives**| 1. To improve the understanding of the dynamic phenotypic spectrum and the disease mechanisms of young onset or atypical Alzheimer’s disease and other dementia syndromes by:  
   a. Providing natural history data including cognitive, behaviour and motor progression and insights into the neurobiology of these diseases  
   b. Collecting data and biosamples to identify genetic and environmental factors influencing or modifying phenotype and disease progression  
   c. Promoting a databank to facilitate projects that may further the understanding of young onset dementia pathophysiology  
2. To promote the development of evidence-based guidelines to inform clinical decision-making and improve health outcomes |
YOUNG-ONSET DEMENTIA ASSESSMENT STUDY (YODA)

for participants/ families by:

a. Assisting in the identification of beneficial interventions (clinical, pharmacological, non-pharmacological)
b. Facilitating and promoting the dissemination and implementation of currently proposed best clinical practices
c. Providing a platform for conducting collaborative research in a clinical setting
d. Promoting exploratory data analysis projects that may identify care processes to further promote care

3. To provide a platform to support the design and conduct of clinical trials by:

a. Providing a resource to identify, develop and qualify novel assessment tools, clinical endpoints and biomarkers
b. Collecting longitudinal data to inform disease modeling studies
c. Facilitating the identification and selection of potential participants to provide data to estimate and quantify rates of progression and trial participation effects
d. Maintaining a list of appropriate participants who qualify for

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therapeutic trials

4. To maximize the use of routinely collected clinical data and optimize future use of such information by:
   a. Obtaining permission to use retrospective medical data
   b. Combining data across multiple sites to increase data analysis power
   c. To improve clinical effectiveness and standards through shared outcome measures

Study Population
Subjects include individuals 18 years or older who have a clinical diagnosis of a possible neurodegenerative disease affecting cognitive function or behaviour; individuals with static brain lesions displaying cognitive impairment; working-age individuals who are cognitively normal at recruitment.

Dementia clinical and care experts
During the course of the project we will also invite a small number (n=5-10) of dementia specialists (e.g. consultants, nurses, researchers) to take part in semi-structured interviews. This will be in order to gain insight into the thoughts and perspectives of NHS and social care professionals on issues related to obtaining a diagnosis, routine clinical care, post-diagnostic support, and service provision.

Number of Subjects
This study aims to recruit all subjects who are eligible and willing to participate in the study across the different study centres

Inclusion Criteria
The study population will comprise
four groups all aged 18 years or older:

1. Individuals affected by a possible or definite neurodegenerative syndrome
2. Individuals with static brain lesions with cognitive complaints
3. Caregivers of individuals affected by possible or definite neurodegenerative syndromes or with static brain lesion and cognitive complaints
4. NHS and social care professionals who are specialists in dementia care to take part in semi-structured interviews.

Participant status will be based on clinical signs and symptoms, imaging and biomarker profiles in line with current internationally accepted criteria (primarily, but not limited to, Mild Cognitive Impairment (MCI), Alzheimer’s disease (AD), Vascular Dementia (VaD), Frontotemporal dementia (FTD), Huntington’s disease (HD), Progressive Supranuclear Palsy (PSP), Corticobasal degeneration (CBD), Multiple System Atrophy (MSA) and traumatic brain injury (TBI)).

Exclusion Criteria

1. Participants who do not meet inclusion criteria
2. Participants who are unable to understand the study protocol at enrollment
3. Participants with non-progressive learning disability

Study Procedures

This study is a prospective, observational, multicentre cohort study. Study visits will take place annually and may occur at the time of the participant’s routine clinical care visit. Additional visits may be scheduled outside of the annual visit.
with the consent of the participant and/or carer. The duration of baseline and annual study visits will range from 45 minutes (routine clinical and core assessments only) to 2.5 hours (completion of core assessments, extended assessments, optional assessments and/or participation in consented ancilliary studies.) To ensure that the burden to the participant does not change, the maximum visit will be 2.5 hours. Where possible, extended assessments will be conducted in the participant’s home or care environment by one of the study investigators or an appropriately trained member of the study team.

Patients with static brain lesions will have baseline assessment and will then be contacted with specific substudies, but will not have annual assessment unless clinically indicated.

Caregiver assessments will occur at baseline and then annually.

Assessments at baseline and annual follow-up visits include the following components:

1. **Core Assessments.** These data elements are mandatory for all participants at all sites
2. **Extended assessments:** These data elements are to be collected to the extent possible at all sites
3. **Optional components** (according to participant consent): Participating sites and individuals may choose to contribute these data elements.

**Core Assessments**

**In participants with cognitive impairment:**

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Written informed consent/ assent
Creation of unique identifier
Review of Inclusion/ Exclusion criteria
Socio-demographic information
Clinical characteristics
Comorbid conditions
Concurrent medications
Consent for retrospective clinical information, including
- Medical history
- Physical examination findings
- Results of imaging and other investigation findings
Consent for contact between visits
Reportable Event Monitoring

In carers:
Written informed consent
Creation of unique identifier
Review of Inclusion/ Exclusion criteria
Socio-demographic information
Consent for contact between visits

Extended Assessments
To be completed to the fullest extent whenever possible in participants with cognitive impairment.

Cognitive:
Addenbrooke’s Cognitive Examination (ACE-R, ACE-III and new items), and/or Mini-Mental State Examination (MMSE) and/or Montreal Cognitive Assessment (MoCA).

Motor:
Neurological Examination
Apraxia assessment
Hoehn & Yahr scale
Motor Assessment Scales (UHDRS, UPDRS)

Neuropsychological:
Neuropsychological testing performed as part of clinical assessment using standardized cognitive tests and those
derived from the published literature.

**Behavioural:**
Completion of behavioural inventory (CBI, FBI, NPI or similar) and mood scale (HADS, GDS-30) together with symptom specific probes on hallucinations and neuropsychiatric symptoms (PBA).

**Functional:**
Clinical Dementia Rating (CDR) and/or CDR-FTLD, and/or FAQ

**Quality of Life**
Short Form Health Survey -36 (SF-36)
Caregivers Quality of Life Questionnaire
Carer Experience Questionnaire
Diagnostic process acceptability questionnaire

**Health Economics**
Resources Use Questionnaire
Work productivity questionnaire
ADL assessment
Work productivity and Activity Impairment Specific Health Problem Questionnaire (WPAI-SHP)

**Optional Components**
1. Permission to use clinical data collected prior to recruitment to this study
2. Permission to be contacted between study visits
3. Permission to use biosample collected as part of routine clinical diagnosis
4. Permission for video recording

**Sub-Studies See appendices for current sub-studies**

In addition to the study procedures associated with the main protocol, sub-studies are proposed within the YoDA study framework. The purpose of these sub studies is to provide a mechanism for establishing and validating novel assessment tools or assessment.
procedures to gather data in specific young-onset dementia populations and/or control populations. Each substudy will have its own consent form and patient information sheet.

Participation in sub-studies is optional: participants consent to participate in sub-studies and agree to volunteer for these studies. Sub-studies can only be implemented if the participant consents explicitly to this optional component and if the burden of the study visit does not exceed 2.5 hours. These sub-studies are by definition non-invasive and imply minimal burden on the participant.

Each sub-study will have a separate protocol that details study procedures, standard operating procedures for study co-ordination and a data analysis plan. Informed consent for participation in sub-studies will be explicit and separate and each sub-study will have its own patient information sheet.

Proposed sub-studies are listed below and see appendices:

1. Biosample collection
2. Oxford Memory Study

Ancillary Studies: See appendices for current ancillary studies

Ancillary studies are defined as studies that are added on to the YoDA studies. These studies may involve more invasive procedures and will entail separate protocols, ethical review and informed consent forms. Ancillary studies can be added throughout the life of the YoDA Study.

Ethical Considerations

Independent ethics committees will review and approve the protocol
before any participant is enrolled. Informed consent is an unconditional prerequisite for patient participation in the study and procedures for obtaining informed consent will be based on participant competency and will adhere to local regulations and requirements. Data protection and privacy legislation will be observed in capturing, forwarding, processing and storing participant data. By signing the protocol, the institution and/or physician commit to complying with all related applicable international and local laws and regulations.

Study Schedule of Activities

Table 1a: Overall Assessment Plan for YoDA Study Participants with cognitive impairment

<table>
<thead>
<tr>
<th></th>
<th>Baseline Visit</th>
<th>Annual Visit</th>
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<tbody>
<tr>
<td>Creation of Unique ID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
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<tr>
<td>Family History</td>
<td></td>
<td></td>
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<tr>
<td>Clinical/ Motor rating</td>
<td></td>
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<tr>
<td>Behavioural assessment</td>
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<tr>
<td>Cognitive assessment</td>
<td></td>
<td></td>
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<tr>
<td>Quality of Life (QoL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1b: Overall assessment plan for YODA carer participants

<table>
<thead>
<tr>
<th></th>
<th>Baseline Visit</th>
<th>Annual Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creation of Unique ID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive assessment</td>
<td></td>
<td></td>
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<tr>
<td>QoL assessments</td>
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</tbody>
</table>

Table 1c: Overall Assessment plan for YODA participants with static brain injury

<table>
<thead>
<tr>
<th></th>
<th>Baseline Visit</th>
<th>Additional visit(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creation of Unique ID</td>
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<tr>
<td>Demographics</td>
<td></td>
<td></td>
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<tr>
<td>Cognitive assessment</td>
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<tr>
<td>QoL assessments</td>
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</tbody>
</table>
Background and Rationale

It is estimated that over 15000 people in the United Kingdom suffer from dementia where the onset occurs before the age of 65, and some estimates are three times this figure (Dementia UK, 2007). In this age-group, while Alzheimer’s disease remains a predominant cause of dementia, it often presents in unusual and diagnostically challenging ways (Koedam, et. al, 2010; Snowden 2011). A third or more of such patients will present with disturbance of language, object use, judgement or visuo-spatial deficits and will have variable memory dysfunction. In those with non-Alzheimer’s dementias, particularly the frontotemporal dementias and atypical parkinsonian syndromes there may be more behaviour disturbance and disruption to social function with well preserved function on standard measurements of cognitive performance (Kipps et. al 2007,2009). Often these individuals are still in active employment and have both parental and financial responsibilities. Previous studies have highlighted the marked carer stress involved in providing care in this situation (Rossness et. al, 2008; Svanberg 2011, Mioshi et al,2007; Piguet et. al, 2011 ), but have not linked this to particular neuropsychiatric symptoms, specific functional deficits or the loss of particular cognitive skills. There is little data on the financial and social impact of these diagnoses in a younger population, how individual syndromes may influence this, and how this relates to delay in diagnosis (Rosness, 2008; National Dementia Strategy, 2010, Alzheimer’s Research Trust, 2010; Van Vliet, 2011).

The issues faced by this group extend beyond difficulties in diagnosis, and encompass both clinical and social domains. While assessment tools are available, there are few studies that prospectively evaluate their reliability (Larner, 2007), and some tools may simply be insensitive to the types of cognitive impairment that are present. While the advent of biomarkers for Alzheimer’s disease (amyloid PET imaging, CSF tau and a-beta) may improve the diagnosis of these conditions, there may be limited benefit from longitudinal assessments of these parameters in monitoring progression. In other conditions such as frontotemporal dementia, despite very marked abnormalities on behavioural rating scales and functional assessments, many patients perform extremely well on standard neuropsychological tests (Lough, 2001, 2005). Where assessment tools exist, they have seldom been studied longitudinally (Kipps, 2007), and where they have, assessment is generally retrospective, not prospective. Where biomarkers exist, there remains uncertainty as to whether these are adequate (Davies 2006; Josephs, 2006; Kipps 2007). There are no studies that compare cognitive performance and symptom profiles using prospectively acquired...
information using different tools across a range of young-onset dementias.

Ultimately the use of disease-modifying agents will need to be informed by accurate longitudinal assessment sensitive to both clinical and disease progression. At present entry into clinical trials of atypically presenting patients is compromised by inclusion criteria more appropriate to individuals with predominantly amnestic (memory-related) symptoms. This may be reasonable, as inclusion of such atypical participants may dilute power in clinical trials to detect meaningful improvements by creating additional variance (noise) in clinical outcomes; however, such exclusion limits ability to generalise trial results to the young-onset dementia group. Since these individuals are by definition younger, they potentially stand to gain the most by effective interventions. Individuals with static brain injury will be recruited to test experimental cognitive paradigms sensitive to focal cognitive deficits in order to validate their use in cognitive deficits in a young-onset dementia population. Carers will be recruited to assess carer burden and service use and distribution dependent on pattern of cognitive deficits in cognitively affected participants.

There are relatively few centres with a specialist interest in younger onset dementia, and where these exist, clinical protocols and assessment tools differ. As a consequence, research into these disorders is hampered, particularly in relatively rare subgroups within the frontotemporal dementia syndromes. The YoDA study, which involves no experimental treatment, aims to address these issues by facilitating collaborative research in a clinical setting, maximising the use of routinely collected clinical information and providing a platform to test novel assessments with the aim of developing evidence-based guidelines for the clinical assessment and longitudinal monitoring of young-onset dementia. The YoDA study will prospectively recruit individuals with young-onset dementia and static brain injury, according to accepted criteria (e.g. McKeith, 1996; Erkinjuntti, 2000; Rascovsky 2007; Zerr, 2009; McKhann 2011; Gorno-Tempini, 2011, Albert, 2011); and their carers and follow them longitudinally using structured assessments as long as possible to identify the best clinical assessment tools which predict progression and outcome.

**Study Objectives**

a. To improve the understanding of the dynamic phenotypic spectrum and the disease mechanisms of young onset or atypical Alzheimer's disease and other dementia syndromes by:
i. Providing natural history data including cognitive, behaviour and motor progression and insights into the neurobiology of these diseases

ii. Collecting data and biosamples to identify genetic and environmental factors influencing or modifying phenotype and disease progression

iii. Promoting a databank to facilitate projects that may further the understanding of young onset dementia pathophysiology

b. To promote the development of evidence-based guidelines to inform clinical decision-making and improve health outcomes for participants/families by:
   i. Assisting in the identification of beneficial interventions (clinical, pharmacological, non-pharmacological)
   ii. Facilitating and promoting the dissemination and implementation of currently proposed best clinical practices
   iii. Providing a platform for conducting collaborative research in a clinical setting
   iv. Promoting exploratory data analysis projects that may identify care processes to further promote care

c. To provide a platform to support the design and conduct of clinical trials by:
   i. Providing a resource to identify, develop and qualify novel assessment tools, clinical endpoints and biomarkers
   ii. Collecting longitudinal data to inform disease modeling studies
   iii. Facilitating the identification and selection of potential participants to provide data to estimate and quantify rates of progression and trial participation effects
   iv. Maintaining a list of appropriate participants who qualify for therapeutic trials.

de. To maximize the use of routinely collected clinical data to optimize future use of such information by:
   i. Obtaining permission to use retrospective medical data
   ii. Combining data across multiple sites to increase data analysis power
   iii. To improve clinical effectiveness and standards through shared outcome

Study Description

a. Study Period

YoDA is an open-ended, prospective study (except for dementia care NHS and social care professionals). Participants are asked at the time of signing up for YoDA to attend as many prospective annual visits as possible. In addition, participants will be asked to give consent to the study site for the registration of available
YOUNG-ONSET DEMENTIA ASSESSMENT STUDY (YODA)

retrospective clinical data obtained prior to enrolment in the study.

b. Study Population
   i. Inclusion criteria

   The study population will comprise 4 groups all over the age of 18:

   1. Individuals affected by a possible or definite neurodegenerative syndrome
   2. Individuals affected by a static brain lesion
   3. Carers of individuals with a possible or definite neurodegenerative syndrome or carers of individuals affected by a static brain lesion
   4. Specialist NHS and social care professionals

   Participant status will be based on clinical signs and symptoms, imaging and biomarker profiles in line with current internationally accepted criteria (primarily, but not limited to, Mild Cognitive Impairment (MCI), Alzheimer's disease (AD), Vascular Dementia (VaD), Frontotemporal dementia (FTD), Huntington's disease (HD), Progressive Supranuclear Palsy (PSP), Corticobasal degeneration (CBD), Multiple System Atrophy (MSA) and traumatic brain injury (TBI)).

   During the course of the project we will also invite a small number (n=5-10) of dementia specialists (e.g. consultants, nurses, researchers) to take part in semi-structured interviews. This will be in order to gain insight into the thoughts and perspectives of NHS and social care professionals on issues related to obtaining a diagnosis, routine clinical care, post-diagnostic support, and service provision. These participants will only be recruited to the interview sub study they will not be recruited to any other components of YoDA and its sub-studies.

   ii. Exclusion criteria

   1. Participants who do not meet inclusion criteria
   2. Participants who are unable to understand the study protocol or unable to give informed consent at enrollment

   c. Study Enrolment
      i. Participant Identification, Recruitment
Participants and carers will be recruited from specialty clinics (Neurology, Psychiatry) that advise and treat people with young-onset dementia (YOD). In addition, in some areas community clinics and neuropsychologists who see YOD patients will recruit participants for this study. The research staff at each site will identify potentially eligible participants and enquire as to their willingness to participate in this study. They may also receive information about the study through a website, clinical practices, support groups, advocacy newsletters, etc. and place a direct request to be considered for participation in the study.

ii. Consent process

Information about the YoDA study will be provided in oral and written form to the participants complementing information available to them from the resources mentioned above. Informed consent is an absolute prerequisite for participation in this study, and procedures for obtaining informed consent will be based on the participant’s competency and will adhere to local regulations and requirements.

An informed consent form will be signed by all competent participants defined as individuals with the cognitive and mental capacities, as determined by the site investigator, to understand the nature and purpose, procedures and risks and benefits of the study and have a non-coerced desire to participate.

All participants should have capacity for consent at the start of the study, and individuals where this is not the case will not be approached. Given the nature of these diseases, participants may lose mental capacity during the course of the study; therefore a recommendation will be made to them to discuss their future study participation wishes with a personal consultee. Explicit consent will be obtained at the start of the study with regards ongoing involvement in the study in the event of loss of capacity. In such cases, where the participant has indicated an interest in continuing with the study, the wishes of the personal consultee will be sought, and any trial participation will be limited to non-invasive clinical observation and documentation only.
Some individuals have capacity, but have physical limitation (e.g. apraxia) which makes it difficult to obtain written signature. In such cases, we will request individuals mark the consent form in some way, but we will write an explanatory note and request carers to countersign.

The consent may be given and the form signed, at a single visit or at a future visit to the study site, based on the choice of the participant. Where a potential participant who attends alone is assessed to need the support of an advocate, we will defer enrollment until such time as they can attend with someone who can advise them.

Signed consent forms will be stored in a designated secure location at the site. A signed copy of the consent will be provided to the participant.

d. Data Collection and Schedule of Assessments
   i. Core Assessments

   The Core Assessments are data elements that are required for all participants at all sites to be collected at baseline and annual follow-up visits. The planned assessments and instruments are described in detail in subsequent sections. Information will be collected regarding comorbid conditions, concurrent medications, clinical characteristics and treatment (pharmaco-therapeutic, non-pharmacologic, nutritional supplements, physiotherapy, etc.). Diagnostic and therapeutic information collected as part of routine clinical care within the previous 6 months may form part of the core assessment if the participant has given consent for the use of retrospective clinical information. All sites are encouraged however to attempt to collect as much of the specified core battery as possible.

   1. Core Clinical

   Clinical characteristics will be recorded in cognitive domains and also include medication history, vascular risk profile, past medical history including smoking and alcohol habits and family history.

   In participants with cognitive impairment:
   Written informed consent/ assent
   Creation of unique identifier
   Review of Inclusion/ Exclusion criteria
Socio-demographic information
Clinical characteristics
Comorbid conditions
Concurrent medications
Consent for use of retrospective clinical information, including
- Medical history
- Physical examination findings
- Results of imaging and other investigation findings
Consent for contact between visits
Reportable Event Monitoring

In carers:
Written informed consent
Creation of unique identifier
Review of Inclusion/Exclusion criteria
Socio-demographic information
Consent for contact between visits

ii. **Extended Assessments**
It is intended that extended assessments are collected on as many participants as possible. The aim of the extended assessments is to characterize the clinical phenotype of YOD participants as fully as possible, and provide a platform for assessing inter-test correlation, reliability and validity. It is accepted that not all participants will have all extended assessments. These assessments may be collected at the time of the clinic visit or as part of a follow-up visit at the participant’s home within a period extending three months before and after a scheduled clinic visit.

1. **Cognitive**
The Addenbrooke’s Cognitive Examination (ACE-R), Mini-mental Score (MMSE) and/or Montreal Cognitive Assessment will be used to characterize the core cognitive deficit. These instruments are commonly used to assess a range of cognitive domains including memory, language, executive function and visuospatial skills.

2. **Functional**
The Clinical Dementia Rating (CDR) and the CDR-FTLD scales will be used to characterize the functional deficits present. The CDR sum-of-boxes will be calculated from this. Sites may use additional functional measures which form part of their clinical assessment protocols such as the Functional Activities Questionnaire (FAQ) or other Activities of Daily Living (ADL) scales e.g. DADS, BADL.

3. **Behavioural**
   A key component of the assessment of those with young onset dementia or cognitive decline is change in behaviour. This will be assessed using structured rating inventories which index multiple behavioural domains and may include the Cambridge Behavioural Inventory (CBI), Frontal Behavioural Inventory (FBI), Neuropsychiatric Inventory (NPI) or other structured measure along with a rating of mood and anxiety e.g. Hospital Anxiety and Depression Scale (HADS).

4. **Quality of Life Assessments**
   Instruments assessing quality of life including the Short Form Health Survey 36 (SF-36) will be administered together with the Caregivers Quality of Life Questionnaire.

5. **Health Economics**
   The impact of available resources (or their lack of provision) will be assessed using a Resource Use Questionnaire. Affect on ability to work will be ascertained through the Work Productivity Questionnaire, and the functional impact on both participants and carers will be quantified with an activities of daily living assessment (ADL assessment).

iii. **Optional Components**
   1. Participants will be asked for permission to use clinical data collected prior to recruitment to this study
   2. Participants will be asked for permission to be contacted between study visits to clarify questions (e.g. concerning YoDA questionnaires), to provide updates on YoDA or to inform them about other studies for which they might be eligible
3. Where blood, CSF, urine or other biosample has been collected as part of routine clinical diagnosis, participants will be asked for permission for long-term storage and use of this biosample. CSF collection will not be performed as part of this study protocol.

4. Participants will be asked for permission to make video recordings of study visits for the purpose of quality control, research and training across the YODA network.

iv. Participation in Sub-studies

Apart from the study procedures associated with the main protocol of the YoDA study, sub-studies are proposed within the YoDA study umbrella. The purpose of these sub-studies is to provide a mechanism for establishing and validating novel assessment tools or assessment procedures to gather data in specific young onset dementia and cognitively impaired populations and/or control populations.

These sub-studies are intended to better inform about specific and/or rare clinical phenotypes not presently captured in the established standardized assessments. Validation of assessment tools implies exploring the clinical metrics of the tool as well as inter-rater reliability. A systematic analysis of each item of the assessment tools used will allow the development of improved, more mature assessment tools. In a first pass, cross-sectional data will be gathered, and in a second pass, data gathering will extend to longitudinal data to look at the rate of changes in the various assessments.

Each sub-study will have a separate protocol that details study procedures, standard operating procedures for study coordination, and a data analysis plan. Sub-studies may be proposed by qualified researchers and will need to be reviewed and approved by the YoDA steering committee and will be implemented only after obtaining appropriate REC approvals. Subjects will be consented for substudies with a specific patient information sheet and separate consent form.

1. Substudy 1: Biospecimen collection
Participants with cognitive impairment will be asked for blood for storage for use in biomarker assessments. For participants who consent to donation of biosamples, up to 20 ml of blood will be collected at each annual visit for storage in a central biospecimen repository which is licensed as a Human Tissue Bank under the Human Tissue Authority Act (2004). Specimens will be de-identified for storage and the central repository will have no access to identifying data. Participants may opt to participate at only the baseline visit or at any of the subsequent annual follow up visits.

At specific sites with required specimen processing capabilities and proper training, plasma separation will be performed. In brief, blood will be drawn in a 9.5 ml EDTA tubes and centrifuged in a refrigerated within 30 minutes of blood draw. Plasma is aliquotted into sterile cryotubes and placed in a -80°C freezer and subsequently shipped on dry ice using an overnight courier service. Shipping labels and detailed packaging instruction will be provided by the central biospecimen repository.

Where agreed, 30ml urine will be collected from participants.

Carers will not be asked to donate biosamples.

2. Substudy 2: Oxford Memory study – see appendix C
3. Substudy 3: Improving understanding of important issues in younger onset dementia – see appendix D
4. Substudy 4: Investigating the relationship between remembering the past and thinking about the future – see appendix E

e. Reportable Event Monitoring
   i. There is no intervention as part of the study protocol. Death will be reported to the YODA chief investigator whilst participants are still enrolled in the trial.

f. Statistical Methods
   i. Sample Size
      In performing an observational cohort study, the larger the
sample size used for data analysis, the more applicable the results are to the population as a whole. Therefore, YoDA will allow each site to enroll as many participants as are eligible and willing to participate. As described in the rationale, YoDA is a cooperative effort to build a large linked dataset of clinical data and biosamples, with the aim of validating results of previous studies with smaller sample sizes and enabling testing of new hypotheses.

While each project proposal defining a specific outcome or endpoint will include a sample size calculation and/or power analysis specific to the objectives of that particular study, in general, the sample size and open ended enrollment is planned a) to facilitate genetic modifier studies that require large numbers to reliably identify genes of interest and their modifiers, b) to identify distinct phenotypes that are infrequent and therefore require large numbers for detection, c) to explore a diversity of environmental modifiers and gene-environment interactions, and d) to build disease models to study prognostic factors and rates of progression.

Since all questions will not necessarily require the entire sample of participants, only a subset of assessments are delineated as core assessments and required on all participants at all sites. Extended assessments are to be collected on most participants as often as possible, but due to the planned large number of participants, it is anticipated that even with missing data, there will be sufficient number of participants with extended assessments, and therefore, sufficient power for proposed analyses.

ii. Data Analysis
Descriptive analyses will be conducted in support of the objective of providing natural history data including cognitive, behavior, motor progression and insights into the neurobiology of young onset dementia. Individual sub-study proposals will develop data analysis plans specific to the objectives of each sub-study. Qualified researchers can apply for and obtain access to the anonymised data to perform additional exploratory or data mining analyses. If necessary, investigators may request guidance for development and implementation of statistical analyses from the Steering Committee.

g. Study Management
i. Participants Lost to Follow-up
For participants who are not seen three months after a regularly scheduled annual visit, the site will attempt to contact the participant to determine if the lack of response is health related and to determine the health status of the participant. The staff will make 3 attempts to contact the participant within 3 months. Participants will be regarded as lost to follow-up if all three attempts fail. Any data collected prior to loss to follow-up will be included in all analyses.

Data Entry/ Electronic Data Capture System

ii. Source Documents
The physician should maintain source documents for each participant enrolled in the study, Source documents such as participant charts and medical notes will be kept as part of the participants’ medical records. Participant files including medical records and signed participant ICFs must be available for review in the event the site is selected for monitoring, audits or inspection.

iii. Quality Assurance and Monitoring
To obtain optimal data quality and reach the highest standards of reliability, YoDA is monitored on the basis of the principles of Good Clinical Practice (GCP) according to International Conference on Harmonization (ICH) guidelines:

1. the rights and well-being of human participants are protected
2. the reported data are accurate, complete and verifiable from source data
3. the conduct of the trial is in compliance with the currently approved protocol/amendments and the applicable regulatory requirements
4. Investigators’ meetings, training and written guidelines and SOPs and data entry requirements will ensure appropriate conduct of the study.

iv. Quality Control
Quality control will be handled by data monitors with site visits to ensure that procedures are being followed, including checking on-site assessments, giving feedback to sites and ensuring up-to-date training and accreditation. Central checking of data for completeness and plausibility at the level of the data repository will be maintained. Sites are monitored at least annually to check source documents.
(i.e. informed consent, date of birth, gender, medical history, completeness of data entry).

v. **Patient Identification Number (PID)**
   This will be generated locally by each site using an indexing facility of the database. It will be the only demographic information synchronized with the central site. This information must be stored separately with the site file.

vi. **Data Storage and Security**
   Each site will maintain their study records in paper form but transfer this to an electronic database. This database, held locally in each case, will be stored on site clinical management storage facilities in a manner that allows regular backup. A partial replica of the database will be defined that includes no identifying demographic information, and will be used to synchronize with the main study site on a regular basis.

vii. **Data Management**
   Each participating site will receive appropriate training, which describes processes required for a clinic to become a study site, enrolling participants, providing follow-up data on enrolled participants, maintaining study documents or files, reporting adverse events, and closing the study. All site staff who participate in enrolling participants, collecting or entering data for the study will be required to undergo appropriate training.

viii. **Changes to Protocol**
   Any substantive modifications of the study protocol will require a formal amendment. Protocol amendments will not be implemented until they are reviewed and approved by the IRB/EC. Investigators must adhere to the study protocol and any major deviations from the protocol are prohibited unless they are preceded by an amendment and approval of the YoDA Steering Committee.

ix. **Study Governance**
   The Steering Committee will comprise the PI for the initiating study sites, and will be responsible for overseeing the conduct of the study. The Steering Committee will be responsible for the following:
   1. Overall safety of research participants
   2. Overseeing the systems that protect the confidentiality of the research participants
   3. Ensuring data integrity and quality
   4. Oversee data sharing and publication policies
   5. Review and approval of any changes to the protocol or inclusion of sub-studies and/or ancillary studies
x. Publication policy
Data used from the assessments will acknowledge the facilities of the YoDA study and list the participating sites and investigators. Authorship will be determined by contribution to any ensuing manuscript. Projects on core and extended assessments should be notified to the study coordinator. Each substudy will have a nominated principal investigator who will be responsible for collating the relevant data and publishing the results. It will be the responsibility of the substudy investigator to determine authorship contributions to any publication.

5. ETHICAL AND REGULATORY CONSIDERATIONS

a. Costs to the Participant
Participants will incur no cost for participation in this study. Participants will receive no payment for participation in this study.

b. Participant Risk
This is a non-interventional study and participants do not undergo specific risks by participating. Information in the core assessments is simply that collected by routine clinical assessment protocols. This extends to participants who undergo clinical diagnostic procedures such as Magnetic Resonance Imaging (MRI), HMPAO- Single Photon Emission Computed Tomography (SPECT) or who have blood drawn to exclude reversible causes of neurodegenerative syndromes or for genetic diagnostic testing.

For clinical, cognitive and functional assessments, participants may experience anxiety or psychological discomfort while completing these tests. Adequate rest breaks and appropriate encouragement will be offered by the investigator to minimize this.

For sub-studies requiring additional imaging, specific protocols and ethical review will be sought.

Where biosamples are donated, there are some additional potential risks associated with blood draw. The collection of blood specimens may cause pain and/or bruising at the site where blood is drawn. Fainting or feeling light-headed may occur shortly after having blood drawn. If a participant experiences this, the participant will be instructed to lie down immediately to avoid possible injuries. Localized clot formation and infections may occur, but this is very rare. Only experienced staff will draw blood for this study.

c. Potential Benefit
Participants will receive no immediate benefit from participation in this study. The only potential benefit is a better understanding of young onset dementia and the possibility that the information obtained in this study lead to potential treatments and to plan future research studies of experimental drugs aimed at slowing disease progression.

d. **Alternatives to Participation**

Any patient can choose not to participate. Any optional component of the study can be declined.

e. **Withdrawal from Participation**

If a participant does not want to continue, the participant can leave the study at any time without giving a reason for their withdrawal of consent. Unless otherwise requested, all data and biosamples obtained up to that point will be retained. At the participant's request, all information obtained so far will be anonymised. At the participant's request, any biosamples stored at the central biorepository will be destroyed. Participants have to be aware that the 'End of Study form' must be completed by the investigator, detailing the reasons for withdrawal (e.g. marking 'patient request').

Participants may be withdrawn from the study for the following reasons:

- failure to complete the required study procedures regardless of reason
- The site investigator feels that it is in the best interest of the participant.

If the participant is withdrawn by the investigator, an 'End of Study form' must also be completed.

f. **End of study/ Withdrawals**

There is no fixed end of study. After patient death, the 'Death Report form' (study form) must be completed by the investigator. If a participant does not want to continue, the participant can leave the study at any time. In this situation, any data already collected will still be available for use in the study. Participants are free to withdraw from the study at any point in time. Reason for study discontinuation or withdrawal will be collected; however, reasons for withdrawal of consent do not have to be disclosed. Unless otherwise requested by the participant, all data and biosamples obtained up to that point will be retained. On explicit request by a participant, all biosamples still stored at the central biorepository at the time of the withdrawal request will be discarded. Data
collected to this point will be de-identified (i.e., made untraceable) and maintained in the database. In addition, an investigator may withdraw participants from the study if he or she feels that it is in the best interest of the participant.

g. Participant Confidentiality
Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. By signing the protocol, the institution and/or physician commit to complying with all related applicable international and local laws and regulations (see appendix) as well as any applicable Safe Harbor privacy principles.

There are several provisions in place to maintain integrity, confidentiality, and security of participant information. Data are shared using a code or a participant identification number (PID) with no identifying information. Researchers and other users only have access to completely de-identified data.

a. Independent Ethics Committee
REC approval consistent with local regulations will be obtained for each site. The written favorable opinion/approval of the REC will be provided to each study physician, and a copy will be filed in the Study Master File. Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant REC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant REC during the course of the study in accordance with local regulations and requirements.

6. APPENDICES
a. Appendix A: References
b. Appendix B: Patient information sheets and consents
c. Appendix C: Sub-study Investigating the Nature of Memory complaints in dementia
d. Appendix D: Improving understanding of important issues in younger onset dementia
e. Appendix E: Investigating the relationship between remembering the past and thinking about the future
APPENDIX A

References


Appendix B: Patient information sheets and consents – see separate sheets

Appendix C: Substudy Investigating the nature of memory complaints in dementia.

<table>
<thead>
<tr>
<th>Substudy Title</th>
<th>Investigating the nature of memory complaints in dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Lead</td>
<td>Dr Christopher Butler &amp; Dr Samrah Ahmed</td>
</tr>
<tr>
<td>Funding Source</td>
<td>NIHR Oxford Biomedical Research Council</td>
</tr>
<tr>
<td>Background</td>
<td>Memory complaints are very common in older adults, and in some cases, can signal the onset of a progressive, degenerative condition such as Alzheimer's disease. Separating out the profile of memory impairment that is reflective of a dementing process, as distinct from other treatable causes of memory impairment, can sometimes be difficult.</td>
</tr>
<tr>
<td>Aim</td>
<td>The aim of this sub-study is to investigate the profile of memory impairment in patients with dementia, by comparing recent (i.e. new) and remote (i.e. old) memories.</td>
</tr>
<tr>
<td>Study Population</td>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>(i) Patients attending for cognitive assessment who have enrolled in the YoDa protocol and who have given permission for use of retrospective clinical information and contact for additional studies.</td>
</tr>
<tr>
<td></td>
<td>(ii) Diagnosis of dementia.</td>
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<tr>
<td></td>
<td>(iii) Capacity for consent at the start of the study: Informed consent forms will be signed by all competent participants; defined as individuals with the cognitive and mental capacities as determined by the site investigator; to understand the nature and purpose, procedures and risks and benefits of the study and have a non-coerced desire to participate. It is the responsibility of the researcher who takes informed consent to re-assess mental capacity and understanding if there is a time-lag between the clinician seeing the patient and enrollment of the patient into the sub-study. Individuals who lack capacity will not be approached for enrollment into the study. Where a potential participant who attends alone is assessed to need the support of an advocate, we will defer enrollment until such a time as they can attend with someone who can advise them. A signed copy of the</td>
</tr>
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</table>
consent will be provided to the participant.

| **Assessment protocol** | In addition to assessments conducted as part of the standard clinical assessment (as detailed in the YoDA protocol), consenting patients will be asked to complete the following assessments:

1. Remote memory and imagination:
   We will examine remote memory (e.g. for autobiographical events, public events and facts, famous faces, words) and the ability to imagine the future. We will use standard and specifically designed tasks that involve the presentation of visual or auditory stimuli relating to a real or imagined event, following which the participant describes the event in as much detail as possible (e.g. the Autobiographical Memory Interview (Levine et al. 2002, Kopelman et al. 1989), Episodic future thinking task (Addis et al. 2008), and Spontaneous Use of Imagery Scale (Reisberg et al. 2003)).

2. Anterograde memory:
   We will administer a series of tests to examine learning and forgetting of new information over standard (30 minute) and extended delays (e.g. weeks). These tests, in which we present verbal and non-verbal stimuli on a computer screen or paper, are based upon our previous work (e.g. Butler et al 2007) and include the Modified Rey auditory verbal learning test (Schmidt 1996), Graham-Kendall Designs (Graham & Kendall 1968) and Rivermead Behavioural Memory Test (Wilson et al. 1989).

Assessments will be conducted by members of the clinical and research team, affiliated with the Oxford Cognitive Disorders Clinic. Assessment schedules will be informed by the level of functioning of the patient i.e. by informing the selection of appropriate tasks, or informing minor modifications where necessary.

| **Assessment duration** | Assessments will be conducted over 2 sessions. Each session will last no longer than a standard clinical consultation, i.e. approximately 2.5 hours or less, depending on the patient’s level of functioning, and inclusive of breaks.

| **Methodological approach** | **Recruitment:**
   This study will recruit patients from all YODA sites in order to allow comparisons across sites. An estimated 100

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patients would be recruited across the sites (25 per site) over 1-2 years, across a range of diagnoses.

**Statistical analysis:**
T-tests or Analysis of Variance (ANOVA), or equivalent non-parametric statistics if assumptions are violated, will be used to compare demographic, cognitive and behavioural measures between groups. Relationships between variables will be examined using correlational analyses. Regression analyses will be used to examine predictive utility of cognitive and behavioural variables for identified outcomes (such as disease classification, cognitive or functional change). To address Type 1 errors, appropriate statistical corrections (e.g. Bonferroni correction) for multiple comparisons will be applied to all p-values.

| **Outcome** | The primary outcome measure is the relationship between remote memory and recent memory in dementia. |
### Appendix D:

<table>
<thead>
<tr>
<th>Sub-study Title</th>
<th>Improving understanding of important issues in younger onset dementia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Lead</td>
<td>Dr Christopher Kipps &amp; Dr John Spreadbury</td>
</tr>
<tr>
<td>Funding Source</td>
<td>NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC)</td>
</tr>
</tbody>
</table>

#### Background
Younger onset dementia (i.e., dementia with symptom onset before the age of 65 years) often presents in unique and challenging ways and is often poorly assessed and managed. Recent literature reviews on the research conducted in these complex and other atypical dementias recognise that this remains a neglected area in comparison with research on dementia more generally (Hunt, 2011; Roach et al. 2008; Svanberg et al. 2011). As such, much is unknown about the experiences of younger individuals with dementia and their caregivers, particularly relating to how they experience routine clinical care and post-diagnostic support.

#### Aim
The aim will be to conduct a series of exploratory semi-structured interviews and focus groups in order to develop a better understanding of the most important issues related to living with younger onset dementia, dementia care, and quality of life.

#### Study Population
Semi-structured interviews will recruit three groups of participants: (i) health care professionals with specialist expertise in younger onset dementia (from medicine, nursing, allied health, and social care); (ii) patients with younger onset dementia; and (iii) informal caregivers to younger onset dementia patients.

Focus groups will recruit patients with younger onset dementia and informal caregivers to younger onset dementia patients. Each group will have between 4 and 10 participants.

Patients and their informal caregivers will be those who have already been recruited, via specialist clinics (Neurology, Psychiatry) that advise and treat people with younger onset dementia, and given written informed consent to participate in the Young Onset Dementia Assessment (YoDA) project and its sub-studies.
### Inclusion criteria:

(A) Patients will have a clinical diagnosis of a possible neurodegenerative disease or static brain lesion and present symptoms of difficulty or impairment in cognitive functioning or behaviour - as per the inclusion criteria for the YoDA project.

(B) Caregivers will be recruited as per the YoDA protocol.

(C) Health care professionals will be recruited as per the YoDA protocol.

### Assessment procedure

The study comprises two parts: (A) semi-structured interviews; and (B) focus groups.

Eligible participants will be offered the opportunity to participate in either a semi-structured interview or a focus group investigating important issues related to the experience of younger onset dementia, about routine clinical care and post-diagnostic support, and about quality of life.

(A) Semi-structured interviews will take place in the participant’s own home (or at another location where the participant feels comfortable to talk) with one of our research team. Patients and their caregiver will be given the option of either being interviewed alone or with the patient/caregiver present. Health care professionals will be interviewed individually.

The researcher will administer the questions on the semi-structured interview schedule in a flexible way changing the order or wording of questions where necessary and following up interesting material based on the responses from participants. We aim to ask questions about participants present circumstances, about their experience of obtaining a diagnosis, about routine clinical care, about post-diagnostic support and service provision, and about what participants think are the most important issues in dementia care.

Before the interview ends the researcher will give each participant the opportunity to clarify or add anything that has been discussed during the interview.
Focus groups will be run separately for patients and caregivers and will include between 4 and 10 participants in each group. Focus groups will be held at Southampton General Hospital and we will reimburse participants for their travel expenses in attending the group.

The group facilitator will administer the questions on the discussion schedule in a flexible way, changing the order or wording of questions where necessary and following up interesting material based on the group discussion. We aim to have as a central topic of discussion issues related to quality of life. We will ask the group what they think are the most important issues related to quality of life in younger onset dementia and to rank issues from most important to less important.

Before the focus group ends, the group facilitator will give participants the opportunity to clarify or add anything that has been discussed during the group.

Semi-structured interviews and focus groups will be recorded using a digital voice recorder and transcribed for qualitative analysis.

**Assessment duration**

We anticipate that each interview will last for between 1 and 2 hours; and each focus group will last for between 1 and 1.5 hours.

Participants will be given rest breaks whenever necessary and during focus groups we will ensure that refreshments are available.

**Methodological approach**

The design of the study is: (A) exploratory qualitative semi-structured interviews; and (B) focus groups.

Participants will be asked to take part in either a semi-structured interview or a focus group where they will be asked questions about their knowledge or experience related to obtaining a diagnosis, routine clinical care, post-diagnostic support and service provision, and issues of quality of life. We will also ask participants about whether they would recommend any changes or modifications to
the present system of dementia care.

Semi-structured interviews and focus groups will be transcribed and analysed using thematic analysis. Transcripts will use pseudonyms and will maintain participants’ anonymity.

### Outcome

The aim of using semi-structured interviews will be to allow each participant to express their own thoughts and experiences related to different aspects of the system of care in younger onset dementia. By using this approach we will aim to gain access to each group’s unique understanding and perspective of younger onset dementia care from which we will be able to investigate similarities and differences in group perspectives, to identify care issues that appear most important to each group and across groups, and to learn what aspects of care meet and fail to meet each group’s needs.

The aim of using focus groups will be to give each group of participants the opportunity to interact, discuss, and express as a group their thoughts and feelings related to several salient areas of living with younger onset dementia. By using this approach we aim to gain a better understanding about the most salient issues related to quality of life and the experience of dementia care for each group.

### Ethical Issues

In order to assist participants in giving meaningful informed consent all participants will receive both verbal and written information about the research study. Participants will be given an information sheet explaining about the nature of either the semi-structured interviews or the focus groups which will include the contact details of the researchers involved in the study and the contact details of the Patient Support Service.

The information sheets and informed consent forms will make clear to participants that their participation in the study is entirely voluntary and that they may withdraw from the study at any time without any consequence to themselves or their on-going or future care/treatment.

Any published results from the study involving participant quotations will use pseudonyms and will be screened to
<table>
<thead>
<tr>
<th>References</th>
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</table>
Appendix E: Investigating the relationship between remembering the past and thinking about the future

<table>
<thead>
<tr>
<th>Substudy Title</th>
<th>Investigating the relationship between remembering the past and thinking about the future</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Lead</td>
<td>Georgina Knott, Trainee Clinical Psychologist</td>
</tr>
<tr>
<td></td>
<td>Supervised by Professor Rosaleen McCarthy, Consultant Neuropsychologist</td>
</tr>
<tr>
<td>Funding Source</td>
<td>Postgraduate research training budget allocated by the University of Southampton</td>
</tr>
<tr>
<td>Background</td>
<td>The ability to imagine oneself in the future in order to prepare for possible eventualities is a psychological construct known as future episodic thinking (Atance &amp; O’Neil, 2001). Neuropsychological research over the last decade has suggested that people suffering from amnesia, who are unable to remember events from their personal past and consequently are described as having deficits in episodic thinking, are also not able to describe themselves in hypothetical future scenarios (Verfaellie, Race &amp; Keane, 2012).</td>
</tr>
<tr>
<td>Aims</td>
<td>This sub-study of the Young Onset Dementia Assessment Study (YoDA) intends to test the hypothesis that impaired episodic memory (recalling events from one’s personal past) leads to a deficit in future thinking (imagining oneself experiencing an event in the future). It will also investigate whether the use of scaffolding, in the form of structured questions can assist patients with impaired memory to the same extent whether they are recalling the past or imagining the future</td>
</tr>
<tr>
<td>Study Population</td>
<td>Adult patients aged between 18 and 75 with known episodic memory difficulties, but with minimal additional cognitive difficulties will be recruited together with a small group of control participants, with no deficits in recalling their personal past.</td>
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<tr>
<td></td>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>(i) Patients who have enrolled in the YoDa protocol</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>(i) Patients who are deemed to lack capacity to</td>
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In addition to assessments conducted as part of the standard clinical assessment undertaken at the neuropsychology department (as detailed in the YoDA protocol), consenting patients will be asked to complete the following assessments:

1. **Past & Future Word Cue Task.** This is based on the Crovitz-Schiffman word technique (Crovitz-Schiffman, 1974). It will involve asking participants to recall events from their past and imagine events they may experience in the future based on whatever comes to mind when they are read aloud a cue word, which is also written on a card placed in front of them. Initially, participants will be provided with no further prompts and allowed to talk freely for up to two minutes. They will then be asked to elaborate on their descriptions using a list of predetermined questions set out below, that will be asked if such detail has not already been given.

   1. Who is present in the scenario?
   2. What happened/will occur?
   3. When is the memory/imagined event taking place?
   4. Where is the event taking place?
   5. Why did this recalled event/imagined event occur?
   6. Are there any smells, visual sensations sounds or tastes?

   The same 10 words will be asked for both the past and future conditions, using an ABBA design, where A is the past condition and B is the future condition. All descriptions will be audio recorded for analysis.

Participants will also complete the following:

1. **The National Adult Reading Test (NART; Nelson, 1982),** a list of 50 irregularly pronounced words to be read aloud, which can give an estimate of pre-morbid intellectual functioning.

2. **Set I of the Advanced Progressive Matrices**
task (Raven, 1958), which contains 12 items, which measure intellectual reasoning.

3. The Vividness of Visual Imagery Questionnaire (VVIQ, Marks, 1973) a 16 item self-report measure of imagery abilities

4. The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), a 14 item self-report measure assessing the presence of symptoms of depression and anxiety.

<table>
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<tr>
<th>Assessment duration</th>
<th>It is expected that assessment will last no longer than a standard clinical consultation, i.e. approximately 2.5 hours or less, depending on the patient’s level of functioning, and inclusive of breaks.</th>
</tr>
</thead>
</table>
| Methodological approach | Recruitment:  
Patient recruitment will involve suitable patients being identified following routine neuropsychological evaluations undertaken at the department. They will be informed of this study and if interested, will be given the participant information sheet to read through, before obtaining their informed written consent to participate. It is anticipated that majority of patients who will be suitable will have already been recruited to the main YoDA study. If this is not the case, they will be given the participant information sheet for YoDA to consider first, before information on this sub-study is offered.  
Statistical analysis:  
The participant’s scores from their descriptions for each of the 10 words in the past and future conditions will be in four categories; “past unprompted” descriptions, “past scaffolded” descriptions, “future unprompted” descriptions and “future scaffolded” descriptions. Scores will be calculated on the underlying causes of the event (why), number of objects/people (who and what), frequency of temporal-spatial references (when and where) and number of sensory details (smell, sight, sound, taste and touch). A score of 2 will be given for a highly detailed response, 1 for a superficial response and 0 for a non-response. A blind second rater will be used to minimise
bias. It is anticipated that analysis will take the form of non-parametric correlations and appropriate non-parametric tests (Wilcoxon and Mann-Whitney) to determine if there are any statistically significant differences between participants’ scores on the past and future conditions, as well as their scores on the unprompted and scaffolded tasks.

**Outcome**
The primary outcome measures are the differences between participants’ scores on the past and future conditions, as well as their scores on the unprompted and scaffolded tasks.

**References:**


