Application 1195

Protocol to guide the assessment of F-18 Flurodeoxyglucose (FDG) Positron Emission Tomography (PET) for the diagnosis of Alzheimer's disease

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Minister for Health (the Minister) to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a draft decision analytic protocol that will be used to guide the assessment of an intervention for a particular population of patients. Draft protocols will be finalised after inviting relevant stakeholders to provide input to the protocol. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use;

Intervention – specification of the proposed intervention

Comparator – specification of the therapy most likely to be replaced by the proposed intervention

Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of F-18 Flurodeoxyglucose (FDG) Positron Emission Tomography (PET) for the diagnosis of Alzheimer's disease was received from The Department of Nuclear Medicine and Centre for PET at Austin Health, Victoria, by the Department of Health in September 2013.

The use of FDG PET is proposed to establish a diagnosis of Alzheimer's disease where other diagnostic methods are inconclusive.

FDG PET is not currently listed on the MBS for this purpose and therefore, this application is for one new MBS item for patients with evidence of decline in memory or other areas of cognition where the current diagnostic methods are inconclusive.

Intervention

Description

PET is a minimally invasive nuclear medicine imaging technique that uses short-lived radiopharmaceuticals that mimic endogenous molecules to detect and assess perfusion and metabolic activity in various organ systems. It provides information about function and metabolism that is complementary to the structural information provided by anatomical imaging techniques such as x-ray computed tomography (CT).

FDG is the most common molecular imaging biomarker used in PET and is a radiolabeled glucose analogue. By entering the glucose metabolic pathway, FDG provides information about tissue metabolism and is widely used in oncology. FDG uptake by brain tissue as measured by PET evaluates the regional cerebral metabolic rate for glucose (CMRgl), thus giving information about the entity of neuronal loss or synapse dysfunction (Vacante et al., 2013).

A characteristic pattern of hypometabolism may be observed visually, however a semi-quantitative method is proposed in which FDG PET images are assessed using software that analyses the pattern of tracer uptake voxel-wise by comparing the subject's scan with a reference data set to allow better recognition of the pattern of hypometabolism compared with visual interpretation (Filippi et al., 2012).

In this DAP the term 'PET' is used to refer to either PET or PET/CT. The term 'PET/CT' is used where specific reference to this modality is made. Most current and future practice will relate to the use of PET/CT machines, as all PET machines sold now in Australia are PET/CT machines.

Administration, dose, frequency of administration, duration of treatment

Delivery of 18F-FDG PET scanning can be broken down into three phases:

1) 18F-FDG preparation: can be produced either in-house in facilities with a cyclotron, or sourced from a commercial supplier. FDG is administered intravenously 60 minutes prior to

scanning. The dose of FDG will vary according to body mass and PET machine parameters used.

2) PET scanning: done using a standard protocol which usually includes low-dose computed tomography (CT) for attenuation correction and anatomical correlation. A PET study acquisition time ranges from 20 to 45 minutes.

3) Image reconstruction and interpretation: PET images are usually reconstructed using the PET scanner manufacturer's recommended reconstruction protocols and software. The nuclear medicine specialist interprets the images (including correlated imaging where available) and generates a clinical report.

It is expected that patients would have only one PET scan for the diagnosis of Alzheimer's disease. However, those patients in whom the PET scan is equivocal or negative may have a repeat PET scan 2-3 years later if the diagnosis remains inconclusive.

The service will be provided by nuclear medicine specialists upon receipt of a written referral from a medical specialist. The professional groups most likely to order this test are neurologists, geriatricians and psychiatrists.

Co-administered interventions

There are no co-administered or associated diagnostic tests or treatments with 18F-FDG PET. There are four dementia-specific drugs subsidised through the PBS and RPBS for patients who have a diagnosis of Alzheimer disease confirmed by (or in consultation with) a specialist or consultant physician, subject to specific clinical criteria being met (Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE) scores) (Australian Institute of Health and Welfare, 2012). The drugs (and their trade names) are:

- Acetylcholinesterase inhibitors:
  - donepezil (Aricept[®]) (PBS Codes: 2479L, 2532G, 8495D, 8496E)
  - galantamine (Reminyl[®], Galantyl[®]) (PBS Codes: 2463P, 2531F, 2537M, 8770N, 8771P, 8772Q)
  - rivastigmine (Exelon[®]) (PBS Codes: 2475G, 2476H, 2477J, 2493F, 2494G, 2526Y, 2551G, 8497F, 8498G, 8499H, 8500J, 8563Q, 9161E, 9162F)
- Memantine (Memanxa[®], Ebixa[®], APO-Memantine[®]) (PBS Codes: 1956Y, 2492E, 2513G, 9306T).

In 2009–10, a total of 392,796 subsidised dementia-specific medications were dispensed with an average annual growth in the dispensing of subsidised dementia-specific medications of 8% each year between 2002–03 and 2009–10 (Australian Institute of Health and Welfare, 2012). Based on PBS and RPBS data, Australian Government expenditure on dementia-specific medications in 2009–10 was $58.7 million (Australian Institute of Health and Welfare, 2012).

The proposed listing of FDG PET to diagnose Alzheimer's disease could marginally increase the rate of uptake of these medications but any effect is likely to be very small.

Background

Current arrangements for public reimbursement

There is currently no Medical Benefits Schedule (MBS) listing for reimbursing FDG-PET of the brain performed for the diagnosis of Alzheimer's disease. There is also no private health insurance rebate for PET services, so patients need to pay out of pocket for this service. FDG-PET is funded on the MBS for other indications, predominately in oncology.

Regulatory status

There are three PET machines registered on the Australian Register of Therapeutic Goods (ARTG):

- GE Healthcare Australia Pty Ltd. ARTG #156649 and ARTG #114476m
- Phillips Electronics Australia Pty. ARTG #147067

There are two registered PET/CT machine types:

- Siemens Ltd. ARTG #144218
- Philips Electronics Australia Ltd's ARTG #118077

There are 2 registered PET/MRI machine types:

- Siemens Ltd. ARTG #188470
- Philips Electronics Australia Ltd. ARTG #193622.

There are also 4 registered PET imaging software's available:

- Siemens Ltd. ARTG #181848 and ARTG #178420
- GE Healthcare Australia Pty Ltd. ARTG #154936 and ARTG #153390.

There are two registered entries for 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG):

- Austin Health, in Melbourne, ARTG #54251
- PETNET Australia Pty Ltd, with ARTG #78935 (Licence number MI-2009-LI-03349-3).

Additionally, there is a second commercial supplier of radiolabelled FDG in Australia, Cyclotek which is a TGA approved manufacturer (Licence number MI-12092005-LI-000904-2). Radiolabelled FDG is also produced he Royal Prince Alfred Hospital (NSW), Peter MacCallum Cancer Institute (VIC), Royal Brisbane Hospital (QLD), Wesley Hospital (QLD) and Sir Charles Gairdner Hospital (WA).

The requested MBS listing for FDG PET is consistent with the regulatory body approved indication.

Patient population

Proposed MBS listing

The applicant has not provided a proposed MBS listing but does state that the technique is the same as for MBS item number 61559 (FDG PET study of the brain, performed for the evaluation of refractory epilepsy which is being evaluated for surgery.) The assessment group proposes the MBS listing below based on item 61559.

Table 1: Proposed MBS item descriptor for FDG-PET for diagnosis of Alzheimer's disease

Category 5 – DIAGNOSTIC IMAGING SERVICES
MBS [item number]
FDG PET study of the brain, performed for the diagnosis of Alzheimer's disease where clinical evaluation by a specialist, or in consultation with a specialist, and MRI are equivocal (R)
Fee: $918.00 **Benefit:** 75% = $688.50 85% = $841.80

The applicant has specified a fee of $1,180, which is greater than the fee for item 61559 ($918.00) due to the different requirements for semi-quantitation. The applicant has noted that programs for this cost up to $40,000 however the PASC was advised that this software is freely available. Further justification of the proposed fee will be required.

Referrals for the proposed service should be restricted to specialist practitioners who can prescribe acetylcholinesterase inhibitors and memantine (neurologists, neuropsychiatrists, geriatricians), or general practitioners in direct consultation with one or more of these specialists. Currently the legislation requires that PET can be requested by specialists only. This requirement is unlikely to change if this application is passed through MSAC.

Clinical place for proposed intervention

Dementia is a substantial and growing health burden. The Australian Institute of Health and Welfare reports (2012):

- An estimated 298,000 Australians had dementia in 2011, of whom
  - 74% were aged 75 and over, and
  - 70% lived in the community.
- the number of people with dementia is projected to triple between 2011 and 2050, to reach around 900,000 by 2050
- Dementia was the third leading cause of death in 2010 (accounting for 6% of all deaths), with an average of 25 people dying from dementia every day that year.
  - Twice as many women as men died from dementia (6,083 and 2,920 respectively).
- Total direct health and aged care system expenditure on people with dementia was at least $4.9 billion in 2009–10, of which about $2.0 billion was directly attributable to dementia.

Dementia itself is a an umbrella term describing a syndrome associated with more than 100 different diseases that are characterised by the impairment of brain functions, including language, memory, perception, personality and cognitive skills (Australian Institute of Health and Welfare, 2012). Alzheimer's disease is the most common type of dementia accounting for 50-75% of cases of dementia worldwide. Its prevalence increases exponentially with age affecting less than 1% of people 60 to 64 years old, but 24% to 33% of those over 85. The earliest symptoms of Alzheimer's disease dementia include short-term memory loss, a gradual decline in other cognitive abilities and behavioural changes (Vacante et al., 2013). Onset is gradual and decline is progressive.

The neuropathological features of Alzheimer's disease are characterised by cortical intracellular neurofibrillary tangles (NFT) and extracellular-amyloid-β (Aβ) plaques, however at present these can only be observed in brain tissue following autopsy or biopsy (although amyloid PET ligands are moving into clinical practice and have been approved in the US), precluding definite diagnosis for most patients. A variety of assessment tools are therefore used for screening, diagnosis and/or monitoring dementia.

In the context of dementia, assessment tools are employed for two basic purposes:

1. to screen people for the likely presence/absence of cognitive impairment which may be indicative of dementia
2. for in-depth assessment for the purposes of formal diagnosis, care planning, and monitoring of disease progression or treatment efficacy (Australian Institute of Health and Welfare, 2007).

At the primary care level, cognitive decline may be identified based on history from a patient if verified by a reliable informant (usually a spouse) or on a cognitive test score that is below those expected for age and level of education (purpose 1). Patients who have evidence of cognitive decline are then referred for a more comprehensive assessment by a medical specialist (such as a geriatrician, psychiatrist or neurologist, purpose 2).

For formal diagnosis, the following tests are conducted:

1. Specialist clinical evaluation (history, examination, cognitive testing) for the assessment of cognitive function (see Australian Institute of Health and Welfare, 2007 for details of commonly used tools) which serves two main diagnostic purposes:
    I. the diagnosis of dementia requires evidence of multiple cognitive defects; and
    II. initial stages of all principal forms of dementia have a selective anatomical localisation reflected by typical patterns of neuropsychological impairment (Hort et al., 2010).
2. Structural imaging: MRI is the most appropriate test (provided the patient doesn't have a contraindication to having a MRI scan). Patients may or may not have had a CT generally for a range of reasons previously but MRI scans of the brain provide better delineation of the anatomy (atrophy etc) as opposed to CT in the context of investigating memory loss. MRI serves two main purposes:

<ol type="I" start="1">
Exclusion of other, potentially surgically treatable, causes
Identify findings specific for Alzheimer's disease (specific pattern of atrophy) (Hort et al., 2010)

<ol start="3">
Blood tests
<ol type="I">
Routine biochemistry
Haematology
Thyroid function
Vitamins B12 and folate.

FDG PET is a functional neuroimaging test and is proposed to be used where these tests have been conducted and diagnosis remains inconclusive.

Acetylcholinesterase inhibitors or memantine are recommended therapies for treating Alzheimer's disease but are not recommended or available on the PBS for the treatment of other types of dementia (see Co-administered interventions page 6) (National Collaborating Centre for Mental Health, 2007).

Prior tests

Current diagnostic methods consist of clinical evaluation by a medical specialist, a MRI brain scan and blood tests for routine biochemistry and haematology plus blood tests for thyroid function and vitamins B12 and folate.

Utilisation

The applicant has not provided estimates of utilisation. In its most recent report, the AIHW (Australian Institute of Health and Welfare, 2012) considered the incidence of dementia beyond its scope due to limited availability of data but cited updated previous estimates of 63,300 new cases in 2011. Only a proportion of new cases would require an FDG PET scan for a diagnosis.

Comparator

A single-photon emission computed tomography (SPECT) scan of the brain is listed on the MBS (see Table 2) and can be used to image cerebral perfusion, which like FDG PET, reflects brain metabolism and can assist in diagnosing Alzheimer's disease. The most commonly used tracer to examine cerebral blood flow (CBF) using SPECT is [99]m-Tc-hexamethylpropylene (HMPAO). SPECT is technically less demanding and more widely available than PET but also has lower resolution (Filippi et al., 2012).

FDG PET is proposed as a replacement test to SPECT, although the availability of FDG PET may limit the extent to which it replaces SPECT.

Table 2: MBS item descriptor for SPECT

	Category 5 – DIAGNOSTIC IMAGING SERVICES
MBS 61402	
CEREBRAL PERFUSION STUDY, with single photon emission tomography and with planar imaging when undertaken (R)	
Fee: $605.05 **Benefit:** 75% = $453.80 85% = $528.85	

Clinical management algorithms

FDG PET is proposed as a replacement test for SPECT in the diagnosis of Alzheimer's disease for patients who have evidence of cognitive decline and have undergone specialist assessment (clinical evaluation, structural imaging and routine blood tests) but in whom diagnosis remains uncertain.

Figure 1 Clinical management algorithm for Alzheimer's disease diagnosis with FDG PET
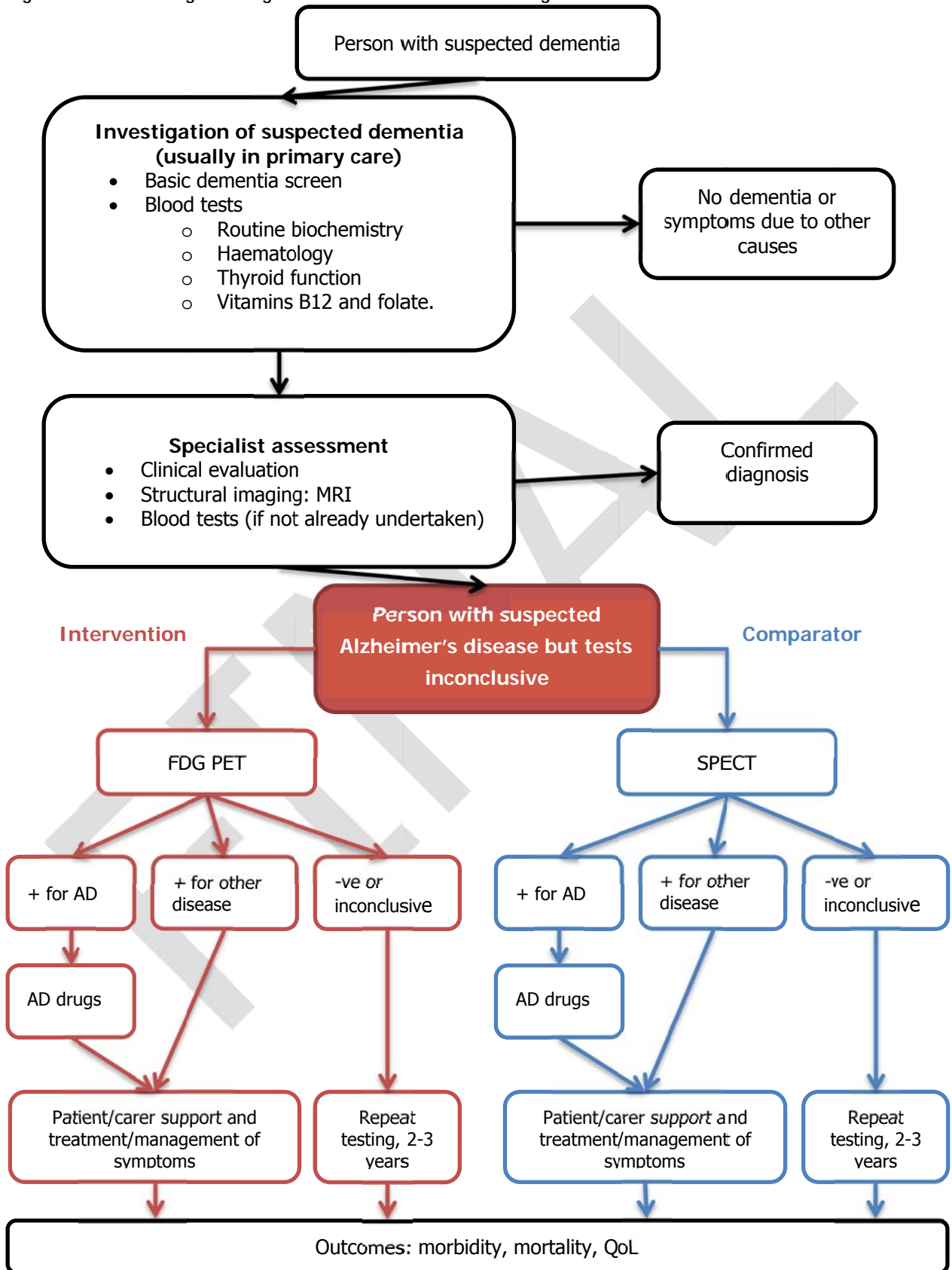
Clinical claim

For people with cognitive impairment who have undergone specialist assessment for suspected Alzheimer's disease including clinical assessment, structural imaging (MRI) and routine blood tests, and in whom the diagnosis remains inconclusive, FDG PET imaging may provide a definitive diagnosis.

The potential advantages of FDG PET compared to SPECT in this indication are:

- Improved patient selection
  - Detects more true positives and fewer false negatives for the presence of Alzheimer's disease than SPECT
  - Detects more true negatives and fewer false positives for the presence of Alzheimer's disease than SPECT
  - Leads to changes in treatment as a consequence of diagnosis (ie Alzheimer's specific therapies)
  - Leads to changes in treatment as a consequence of a differential diagnosis (ie. Alzheimer's specific therapies avoided)
  - Improves patient outcomes by providing the optimal treatment strategy to patients who otherwise would have had a delayed/missed opportunity for optimal first line treatment.

The potential disadvantages of FDG PET compared to SPECT in this indication are:

- False positive diagnosis of Alzheimer's disease, leading to inappropriate treatment with no clinical benefit and the risk of adverse events
- False negative diagnosis of Alzheimer's disease leading to a missed opportunity for optimal treatment
- Higher cost
- Availability and access to PET facilities may be restricted (equity).

Based on these clinical claims, FDG PET is proposed to be non-inferior to SPECT with respect to safety and superior with respect to effectiveness, therefore a cost-effectiveness analysis or cost-utility analysis would be expected to be undertaken (Table 3).

Table 3: Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator			
		Superior	Non-inferior	Inferior	
Comparative safety versus comparator	Superior	CEA/CUA	CEA/CUA	Net clinical benefit	CEA/CUA
				Neutral benefit	CEA/CUA*
				Net harms	None^
	Non-inferior	CEA/CUA	CEA/CUA*	None^	
	Inferior	Net clinical benefit	CEA/CUA	None^	None^
		Neutral benefit	CEA/CUA*		
		Net harms	None^		

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes

Safety

- Adverse events
- Radiation exposure

Diagnostic accuracy

- sensitivity
- specificity
- additional TP & FP

Change in management

- Treatment instigated
- Treatment avoided
- Other changes occurring in $\geqslant$10% patients

Patient outcomes

- disease-specific mortality
- disease progression
  - o Cognitive function
  - o Global outcome

o Activities of daily life
- quality of life
- prognostic value

Proposed structure of economic evaluation (decision-analytic)

Table 4: Summary of extended PPICO to define research question that assessment will investigate

Patients	Prior tests	Intervention	Comparator	Reference standard	Outcomes to be assessed

People with suspected Alzheimer's disease in whom prior tests have been inconclusive	1. Clinical Evaluation
	2. Structural imaging: MRI (or CT only where MRI is contraindicated)
	3. Blood tests
	   a. Routine biochemistry
	   b. Haematology
	   c. Thyroid function
	   d. Vitamins B12 and folate.
		Semi-quantitative FDG PET	SPECT	Histopathologic diagnosis via autopsy or biopsy, or long term clinical follow up	Safety
					• Adverse events
					• Radiation exposure
					
					Diagnostic accuracy
					• sensitivity
					• specificity
					• additional TP & FP
					
					Change in management
					• Treatment instigated
					• Treatment avoided
					• Other changes occurring in ≥10% patients
					
					Patient outcomes
					• disease-specific mortality
					• disease progression
					  o Cognitive function
					  o Global outcome
					  o Activities of daily life
					• quality of life
					• prognostic value

Research question: In people with suspected Alzheimer's disease in whom prior tests (clinical evaluation, MRI and blood tests) have been inconclusive, what is the safety, effectiveness and cost-effectiveness of FDG PET as a replacement for SPECT for establishing a diagnosis?					

References

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