Appendix M: Health Economics Evidence Tables

M.1 Dementia diagnosis

M.1.1 Dementia diagnosis

- What are the most effective methods of primary assessment to decide whether a person with suspected dementia should be referred to a dementia service?
- What are the most effective methods of diagnosing dementia and dementia subtypes in specialist dementia diagnostic services?

M.1.1.1 GP administered diagnostics

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER (£/QALY)		
Tong et al., (2016) A patient level cost-effectiveness model simulating a population of over 65 years old, who are assessed for cognitive impairment by their GP's in England.	Effects Diagnostic outcomes of patients who were referred to a memory clinic in England over one year from Abdel-Aziz and Larner (2015) were used to calculate the prevalence of dementia and mild cognitive impairment (MCI) in the simulated cohort. Diagnostic accuracy for 6CIT was calculated from Abdel-Aziz and Larner (2015). The performance of 6CIT in	Economic evaluation conducted from NHS and PSS perspective. Time horizon of model was patient lifetime.	**GPCOG vs GP unassisted judgement**			'These analyses estimated that using any of the three cognitive screening tests was more cost-effective than the GP unassisted judgement. Among the three cognitive tests, the	'A probabilistic sensitivity analysis was undertaken examining which diagnostic test had the highest incremental net benefit (INB) compared to unassisted GP judgement when the cost-effective
			£185.85	0.0003 QALYs	Dominant		
			MMSE vs GPCOG				
			£119.13	-0.0002 QALYs	Dominated		
			6CIT vs GPCOG				
			£66.49	0.0032 QALYs	£58,689 /QALY		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER (£/QALY)		
	detecting dementia and MCI was compared with that of the simultaneously administered Mini-Mental State Examination (MMSE). Diagnostic accuracy for GPCOG was calculated from Brodaty (2002). Diagnostic accuracy for the unassisted strategy was calculated from O'Conner (1998). Diagnostic accuracy of unassisted GP clinical judgement calculated from Mitchell (2011). Transition probabilities were calculated from five pooled studies from the Ward et al. (2012) systematic review. <u>Costs</u>: Resource-use per assessment was derived from NICE (2010). Administration time for each assessment taken from Cordell (2013). Data for health, social care and informal care costs were from Prince et al., (2014). Cost of medication	Future costs and benefits discounted at 3.5%. The authors did not declare any conflict of interest. The analysis for MMSE presented here was adjusted to remove the cost of the licence fee for using MMSE. This is because a royalty free version of the MMSE test is available and is the most appropriate comparator.				GPCOG was considered the most cost-effective option for the NHS [using net monetary benefit] given the referenced NICE threshold [of £30,000 per QALY]. The results are sensitive to assumptions about the effectiveness of dementia medications. The model results should be treated with caution because limitations in the analyses.'	(CE) threshold was varied between £0 and £80,000. At the CE threshold of £30,000 per QALY, the probability of the GPCOG being the best option was 75% from the NHS PSS. The probability of the 6CIT being the best option became higher than the GPCOG's when the threshold was above £50,000 per QALY from the NHS PSS perspective.'
Directly applicable							
Potentially serious limitations [a, b]							

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER (£/QALY)		
	from BNF (2016). Price year 2016 in UK pounds. Utilities: Equation reported in Getsios (2010) was used to calculate utility for patients.	The model was coded in SIMUL8 with the use of VBA code.					

a. Screening studies were used to calculate sensitivity and specificity for comparators.
b. Diagnoistic accuracy for GP unassisted strategy is from a 1998 paper.

Study, population, country and quality	Data sources	Other comments	Cost	Effect (95% CI)	ICER [e]	Conclusions	Uncertainty [d]
Wolfs et al., (2009) Inclusion criteria: Age 55 years or older, suspicion of dementia or cognitive disorder, no referral to other local/regional	Effects: The MEDICIE study (NCT00402311) – a randomised controlled trial run between July 2002 and August 2004. Patients were followed up for 12 months. (33 GP practices were randomised to DOG-PG whilst 37 were randomised to usual care). Trial-based	Economic evaluation conducted from a societal perspective. DOC-PC The diagnostic screening	**Usual Care**			'In conclusion, this full economic evaluation shows that an integrated approach to dementia by means of the	'The mean ICER in the main bootstrap simulation was €1,267/QALY. The incremental costs in the bootstrap simulation ranged from −€7,435 (2.5th percentile) to €6,750 (97.5th percentile). The incremental effectiveness ranged from −0.01 (2.5th percentile) to 0.13 (97.5th percentile). On the cost-
			€26,171	0.452 QALYs (0.432 to 0.472)	-		
			DOC-PG				
			€26,758	0.503 (0.487 to 0.519)	€11,510 /QALY		

Study, population, country and quality	Data sources	Other comments	Cost	Effect (95% CI)	ICER [e]	Conclusions	Uncertainty [d]
services in the past 2 years, and availability of a proxy (visiting the patient at least once a week), in the Netherlands. **Partially applicable** [a,b]	analysis (no extrapolation). A total of 414 patients were referred for further treatment. Of these patients, 351 were eligible for the study and 230 agreed. Costs: Cost analysis was performed	conducted by the DOC-PG consists of a home visit by the community mental health team (CMHT) and 2 visits to the University Hospital Departments of Geriatric				DOC-PG is not demonstrably more expensive and has a high probability of being more effective in	effectiveness plane, most of the incremental cost-effectiveness pairs (94%) are situated in the east section, meaning that DOC-PG is more effective than usual care. The majority of these incremental cost-effectiveness pairs (51%) are situated in the quadrant indicating dominance for the DOC-PG, whereas 43%

Study, population, country and quality	Data sources	Other comments	Cost	Effect (95% CI)	ICER [e]	Conclusions	Uncertainty [d]
Potentially serious limitations [c,d]	according to Dutch guidelines. Costs were calculated by multiplying volumes of resource use during follow-up by the cost price per resource unit. Health care costs and costs outside the health care sector were included. All costs were expressed in euros at 2005 values. All cost prices were adopted from Oostenbrink et al. (2004). Utilities: The EuroQoL-5D (EQ-5D) was used to measure patients' HRQoL at baseline and at 6 and 12 months of follow-up and was filled out by each patient's proxy.	Medicine and Geriatric Psychiatry. In addition, a computed tomographic scan and various blood tests are performed. The results are then discussed at a weekly interdisciplinary meeting in which a definitive diagnosis is made and a treatment plan is formulated. Usual Care Usual care means that either the diagnosis was				terms of QALYs.'	are situated in the northeast quadrant. When the ceiling ratio is €45,000 (corresponding to the threshold put forth by the National Institute for Health and Clinical Excellence guidelines: ±£30,000), the probability that the DOC-PG is cost-effective is 72%.'

Study, population, country and quality	Data sources	Other comments	Cost	Effect (95% CI)	ICER [e]	Conclusions	Uncertainty [d]
		made by the GP or the GP referred the patient to one of the existing separate regional services, such as the Maastricht Memory Clinic, geriatric medicine clinic, or the Department of Mental Health for the elderly of the CMHT.					

a. Only effects on patients considered. Effects on carers not considered.
b. Indirect costs not relevant to the NICE reference case were considered. However, disaggregated results are reported, enabling the recalculation of results with a perspective that is consistent with the NICE reference case (that is, NHS and PSS costs only).
c. Costs used by the study are old and may not be relevant today.
d. It was not possible to remove indirect costs not relevant to the NICE reference case from the bootstrap results.
e. ICER is relative to usual care.

M.1.1.2 Imaging diagnostics

Study, population, country and quality	Data sources	Other comments	Cost	Effect	ICER [c]	Conclusions	Uncertainty
Biasttu et al., (2012) Three diagnostic strategies (Standard Diagnosis, Standard Magnetic Resonance Imaging (MRI), and Magnetic Resonance Imaging + contrastophore -linker-pharmacophor e (MRI+CLP)) over a three year period for a cohort of 70 year-old individuals consulting for the first time following mild	Effects: Sensitivity and specificity taken from Harris (1998), Momino (2009) and Hansson (2006). Costs: Costs included costs of diagnostic tests, AD follow-up, treatment with generic drugs, care (both community living and institutionalisation), and indirect costs (of informal care givers). All costs were measured at their 2009 level in Euros. Utilities: The authors estimated quality-of-life weights (QALYs) for over-60 patients without Alzheimer disease at 0.826 on a scale of 0 to 1, on the basis of the mean of time trade-off scores	Economic evaluation conducted from a societal perspective – but also includes indirect costs which could not be excluded. The first part of the "Screen and treat" looks at population-wide screening everyone over 60 years old, whilst the second part targets individuals carrying the e4 allele of the apolipoprotein E gene (ApoE4). The time horizon for this analysis was 15 years. Future costs and QALYs were discounted at 5% annually. Treatment strategies were compared to Standard MRI. Authors have declared no competing interests exist.	**(ApoE4 individuals) Standard MRI**			'Assuming that a treatment with proven efficacy in early AD becomes available, as well as a diagnostic test allowing early detection of the disease, the issue of screening the population will arise. Our study suggests that, in order for this screening to be cost-effective, key parameters are the specificity of the new diagnostic test and the cost and effectiveness of the new treatment. These preliminary results ought to be	For the multivariate sensitivity analyses, the authors performed Monte Carlo simulations with 10.000 trials, in order to derive the distribution of incremental cost-effectiveness ratios for the MRI+CLP strategies, as well as acceptability curves for all strategies.
			€44,180	8.0386 QALYs	-		
			(ApoE4 individuals) Standard Diagnosis vs Standard MRI				
			€44,711	8.0377 QALYs	Dominated		
			(ApoE4 individuals) MRI+CLP vs Standard MRI				
			€46,075	8.0415 QALYs	€641,326 /WQALY		

Study, population, country and quality	Data sources	Other comments	Cost	Effect	ICER [c]	Conclusions	Uncertainty
cognitive impairment (MCI) symptoms in France. **Partially applicable** [a,b,] **Potentially serious limitations** [d, e, f]	for men and women aged 65–84 years old published in a study of health outcomes in the general population (Fryback, 1993). Quality-of-life weights for patients with Alzheimer disease at each disease stage and care setting (institution or community) were based on previously published Health Utilities Index Mark 2 (HUI:2) scores.					taken into account in the currently underway research on early detection and treatment of AD, including work on b-amyloid plaques detection and elimination. When this research yields results, a new cost-effectiveness analysis should be performed in order to evaluate the available tools with observed data.'	The probability that MRI+CLP being cost-effective compared to Standard MRI remains lower than 4% even assuming a willingness-to-pay at €200,000/QALY.

a. Study is from a societal perspective, but also includes indirect costs, of which it is not possible to exclude ourselves. There is no sensitivity analysis that excludes the indirect costs.
b. Costs and outcomes from other sections are not fully and appropriately measured and valued – but the omission is immaterial.
c. ICER's are relative to Standard MRI.
d. Discount rate used for future costs and QALYs not consistent with the NICE reference case.
e. Data for test charecteristics are taken from a 1998 study which may not reflect current practice in England.
f. QALY weights taken from a 1993 study which may not be indicative of current socital preference.

Study, population, country and quality	Data sources	Other comments	Cost	Effect	ICER [d]	Conclusions	Uncertainty
Hornberger et al., (2015) A decision-tree based analysis, comparing Florbetapir-PET with Standard Clinical Examination (SCE) with SCE alone. The target population was 70-year-old Spanish patients with an MMSE score of 20, who were undergoing initial assessment for cognitive impairment. Country of study is Spain. **Partially applicable** [a]	Effects: Test characteristics (sensitivity and specificity) for Florbetapir-PET were derived from the A16 phase III trial. Test characteristics of comparator (SCE) was extracted from a meta-analysis (Cure, 2014) and a review of registry data (Beach, 2012). Costs: Healthcare costs included diagnostic testing, medication, caregiver time and residence in a public nesting home. Caregiver time burden was derived from the GERAS study, and multiplied by the hourly cost of a district nurse in Spain in 2013. Annual cost of living in a nursing home	Economic evaluation conducted from a Spanish societal perspective. Time horizon was a 10-years. Cycle length was one month. Future costs and benefits discounted at 3%. Software package the model was created in is not stated.	**SCE alone**			‘The addition for Florbetapir-PET to SCE could facilitate the diagnostic decision-making as to whether one of the hallmark pathological features of Alzheimer’s Disease is contributing to a patients’ clinical symptoms, of dementia, thereby improving the tailoring the treatment strategies of patients under evaluation for cognitive impairment.	‘The authors conducted a one-way sensitivity analysis (OWSA) and a probabilistic sensitivity analysis (PSA) with 1,000 Monte Carlo simulations. The OWSA showed that the model was most sensitive to the hazard ratio of institutionalisation per unit increase in MMSE. Over 82% of the PSA simulations
			€155,686	3.022 QALYs	-		
			Florbetapir-PET+SCE vs SCE alone				
			€155,722	3.030 QALYs	€4,769 /QALY		
			Incremental Cost	**Incremental Effect)**	**ICER [d]**		
			Florbetapir-PET+SCE vs SCE alone (when assessment is conducted with an MMSE score of 22)				
			€-1,534	0.019 QALYs	**Dominant**		

Study, population, country and quality	Data sources	Other comments	Cost	Effect	ICER [d]	Conclusions	Uncertainty
Potentially serious limitations [b, c, e, f]	was taken from Coduras (2010). The cost of Florberapir-PET included expected rebates and discounts. All costs were adjusted to 2013 using the Spanish Consumer Price Index and were expressed in Euros (€). <u>Utilities</u>: Health utility scores for patients with Alzheimer's Disease from the GERAS study were used. Health utility scores for patients residing in nursing home settings were based on findings by Neumann et al (1999).	QALY gains for Florbetapir-PET resulted from the identification of additional patients who could receive earlier pharmacological intervention.				Results of the alternative scenario, which assumed diagnosis and treatment occurred earlier in disease progression, demonstrated that enabling earlier access to treatment would be a dominant option for the Spanish population.'	showed Flobetapir-PET to be cost-effective at a willingness-to-pay (WTP) threshold of €30,000 per QALY. When the WTP threshold was €100,000 Florbetapir-PET was cost-effective in over 99% of simulations.'

a. The study is conducted for Spain, a non-UK setting.
b. The project was funded by Eli Lilly and Company.
c. Costs were Spanish costs expressed in Euros.
d. ICER is relative to SEC alone.
e. Discount rate used for future costs and QALYs not consistent with the NICE reference case.
f. Test charecteristics taken from a case-controlled trial.

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
Hornberger et al., (2017) A decision-tree based analysis, comparing Amyloid-β (Aβ) positron emission tomography (PET) imaging as an adjunct to standard diagnostic assessment for the diagnosis of Alzheimer's disease in France. **Partially applicable** [a]	Effects: Test characteristics (sensitivity and specificity) for Aβ –PET Florbetapir-PET were derived from the A16 phase III trial. Test characteristics of the standard diagnostic assessment were based on the NINCDA-ADRDA study. Test characteristics for CSF was extracted from a meta-analysis (Cure, 2014). Costs: All costs were from France- specific sources to allow the analysis to take on the French Health Technology Assessment (HTA) perspective per AD diagnosis and treatment practice guidance. Resource utilization	Economic evaluation conducted from a French Health Technology Assessment (HTA) perspective. Time horizon was a 10-years. Future costs and benefits discounted at 4%. Software package the model was created in is not stated.	**Base-case scenario** [c] Standard diagnostic assessment vs Aβ –PET			'Aβ-PET is projected to affordably increase QALYs from the French HTA perspective per guidance over a range of clinical scenarios, comparators, and input parameters.'	'The maximum cost per QALY gained (€34,586) was associated with high initial reimbursement rate of Aβ-PET (€1,363). The cost per QALY gained was also influenced by cost of caregiver care and age at initiation of testing. The results showed that ICERs were below a willingness to pay threshold of €40,000 per QALY in more than 95% of simulations.'
			€909	0.021 QALYs	€43,286 /QALY		
			Alternative scenario [c] CSF vs Aβ –PET				
			€496	0.022 QALYs	€43,000 /QALY		

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
Potentially serious limitations [b, c, d, f]	estimates were extracted from multiple sources, including government websites. Currency was standardized to 2016 Euros using the French National Authority for Health guide for AD and were expressed in Euros (€). Utilities: Health utility scores for patients with Alzheimer's Disease from the GERAS study were used. Health utility scores for patients residing in nursing home settings were based on findings by Neumann et al (1999).	QALY gains for Florbetapir-PET resulted from the identification of additional patients who could receive earlier pharmacological intervention.					

a. The costs are not discounted in line with the NICE reference case.
b. The project was funded by Eli Lilly and Company.
c. Discount rate used for future costs and QALYs not consistent with the NICE reference case.
d. Costs in study presented from a French prespectice and given in Euros (€).
e. Test charecteristics taken from a case-controlled trial.

Study, population, country and quality	Data sources	Other comments	Cost	Effect	ICER	Conclusions	Uncertainty
McMahon et al., (2000) A hypothetical cohort of patients on presentation to an Alzheimer's Disease centre in the US. **Partially applicable** [a, f]	Effects: Diagnostic test characteristics (sensitivity/specificity) of dynamic susceptibility contrast-enhanced MR imaging and visual computed SPECT, were taken from Harris et al., (1998). The authors estimated the number of false-negatives diagnoses from the standard examination, so found the examination of sensitivity difficult. The authors also estimated the specificity of the standard examination for the base-case analysis. Costs: Resource use for the initial diagnostic work-up was based on Duncan et al., (1998), Growdon et al., (1995) and assessment of resource use at	Analysis was conducted from a societal perspective. The base case analysis patient time, and travel costs; but a sensitivity analysis where these costs have been removed. All future costs and outcomes were discounted at 3%.	**Standard Examination**			'The results of [the authors] base-case analysis suggest that it is not cost-effective to add functional imaging to the standard diagnostic work-up for Alzheimer disease, given the effectiveness of currently available therapeutic agents. The ICER of MR imaging plus dynamic susceptibility	A probabilistic sensitivity analysis was not conducted. However, the authors conducted a robust sensitivity analysis, including the use of hypothetical drugs, altered rates of disease progression, disease prevalence, cost scenarios and use of differing sets of quality-of-life weights. Both Visual SPECT
			$54,762	0.9889 QALYs	-		
			Visual SPECT				
			$55,362	0.9581 QALYs	Dominated		
			Computed SPECT				
			$55,549	0.9888 QALYs	Dominated		
			MRI imaging plus DSC MR imaging [d]				
			$55,769	0.9910 QALYs	$479,500 /QALY		

Study, population, country and quality	Data sources	Other comments	Cost	Effect	ICER	Conclusions	Uncertainty
Potentially serious limitations [b,c, e, g, h, l, j]	Massachusetts General Hospital. Costs were mostly based on Medicare reimbursement rates. All costs were adjusted to the price year 1998 and were expressed in US dollars ($).[c] Utilities: Quality of life weights for patients without Alzheimer's Disease were based on Fryback et al., (1993). Quality of life weights for patients with Alzheimer's Disease at each disease stage and care setting were based on Health Utilities Index Mark 2 (HUI:2) scores (Neumann et al., 1998, Neumann et al., 1999).	The model was a Markov model, and was programmed in TreeAge 3.5.2. Cycle length was 6-weeks whilst the time horizon was 18-months. Three cohorts of 32,000 patients each were modelled for each of the diagnostic strategies. Patients were classified by disease states and health care settings (community or nursing home).	The sensitivity analysis where patient time and travel costs (neither of which are relevant to the NICE reference case) were removed shows a similar pattern to the authors base case in that Visual SPECT and Computed SPECT were dominated treatment strategies. MRI imaging plus DSC MR imaging had an ICER of $328,830.			contrast-enhanced MR imaging was $479,500 per QALY gained, a ratio at the high end of the range of those typically calculated for funded interventions in the United States'.	and Computer SPECT were dominated in almost all scenarios considered. In the scenario of treatment with the hypothetical superior drug X, the ICER of MR imaging plus dynamic susceptibility contrast-enhanced MR imaging compared with the standard diagnostic examination was $174,470 per QALY.

a. The paper does not provide information about the average age, gender or severity of disease of the simulated cohort that is required before they can present to an Alzheimers Disease Centre.
b. The paper is funded by Pfizer.
c. The authors estimated the effectiveness rate of standard examination.
d. Costs and QALYs to calculate the ICER are incremental to standard investigation, as Visual SPECT and Computed SPECT are dominated strategies.

Study, population, country and quality	Data sources	Other comments	Cost	Effect	ICER	Conclusions	Uncertainty
e. Diagnostic test characteristics (sensitivity/specificity) of dynamic susceptibility contrast-enhanced MR imaging and visual computed SPECT, were taken from a 1998 paper. f. The study is for the US setting and not for a UK NHS setting. g. Quality of life weights for patients with and without Alzheimer's disease are based on relatively old studies (between 1993 and 1999). h. Study costs are taken from a US setting and expressed in dollars ($). i. Discount rate used for future costs and QALYs not consistent with the NICE reference case. j. Time horizon of the study was too short to capture costs and QALY difference over patients' life time.							

Study, population, country and quality	Data sources	Other comments	Cost (SD)	Effect (SD)	ICER [b]	Conclusions	Uncertainty
McMahon et al., (2003) Community-dwelling patients with mild or moderate dementia who present to specialized AD centres in the US.	Effects: Diagnostic test characteristics (sensitivity/specificity) of the standard clinical examination from Morris et al., (1991). Base case estimates for FDG PET taken from Silverman (2000) and Silverman (2001). Costs: Only changes in the model from the paper were reported. No information about	Analysis was conducted from a societal perspective. All future costs and	**Standard Examination**			'The results of this analysis suggest that a combined structural and functional examination, such as dynamic susceptibility weighted contrast-enhanced MR imaging, may be preferable to PET for	'The sensitivity analysis where a perfect examination could be performed, resulted in a cost of $57,339 (CD $18,009) and 0.7138 QALYs (SD 0.4085). Compared to Standard
			$56,859 (18,569)	0.7092 QALYs (0.4120)	-		
			DSC MR Imaging				
			$57,877 (18,927)	0.7109 QALYs (0.4110)	$598,800 /QALY		
			SPECT				

Study, population, country and quality	Data sources	Other comments	Cost (SD)	Effect (SD)	ICER [b]	Conclusions	Uncertainty
	resource use was provided, and is therefore assumed to be the same as McMahon (2000). Costs were mostly based on Medicare reimbursement rates. All costs were adjusted to the price year 1999 by using the medical component of the consumer price index and were expressed in US dollars ($). <u>Utilities</u>: Health related quality-of-life weights based on the Health Utilities Index Mark 3 (HUI:3). The HUI3 weights for patients with Alzheimer's Disease were derived from existing data (Neumann et al., 2000) that were stratified by care setting (community or nursing home). HUI:3 weights for patients without Alzheimer's Disease were from age-matched community-dwelling Canadians (Neumann et al., 2000). Caregiver utility does not	outcomes were discounted at 3%. The model structure is the same as reposted in McMahon et al., (2003) with the key difference being that 100,000 Monte Carlo simulations were carried out for each scenario.	$58,590 (18,799)	0.7063 QALYs (0.4127)	Dominated	the diagnosis of AD. However, the cost-effectiveness ratios of dynamic susceptibility-weighted contrast-enhanced MR imaging have been more than $100,000 per QALY in most analyses: With improvements in therapies or with negative consequences of inappropriate treatment, the incremental cost-effectiveness ratio of dynamic susceptibility weighted contrast-enhanced MR imaging becomes more favourable. Improved non-	Examination, this represents $1,017 in additional costs and produces 0.0046 more QALYs, resulting in an ICER of $221,100 per QALY. The sensitivity analysis where a 'treat all dementia' strategy was implemented, resulted in a cost of $57,339 (CD $18,009) and 0.7126 QALYs (SD 0.4083). Compared to Standard Examination, this represents $480 in additional costs and produces 0.0034 more QALYs, resulting
			Computed SPECT				
			$58,872 (18,736)	0.7093 QALYs (0.4137)	Dominated		
			Additional Strategies				
			Perfect Examination				
			$57,876 (18,907)	0.7138 QALYs (0.4085)	$221,100 /QALY		
			Treat all dementia				
			$57,339 (18,009)	0.7126 QALYs (0.4083)	$141,200 /QALY		
Partially applicable [a]							

Study, population, country and quality	Data sources	Other comments	Cost (SD)	Effect (SD)	ICER [b]	Conclusions	Uncertainty
Potentially serious limitations [c, d]	appear to have been considered.					pharmacologic strategies for AD management could also make functional imaging more useful.'	in an ICER of $141,200 per QALY.'

a. The paper does not provide information about the average age or gender of the simulated cohort that is required before they can present to an Alzheimer's Disease Centre.
b. ICERs are calculated relative to Standard Examination.
c. Discount rate used for future costs and QALYs not consistent with the NICE reference case.
d. Costs used in the study are relatively old (price year 1999) and are expressed in US dollars.

M.1.2 Distinguishing dementia from delirium or delirium with dementia

- What are the most effective methods of differentiating dementia or dementia with delirium from delirium alone?

No health economic evidence

M.1.3 Case finding for people at high risk of dementia

- What are the most effective methods of case finding for people at high risk of dementia?

No health economic evidence

M.2 Involving people with dementia in decision about care

M.2.1 Barriers and facilitators to involvement in decision making for people living with dementia

- What barriers and facilitators have an impact on involving people living with dementia in decisions about their present and future care?
- What barriers and facilitators have an impact on how people living with dementia can make use of advance planning?

No health economic evidence

M.3 Care planning, review and co-ordination

M.3.1 Health and social care co-ordination

- What are the most effective methods of care planning, focussing upon improving outcomes for people with dementia and their carers?
- How should health and social care be co-ordinated for people living with dementia?

Study, population, country and quality	Data sources	Other comments				Conclusions	Uncertainty
Vroomen et al. (2016) Patients with dementia. Netherlands.	Effects: The COMPAS (Case management of persons with dementia and their caregivers) project was a two-year prospective, observational, controlled, cohort study with 521 informal caregivers and community-dwelling persons with dementia. The study	Case management provided within one care organization (intensive case management model, ICMM) (n=234), case management	**ICMM vs control**			Compared to control, both ICCM and LM produced slightly less QALYs but were significantly cost saving. ICMM	We were not able to exclude societal costs from the uncertainty analysis conducted by the authors.
			€-25,755	-0.004 QALYs	€6,438,750 /QALY		
			LM vs control				

Study, population, country and quality	Data sources	Other comments				Conclusions	Uncertainty
	protocol was registered with the Dutch Trials Registry (NTR3268). The primary informal caregivers (n = 521) and persons with dementia were recruited from various regions of the Netherlands from April 2011 to November 2012.	where care was provided by different care organizations within one region (Linkage model, LM) (n=214), and a group with no access to case management (control) (n=73) were compared.	€-24,335	-0.01 QALYs	€2,433,500 /QALY	compared to LM cost €1,420 less but produced an additional 0.01 QALYs, was dominant, and is therefore the preferred case management strategy from the two strategies.	
			ICMM vs LM				
Partially applicable [a,b,c]	Costs: Cost diaries were used to collect data on use of care and support by persons with dementia and the informal caregiver to estimate costs from a societal perspective. Costs were adjusted to price year 2010 using the consumer price index and expressed in Euros (€).	Trial based analysis.	€-1,420	0.01 QALYs	**Dominant**		
Very serious limitations [d,e,f, g]	Utility EQ-5D-3L data for the person with dementia were collected	Costs and effects in the second year were discounted at 4% and 1.5% respectively based on Dutch guidelines for economic evaluations.	The economic evaluation conducted here compares costs and QALYS over 2 years.				

Study, population, country and quality	Data sources	Other comments				Conclusions	Uncertainty
	by interviewing the informal caregiver.						

a. Study was conducted from a societal perspective in the Netherlands.
b. QALYS were measured using the EQ-5D-3L via proxy (carer).
c. Future costs and discount rate was not in line with the NICE reference case.
d. The COMPAS study was not a randomised controlled trial.
e. The incremental effect in quality adjusted life years (QALYs) was estimated using a using a generalized linear regression model adjusted for baseline utility scores with a Gaussian distribution and an identity link.
f. Discount rate used for future costs and QALYs not consistent with the NICE reference case.
g. Costs taken from a Dutch setting and expressed in Euros (€).

M.3.2 Post diagnosis review for people living with dementia

- How should people living with dementia be reviewed post diagnosis?

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect (QALYs)	ICER (€/QALY)		
Meeuwsen et al., (2013)	Effects AD-Euro study - pragmatic multicentre RCT with 12 months' follow-up (n=175 [1:1]).	Economic evaluation conducted	**Memory clinics vs general practitioner care c**			'No evidence was found that memory clinics were more cost effective compared to	The uncertainty analysis was not able to be disaggregated to remove
			€-512	-0.025	€20,480 saved per		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect (QALYs)	ICER (€/QALY)		
Inclusion criteria: adults, children and seniors with newly diagnosed mild-to-moderate dementia in the Netherlands. **Partially applicable** [a, b] **Potentially serious limitations** [c,d,e]	Trial-based analysis (no extrapolation). Costs: Resource-use derived from the case report form provided by the caregiver, the hospital information system, the electronic medical record of the GPs, and information from different healthcare workers involved (e.g. physiotherapists, occupational therapists, psychologists). Unit costs based on Dutch guidelines. 2009 Euros. Utilities: EQ-5Q for patient and caregiver (Dutch utility weights).	from a societal perspective.			QALY forgone	general practitioners with regard to post-diagnosis treatment and coordination of care of patients with dementia in the first year after diagnosis.'	costs not considered by the NICE reference case. The uncertainly analysis presented by the authors' shows that 59% of the bootstrapped ICERs were situated below the horizontal axis of the cost-effectiveness plane, meaning that the majority of the ICERs indicate that the treatment in the memory clinic is cheaper than for the general practitioner. Further, 66% of the simulations were situated left from the vertical axis on the cost-effectiveness plane, meaning that a majority of the simulated ICERs indicate that the general practitioner is more effective than the memory clinic.

a. Although the study protocol included children, adults, and seniors with newly diagnosed mild to moderate dementia, the patient baseline characteristics showed that the average age of patients was 78.2 (SD 6.2) in the memory clinic group and 77.9 (SD 5.2) in the

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect (QALYs)	ICER (€/QALY)		
GP group. This means it is likely that all patients who took part in the study were over the age of 40, as per the inclusions requirements but the possibility of patients under the age of 40 cannot be ruled out. b. Study was condutected for the Netherlands and is therefore a non-UK study. c. The authors' base case adopted a broad societal perspective, including an attempt to value informal care and associated production loss costs; however, disaggregated results are reported, enabling the recalculation of results with a perspective that is consistent with the NICE reference case (that is, NHS and PSS costs only). This analysis excluded informal care and production loss costs. d. Time horizon of the study was too short to capture costs and QALY difference over patients' life time. e. Utility used Dutch weightings.							

M.4 Inpatient care

M.4.1 Caring for people living with dementia who are admitted to hospital

- How should people living with dementia be cared for when admitted to hospital?

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost (95% CI)	Effect (95% CI)	ICER		
Tanajewski et al., (2015) Patients over 65 years of age with cognitive impairment, admitted for acute medical care in England (as part of the TEAM RCT) **Directly applicable** **Minor limitations**	Effects: TEAM (Goldberg et al., 2013), an RCT conducted between 2010 and 2012 in the UK. (n=600 [1:1]) Trial-based analysis (no extrapolation). Costs: Electronic administrative records systems. Unit costs for care services from PSSRU 2011/12. Salary calculated using NHS pay scales 2011/12. Utilities: EQ-5Q-3L	Length of analysis was 90 days. At 90-day follow up, 139 patients (MMHU 68) had died. Missing values for cost, EQ-5D, and for other variables, were assumed to be missing at random (MAR) and were imputed using Multiple Imputation by Chained Equations (MICE).	-£149 (-298, 4)	0.001 (-0.006, 0.008)	Dominant	'The specialist unit for people with delirium and dementia did not demonstrate convincing benefits in health status over usual hospital care, as no significant effect on QALY gain was observed. However, the results did show a trend towards cost savings and a high probability of cost-effectiveness (94%) from a combined health and social care perspective, when usual criteria were applied.'	There was 'a 58% probability of the MMHU being dominant (cost-saving with QALY benefit) and a 94% probability of cost-effectiveness (at a £20,000/QALY threshold). The probability of the MMHU being cost-saving with QALY loss (SW quadrant) was 39%.'

M.5 Care setting transitions

M.5.1 Managing the transition between different settings for people living with dementia

- What are the most effective ways of managing the transition between different settings (home, care home, hospital, and respite) for people living with dementia?

No health economic evidence

M.6 Modifying risk factors for dementia progression

M.6.1 Risk factors for dementia progression

- What effect does modifying risk factors have on slowing the progression of dementia?

No health economic evidence

M.7 Cholinesterase inhibitors and memantine for dementia

M.7.1 Acetylcholinesterase inhibitors and memantine for people living with Alzheimer's disease

- Who should start and review the following pharmacological interventions: (donepezil, galantamine, rivastigmine, memantine) for people with Alzheimer's disease and how should a review be carried out?

No health economic evidence

M.7.2 Cholinesterase inhibitors and memantine in Alzheimer's disease

- How effective is the co-prescription of cholinesterase inhibitors and memantine for the treatment of Alzheimer's disease?
- When should treatment with donepezil, galantamine, rivastigmine, memantine be withdrawn for people with Alzheimer's disease?Non-pharmacological interventions for dementia

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Lachaine et al. (2011) Implicitly: probable AD, age 76 (AChEI) / 73 (AChEI+mem), mean MMSE 18.7 (US cohort) Canadian perspective **Partially applicable**[a,b,c,d,e] **Very serious limitations**[f,g,h,i]	Effects: Time to care from Lopez et al. (2014) – US retrospective cohort study; time to death from national lifetables + AD-specific HR (no source) Costs: Medication costs from standard Canadian payer reimbursement source; care costs from Canadian Study of Health and Aging (Hux et al, 1998, inflated to 2010) Utilities: Neumann (1999) (US; carer-rated HUI2): non-institutionalised = mean for mild–moderate AD (0.60); institutionalised = mean for severe, profound or terminal AD (0.34)	• Home–Care–Dead Markov model • 7-yr time horizon • Discounted at 5% • Memantine and AChEIs at proprietary prices • Funded by manufacturer of memantine	**Healthcare perspective:**			'From both a societal and a Canadian health care system perspective, the use of memantine combined with a ChEI to treat AD is a cost-effective alternative, compared with the use of a ChEI alone.'	• Deterministic sensitivity analyses: combination remains dominant when all cost and utility parameters are examined (both societal and healthcare perspectives) • PSA: combination dominant in 100% (healthcare perspective) and 99.8% (societal perspective) of simulations
			−30,512 CAN$	0.26	Combination dominates		
			Societal perspective:				
			−21,391 CAN$	0.26	Combination dominates		
			Healthcare perspective:				

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Pfeil et al. (2012) As per Lachaine et al (2011) but with Swiss perspective **Partially applicable**[a,c,d,j,k] **Very serious limitations**[f,g,h,l,p]	Effects & utilities: As per Lachaine et al (2011) Costs: Medication costs from the largest health insurer in Switzerland; healthcare costs from ECOPLAN (2009). Costs (except medication) assumed to increase by 5% per yr.	As per Lachaine et al (2011), except • 5-yr time horizon • Discounted at 3%	−27,656 CHF	0.12	Combination dominates	'Based on long-term considerations, the combination treatment was the dominant strategy over the mono treatment.'	Sensitivity analysis (not reported) 'showed the robustness of the base case findings.'
			Societal perspective:				
			−4,780 CHF	0.12	Combination dominates		
Touchon et al. (2014) As per Lachaine et al (2011), but with French perspective **Partially applicable**[a,c,d,k,l]	Effects & utilities: As per Lachaine et al (2011) Costs: Medication costs from French national health insurance; care costs from 2005 government survey (inflated to 2010	As per Lachaine et al (2011), except • Discounted at 3%	**Healthcare perspective:**			'Combination therapy with memantine and a ChEI is a cost-saving alternative compared to ChEI alone, as it is associated with lower costs and increased QALYs from both societal and healthcare perspectives.'	• In scenario in which probability of entry to care was doubled for combination and halved for AChEI, ICER rose to €13,342/QALY (healthcare perspective) / €33,082/QALY (societal perspective)
			−€8,341	0.25	Combination dominates		
			Societal perspective:				
			−€3,318	0.25	Combination dominates		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Very serious limitations[f,g,h,i]							• PSA: combination dominant in 99.5% (healthcare perspective) and 87.0% (societal perspective) of simulations

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Weycker et al. (2007) Moderate-to-severe Alzheimer's disease on stable donepezil US perspective	Effects: Based on SIB effect – combination from Tariot et al. (2004); donepezil from Feldman et al. (2001) (not from donepezil arm of Tariot RCT – 'We felt compelled to do this because in the trial, patients in the donepezil arm had increased or stable mean SIB scores over the first 12 weeks') Costs: drugs at average wholesale prices, assuming a standard discount of 15%; other care from Leon et al. (1998) Utilities: estimated from SIB → MMSE → CDR → HUI3 (carer-rated US; Neumann 2000)	• Patient-level cohort 'micro-simulation' model • Model estimates people spend 2/3 of their lives in full-time care, and accrue negative aggregate QALYs • Assumed 1-year treatment, after which cognitive function reverts immediately to what it would have been without treatment • Funded by manufacturer of memantine	−63 US$	0.027	Combination dominates	'Our study suggests that [combination] therapy – administered for 12 months… improves outcomes and reduces lifetime total costs of care. The cost-effectiveness of memantine therapy appears sensitive to the level of cognitive function at therapy initiation, and is better for those with less advanced disease.'	• Cost effectiveness of combination therapy appears to be sensitive to severity (SIB score) at therapy initiation, with better value for less advanced disease. Appears that ICER >$50,000/QALY for baseline SIB scores <50. • In a worst-case scenario (all parameters – except initial SIB score – set least favourable to memantine), ICER was $7,867 / QALY.
Partially applicable[d,k,m]							
Very serious limitations[i,n,o,p]							

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Knapp et al. (2016) **DOMINO-AD** Community-living people with moderate–severe AD (sMMSE score of 5–13), continuously prescribed donepezil for >3mo; prescriber considering change of medication England and Scotland	<u>Effects / utilities:</u> QALYs calculated from directly measured EQ-5D (carer-rated) <u>Costs:</u> Resource use covered: inpatient stays, outpatient attendances, day hospital, social clubs, lunch clubs, day care, community-based professional contacts (e.g. psychologists, psychiatrists, GPs, nurses, social workers, occupational therapists, home care) and all other services. Unit costs from standard UK sources.	• RCT-based analysis with 12-mo time horizon • Donepezil and memantine costed at generic prices	**MODERATE – donepezil -v- placebo:**			In combined moderate–severe group, 'Continuing donepezil for 52 weeks was more cost-effective than discontinuation. … Starting memantine was more cost-effective than donepezil discontinuation. Donepezil–memantine combined is not more cost-effective than donepezil alone.'	• In combined moderate–severe group, the probability that combination is better than donepezil alone is 50% at £20,000/QALY and 55% at £30,000/QALY • In combined moderate–severe group, the probability that memantine is better than placebo is 92% at £20,000/QALY and 95% at £30,000/QALY
			£974 (−£2,383 to £4,332)	0.26 (0.08 to 0.45)	£3,746/ QALY		
			MODERATE – combination -v- donepezil:				
			£1,310 (−£3,021 to £5,641)	−0.07 (−0.22 to 0.08)	Donepezil dominates		
			SEVERE – combination -v- memantine:				
			−£1,658 (−£6,399 to £3,082)	0.11 (−0.06 to 0.28)	Combination dominates		
			SEVERE – combination -v- donepezil:				
			−£240 (−£4,759 to 4,279)	0.11 (−0.06 to 0.28)	Combination dominates		
			SEVERE – donepezil -v- memantine:				
			−£1,418 (−£6,395 to £3,558)	−0.01 (−0.17 to 0.15)	Memantine dominates		
			SEVERE – donepezil -v- placebo:				
Directly applicable **Minor limitations[g]**			−£5,711 (−£19,015 to £7,592)	0.05 (−0.11 to 0.21)	Donepezil dominates		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
[a] Heterogeneous population based on US retrospective dataset that does not distinguish severity of dementia [b] Canadian perspective [c] Not possible to meet reference case re PSS costs and informal care costs: healthcare perspective appears to exclude PSS costs; societal perspective includes PSS costs but also informal care costs [d] Medicines that are now available much cheaper generically evaluated at proprietary prices [e] Discounting at 5% [f] 3-state model structure with homogeneous costs and QALYs in each [g] Time horizon may be insufficient: significant survival and potential for additional care events beyond horizon						[h] Effectiveness data from retrospective observational study, subject to numerous selection biases [i] Potential conflict of interest [j] Swiss perspective [k] Discounting at 3% [l] French perspective [m] US perspective [n] Randomised effectiveness data rejected in favour of nonrandomised comparison [o] Questionable plausibility of average duration of care (2 years in community; 4 years in full-time care) and final QALY totals (expected negative QALYs over lifetime) [p] No PSA	

M.7.3 Pharmacological management of Parkinson's disease dementia

- What is the comparative effectiveness of donepezil, galantamine, memantine and rivastigmine for cognitive enhancement in dementia associated with Parkinson's disease?

No health economic evidence

M.7.4 Cholinesterase inhibitors and memantine for types of dementia other than typical Alzheimer's disease

- How effective are cholinesterase inhibitors and memantine for types of dementia other than typical Alzheimer's disease?

No health economic evidence

M.8 Drugs that may worsen cognitive decline

M.8.1 Drugs that may cause cognitive decline

- What drugs that may worsen cognitive decline are commonly prescribed in people diagnosed with dementia?
- What are the most effective tools to identify whether drugs may be the cause of cognitive decline in someone suspected of having dementia?

No health economic evidence

M.9 Non-pharmacological interventions for dementia

M.9.1 Non-pharmacological interventions for people living with dementia

- What are the most effective non-pharmacological interventions for supporting cognitive functioning in people living with dementia?
- What are the most effective non-pharmacological interventions for supporting functional ability in people living with dementia?
- What are the most effective non-pharmacological interventions to support wellbeing in people living with dementia?
- What are the most effective methods of supporting people living with dementia to reduce harm and stay independent?

M.9.1.1 Cognitive rehabilitation

Study, population, country and quality	Data sources	Other comments	Cost	Effect	ICER	Conclusions	Uncertainty
Clare et al. (in press) Patients with an ICD-10 diagnosis of Alzheimer's, vascular or mixed dementia, had	Effects: Effects from the GREAT RCT (ISRCTN21027481) n=475 – patients were randomised 1:1 - n=209 intervention (Cognitive Rehabilitation (CR)), n=218 control (Treatment as Usual	Trial based analysis. No discounting was necessary as trial duration was less than 12 months.	Person with Dementia - Control			'For commissioning purposes, however, we did not find that CR is cost-effective when gauged against	'The probability of cost-effectiveness on the QALY (DEMQOL-U) was very low at all WTP values (from £0 to
			£4,485	0.45 QALYs	-		
			Person with Dementia - CR				
			£5,523	0.45 QALYs	£1,110,000 /QALY		

Study, population, country and quality	Data sources	Other comments	Cost	Effect	ICER	Conclusions	Uncertainty
mild to moderate cognitive impairment (MMSE score ≥ 18) UK study. **Directly applicable** **Minor limitations** [a]	(TAU)). At nine-month follow up, participants were reassessed. The study recruitment period was between April 2013 and March 2016. Costs: Service use taken from Client Service Receipt Inventory. Costs derived from PSSRU and National NHS Reference Costs. Prices were deflated to 2013-14 using the Hospital and Community Health Service (HCHS) index and expressed in British pounds. Cost-utility analysis was undertaken for people with dementia using the total cost of health and social care services and QALYs generated from DEMQOL-U. QALYS for carers generated from the self-completed EQ-5D-3L. Cases included all those for whom complete cost	There was no difference for the QALYs generated for the carers of people with dementia between the control group and the intervention group.	(ICER's are presented as CR incremental to control).			QALY gains for either participants with dementia or carers. It would appear that the attainment of personally set goals did not bring about changes in those domains that are measured in the dementia specific health-related quality of life measure (DEMQOL), nor did it improve carer health related quality of life measure (measured by EQ5D).'	£50,000) from the health and social care perspective; the probability of cost-effectiveness was just at or under 65% for all values of WTP over the same range. The cloud of societal cost outcome difference pairs covers all four quadrants of the plane in approximately equal proportions, indicating that it is not possible to be certain that either strategy is cost-effective at any level of WTP.'

Study, population, country and quality	Data sources	Other comments	Cost	Effect	ICER	Conclusions	Uncertainty
	data were available at 9 months.						

a. QALYS for people with dementia generated using the DEMQOL-U

M.9.1.2 Maintenance cognitive stimulation therapy

Study, population, country and quality	Data sources	Other comments	Incremental mean bootstrapped costs and effects for MCST compared to usual care group			Conclusions	Uncertainty
			Cost	Effect	ICER		
D'Amico et al. (2015) Patients with Alzheimer's in England.	Effects: Based on the Orrell et al. (2014) RCT (ISRCTN26286067) run between 1/11/2008 and 1/11/2012. Costs: Client Service Receipt Inventory (CSRI) used to capture resource use. Costs included residential care, hospital services, day services, equipment and adaptations,	Items providing benefits beyond 1 years discounted at 3.5%.	**EQ-5D**			For QALYs calculated from proxy EQ-5D, MCST was also cost-effective against the NICE threshold of £30,000 per QALY. For the remaining 3 QALY outcomes, MCST was not cost-effective at 6 months.	An uncertainty analysis was conducted from a societal perspective and found that the cost per QALY was £6,841 when generated from proxy-rated EQ-5D.
			£474.81	0.0013 QALYs	£365,276 /QALY		
			Proxy rated EQ-5D				
			£473.60	0.0176 QALYs	£26,835 /QALY		
			DEMQOL				
			£518.39	0.0039 QALYs	£132,539 /QALY		
			Proxy rated DEMQOL				
			£401.52	0.0062 QALYs	£64,785 /QALY		

Study, population, country and quality	Data sources	Other comments	Incremental mean bootstrapped costs and effects for MCST compared to usual care group			Conclusions	Uncertainty
			Cost	Effect	ICER		
Directly applicable **Minor limitations**	community services, medications MCST intervention costs. Unit costs from Personal Social Services Research Unit. Medication costs from British National Formulary. Costs for equipment and adaptations from market sources. Prices adjusted to of 2011 prices using the Consumer Price Index. Costs expressed in British pounds. Utilities: Utility values were calculated from both generic and dementia specific quality of life measures to compare gain in quality adjusted life years (QALYs) using both participant-reported and proxy-reported measures. QALYs were calculated from EQ-5D and Proxy EQ-5D using societal weights, York A1 Tariff. QALYs						

Study, population, country and quality	Data sources	Other comments	Incremental mean bootstrapped costs and effects for MCST compared to usual care group			Conclusions	Uncertainty
			Cost	Effect	ICER		
	were also calculated from dementia-specific measures (DEMQOL-U and DEMQOL-PROXY-U) using an algorithm based on societal weights.						

M.9.1.3 Joint reminiscence group therapy

Study, population, country and quality	Data sources	Other comments	Cost (SD)	Effect (SD)	ICER	Conclusions	Uncertainty
Woods et al. (2016) Patients with mild/moderate dementia as defined by the DSM-IV criteria. UK study.	Effects: Effects from the REMCARE RCT (ISRCTN42430123) n=488 – patients were randomised 1:1 - n=268 intervention, n=220 control; 350 dyads completed the study (206 intervention, 144 control). The study recruitment period	Trial based analysis. No discounting was necessary as trial duration was less than 12 months.	Person with Dementia - Control			'This trial does not support the clinical effectiveness or cost-effectiveness of joint reminiscence group therapy. Possible	'While a full cost-utility analysis had been planned as part of the economic evaluation of the REMCARE trial, the results showed that generating cost-
			£4,309 (8,872)	0.643 (0.150) QALYs	-		
			Person with Dementia - Reminiscence				
			£5,853 (8,880)	0.644 (0.141) QALYs	£1,544,000 /QALY		
			Carer – Control				

Study, population, country and quality	Data sources	Other comments	Cost (SD)	Effect (SD)	ICER	Conclusions	Uncertainty
	was between June 2008 and July 2010. Costs: Service use taken from Client Service Receipt Inventory. Costs derived from PSSRU and National NHS Reference Costs. Costs adjusted to price year 2010 and expressed in British pounds. Cost-utility analysis was undertaken separately for participants with dementia and their carers using the total cost of health and social care services and QALYs generated from the self-completed EQ-5D-3L and associated visual analogue scale EQ VAS. Carers completed the measure from their own perspective and for the person with dementia, who would also complete it whenever possible. Cases included all those for whom		£1,359 (3,743)	0.633 (0.179) QALYs	-	beneficial effects for people with dementia who attend sessions as planned are offset by raised anxiety and stress in their carers. The reasons for these discrepant outcomes need to be explored further, and may necessitate reappraisal of the movement towards joint interventions.'	effectiveness acceptability curves would not be meaningful.'
			Carer – Reminiscence				
			£2,495 (3,866)	0.632 (0.175) QALYs	**Dominated**		
			(ICER's are presented as Reminiscence incremental to control).				
Directly applicable							
Minor limitations [a]							

Study, population, country and quality	Data sources	Other comments	Cost (SD)	Effect (SD)	ICER	Conclusions	Uncertainty
	complete cost data were available (n = 336).						

a. A breakdown of resource use was not given.

M.9.1.4 Exercise

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
Sopina et al. (2017) Patients with mild Alzheimer's disease in Denmark.	<u>Effects</u>: Effects take from a randomised clinical trial NCT01681602. Study focused on individuals with mild AD aged 50–90 years. 200 individuals were randomised to the intervention group (n=107) or the control group (n=93) <u>Costs and resource use</u>:	Discounting was not applied due to the short 16-week time frame. Analysis performed from the Danish healthcare perspective.	Exercise vs Control (participant assessed EQ-5D-5L)			'The findings suggest that the exercise intervention is unlikely to be cost-effective within the commonly applied threshold values. The cost of the intervention might be offset	'The CEAC shows there is a 50% chance of the intervention being cost-effective using participant EQ-5D-5L at the threshold value of € 175,000/QALY. With the participant-
			€492	0.00313 QALYs	€158,520 /QALY		
			Exercise vs Control (proxy assessed EQ-5D-5L)				
			€492	0.00411 QALYs	€120,790 /QALY		
			Exercise vs Control (participant assessed EQ-VAS)				
			€492	0.00688 QALYs	€72,120 /QALY		

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
Partially applicable [a,b] **Potentially serious limitations** [c,d]	The cost analysis excluded the value of participants' and caregivers' time, their private transport costs and other private costs. The cost analysis also excluded potential costs relating to accidents/adverse events during the training sessions and changed demand for healthcare for example, in primary and social care. Costs were collected and recorded in 2015 Danish Crowns (DKK) and are reported in 2015 Euro (€) (€ 1=7.46 DKK). <u>Utility</u>: The Danish version of EQ-5D-5L and EQ-Visual Analogue Scale (VAS). Was used. The instrument was	Control group received treatment as usual. The intervention group performed 1 hour of supervised moderate-to-high intensity aerobic exercise three times weekly for 16 weeks.	Exercise vs Control (caregiver EQ-VAS)			by potential savings from reduction in use of health and social care.'	reported EQ-VAS, the threshold value is reduced to € 75, 000. When using caregivers' scores on both EQ-5D-5L and EQ-VAS, threshold values lie between € 120,000 and € 70,000, respectively.'
			€492	0.00569 QALYs	€87,157 /QALY		
			The average incremental cost for participants in the exercise group was estimated at €608 (95% CI €604 to €612) and €496 (95% CI €495 to €497) with and without transport cost, respectively. QALYs were not provided in the paper so were back calculated from the ICER and the costs.				

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
	administered to both the participants and their caregivers as proxy respondents. The available EQ measurements included data from baseline and 16 weeks completed by participants and caregivers in control and intervention groups.						

a. Study took place in a Danish healthcare setting, and costs were were expressed in Euros.
b. The cost analysis included the programme cost but disregarded potential consequences in the demand for health and social services.
c. Table showing costs and resource use in control and treatment arm not given. Unit cost of resources not given.
d. The study used the Danish version of the EQ-5D-5L.

Study, population, country and quality	Data sources	Other comments	Incremental costs [95% CI]	Incremental effects [95% CI]	ICER	Conclusions	Uncertainty
D'Amico (2016) Patients with a clinical	Effects: This economic analysis was conducted alongside the	Cost-effectiveness analyses were	Exercise vs Control £−169.7 [−1240.0, 900.5]	0.0055 QALYs	**Intervention dominant**	'The exercise intervention has the	An uncertainty analysis was not conducted.

Study, population, country and quality	Data sources	Other comments	Incremental costs [95% CI]	Incremental effects [95% CI]	ICER	Conclusions	Uncertainty
diagnosis of dementia. UK study. **Partially applicable** [a] **Minor limitations** [b]	EVIDEM-E trial (ISRCTN01423159), a 12-week pragmatic, randomised, controlled, single-blind, parallel-group trial of a dyadic exercise regimen (tailored walking) for community-dwelling individuals with dementia and their carers. One hundred and thirty-one dyads were recruited to this study and randomised to each treatment arm in a 1:1 ratio. Control n=64, Intervention n=67. <u>Costs and resource use</u>: Data on care and support service utilisation were collected using an adapted version of the Client Service Receipt Inventory. Whenever possible, unit costs were taken from the	conducted from the Health and Social Care perspective. Where services or equipment would continue to provide a benefit for more than 1 year costs were annuitised using the HM Treasury recommended annual discount rate of 3.5%. The intervention delivered physical exercise in the form of 12-week individually tailored walking		[-0.0031, 0.0140]		potential to be seen as cost-effective when considering behavioural and psychological symptoms but did not appear cost-effective when considering quality-adjusted life year gains.'	
			Each ICER was estimated using the Seemingly Unrelated Regression model within stata (StataCorp, 2013). Each cost and outcome measure in turn was regressed on treatment allocation, controlling, respectively, for cost and that same outcome measure at baseline. Regression models were bootstrapped with 1000 replications in order to address potential skewness within the data. Multiple imputation (using 10 imputed datasets) was employed to deal with missing values in some outcomes and covariates.				

Study, population, country and quality	Data sources	Other comments	Incremental costs [95% CI]	Incremental effects [95% CI]	ICER	Conclusions	Uncertainty
	PSSRU 2011. The BNF database was consulted with regard to costs for medication. Where costs for equipment and adaptations to home were not available in the PSSRU, they were estimated from market sources. Where 2011 unit costs not available, figures were adjusted to 2011 prices. All costs were expressed in UK pounds. Utility: QALYs were calculated using DEMQOL-Proxy scores and societal weights.	programme lasting for 20–30 min daily, designed to become progressively more intensive.					

a. QALYs were derived using the DEMQOL-Proxy, which is not consistent with the NICE reference case
b. The study did not conduct an uncertainty analysis.

M.9.2 Pre, peri and post-diagnostic counselling and support for people living with dementia and their families

- How effective are pre, peri & post-diagnostic counselling and support on outcomes for people living with dementia and their families?

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Søgaard et al., (2014) Inclusion criteria: age ≥50 years, diagnosis of Alzheimer's disease within the past 12 months, MMSE ≥20, and a primary caregiver who was willing to participate. Denmark **Partially applicable** [a]	Effects: Danish Alzheimer's Intervention Study (DAISY) RCT, 2004. (n=330 [1:1]) Trial-based analysis (no extrapolation). Costs: Costs considered include costs for intervention, healthcare services and nursing home. The original analysis also considered informal care and production loss costs. Societal perspective to estimate the long-term average costs of providing the intervention on a routine basis. 2008 Euros.	Length of analysis was 36 months. Missing data on questionnaire-based costs (informal care and production loss) and EQ-5D estimated using multiple imputation. Analysis presented is multiple imputation-based analysis. The dyads in the control group as well as in the	Psychosocial intervention [c] vs Control support (usual care)[d]			'Given that the intervention did not seem to generate QALY gains or cost savings, the potential for cost-effectiveness was limited.'	In bootstrapped PSA from the original analysis where the informal care and production loss costs where considered, the probability of cost effectiveness did not exceed 36% for the imputation-based analysis and
			€-4,433 [f]	-0.09 QALYs [e]	€49,255 saved per QALY forgone [f]		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Potentially serious limitations [b, g, h]	Intervention cost estimated from a microcosting procedure. Other healthcare costs based on national registers for service use in primary and secondary healthcare and Danish governmental tariffs. Utilities: EQ-5D collected at baseline and at 3, 6, 12 and 36-month follow-up. The collected descriptive classifications were converted into health utilities using the Danish scoring algorithm.	intervention group received follow-up visits at 3, 6, 12 and 36 months after randomisation. This means that both groups received a follow-up intervention. Costs and outcomes discounted at 3%.					14% for the complete case analysis over the range of threshold values tested.

a. The study was not conducted in a UK setting.
b. Minor limitations as this was a trial based analysis.
c. The psychosocial intervention group also received control support in addition to the DAISY intervention of multifaceted and semi-tailored counselling, education, and support. Components of the DAISY intervention included:
   - Individual and group-based counselling sessions using a constructivist approach
   - Telephone counselling to the patient or the caregiver

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		

- A two-course series of five sessions each that targeted patients and caregivers individually
- Hand-outs with written information and the assignment of a contact person for each dyad for ad hoc monitoring and follow-up.

The psychosocial intervention group received counselling and support lasting 8-12 months after diagnosis and follow-up at 3, 6, 12 and 36 months.

d. The control support (usual care) comprised structured and systematic follow-up support at 3, 6, 12 and 36 months.

e. Difference is adjusted for baseline utility.

f. The authors' base case adopted a broad societal perspective, including an attempt to value informal care and associated production loss costs; however, disaggregated results are reported, enabling the recalculation of results with a perspective that is consistent with the NICE reference case (that is, NHS and hPSS costs only). This analysis excluded informal care and production loss costs. The original analysis found that the psychological intervention actually cost €3,401 and was therefore a dominated strategy.

g. Discount rate used for future costs and QALYs not consistent with the NICE reference case.

h. The EQ-5D was scored using a Danish tarrif, which is not consistent with the NICE reference case.

M.10 Managing non-cognitive symptoms

M.10.1 Interventions for treating illness emergent non-cognitive symptoms in people living with dementia

- What are the most effective pharmacological interventions for managing illness emergent non-cognitive symptoms, such as psychosis, depression, behavioural changes in people living with dementia?
- What are the most effective non-pharmacological interventions for managing illness emergent non-cognitive symptoms, such as psychosis, depression, behavioural changes in people living with dementia?

No health economic evidence

M.11 Supporting informal carers

M.11.1 Supporting informal carers of people living with dementia

- How effective are carers' assessments in identifying the needs of informal carers of people living with dementia?
- What interventions/services are most effective for supporting the wellbeing of informal carers of people living with dementia?

M.11.1.1 Interventions/services for informal carers

Psychoeducational and skills training

Study, population, country and quality	Data sources	Other comments	Incremental (START intervention vs. Control group)			Conclusions	Uncertainty
			Cost (95% CI)	Effect (95% CI)	ICER		
Livingston et al., (2014) [a]	Effects: EQ-5D health profiles,	24-month time horizon as per	24-month time horizon			'It would appear that the	Intervention has a 65%
			£336	0.030 QALYs	£11,200 /QALY		

	for befriended carers and control group carers, were collected at baseline, 4, 8, 12 and 24 months in order to calculate QALYs (UK RCT, n=260 [2:1]). Trial-based analysis (no extrapolation).	the RCT endpoint.	(-223 to 895)	(-0.010 to 0.060)		intervention is likely to be perceived as cost-effective by reference to NICE thresholds; there is, therefore, both a clinical and an economic case for supporting carers of people with dementia using such an approach.'	probability of being at cost-effective at a threshold of £20,000/QALY over 24 months, and a 75% probability at a threshold of £30,000/QALY.
			8-month time horizon (primary cost-effectiveness analysis)				
			£252 (-28 to 565)	0.042 QALYs (0.015 to 0.071)	£6,000 /QALY		
Population: Family primary carers of people with dementia not living in 24-hour care.	<u>Costs:</u> Resource use from study RCT (retrospective carer completion of Client Service Receipt Inventory). Unit costs were from NHS and national sources (NHS RefCosts;	A health and social care perspective is taken. The analysis used carer outcomes only. Primary analysis includes adjustment for baseline characteristics and is a complete case analysis.					Long-term results are not sensitive to the discount rate, adjustment for predictors of missing values, or adjustment for baseline imbalances.

Intervention: Manual-based coping strategy programme with support sessions for carers, compared with usual care. UK setting.	PSSRU). £2009-10 Utilities: EQ-5D conducted in study RCT. Societal weights from a UK sample.						
Directly applicable							
Minor limitations [b]							

[a] The same study was reported by Livingston et al. (2014), and Knapp et al. (2013) presented the same 8-month study results.
[b] The applicability of estimates of baseline data, intervention effects and resource use are from 1 RCT.

Study, population, country and quality	Data sources	Other comments	Incremental (Family meetings intervention vs. Control group)			Conclusions	Uncertainty
			Cost	Effect (95% CI)	ICER		
			Carer and person with dementia dyad outcomes				

Joling et al., (2013)	Effects: Quality of life, for intervention carers and control group carers, was elicited using the SF-12 at baseline, 6 months and 12 months in order to calculate QALYs (Dutch RCT, n=192 [1:1]). Trial-based analysis (no extrapolation).	12-month time horizon as per the RCT primary analysis endpoint.	€75 [a]	0.04 QALYs (-0.03 to 0.08)	€1,875 /QALY	'Over 12 months, we observed no significant differences in total costs between both groups. There were also no differences between groups in QALYs.'	CEACs and likelihood of being cost-effective only presented including informal care and absenteeism costs. This societal perspective reduces the cost-effectiveness of the intervention.
			Carer outcomes only				
			€- 845 [a]	0.02 QALYs (-0.005 to 0.05)	**Dominant**		
Population: Carers of people with a clinical diagnosis of dementia living in the community.	Costs: Resource use from study RCT (cost diaries). Unit costs were from Dutch health economics guidelines, tariffs and drug list prices. €2009	A societal analysis perspective is taken. Lost productivity costs can be removed from the total cost to estimate an ICER from the health and social care perspective, subject to rounding error.				'Cost-effectiveness planes showed that there was substantial uncertainty. Based on these findings, we conclude that family meetings are not cost-effective in comparison with usual care.'	From societal perspective: Intervention is 33% likely to be dominant per dyad, and 73% likely to be dominant in carer-only analysis

Intervention: Psychoeducation and problem-solving family meetings with carer, compared with usual care. Netherlands setting.	<u>Utilities:</u> SF-12 conducted in study RCT. Societal weights from a UK tariff.						Cost-effectiveness results are highly sensitive to adjustment for baseline characteristics and the use of complete vs. incomplete case analyses.
Partially applicable [f]							
Very serious limitations [b,c, d, e]							

a. Incremental costs estimated by subtracting adjusted incremental costs of informal care and absenteeism respectively. Informal care costs are the largest incremental cost category.
b. Time horizon of 12 months means the analysis is shorter than the expected lifetime of a person with dementia (mean age of persons with dementia in the study is 72.8-76.7 years).
c. The applicability of estimates of baseline data, intervention effects and resource use are from 1 RCT from the Netherlands, and all analyses are in the Netherlands setting.
d. Quality of life was elicited using the 12-item Short Form Health Survey (SF-12) rather than the EQ-5D questionnaire, which is consistent with the NICE reference case.
e. Probabilistic sensitivity analysis conducted only for a societal analysis, and there is a high degree of uncertainty associated with the cost-effectiveness results.
f. Study conducted in a non-UK setting.

– Supportive interventions

Study, population, country and quality	Data sources	Other comments	Incremental (Befriending intervention vs. Control group)			Conclusions	Uncertainty
			Cost (95% CI)	Effect (95% CI)	ICER		
Charlesworth et al., (2008)	Effects: EQ-5D health profiles, for befriended carers and control group carers, were collected at baseline, 6 months, 15 months and 24 months (UK RCT, n=236 [1:1]). Trial-based analysis (no extrapolation).	15-month time horizon as per the RCT primary analysis endpoint.	£2,003 (-1,981 to 6,884)	0.017 QALYs [a] (-0.049 to 0.084) [a]	£117,039 /QALY	'[Cost-effectiveness analysis from a health and social care perspective] …did not offer any convincing evidence for the value of the intervention, and extending the time-frame strengthened the evidence against the intervention.'	CEACs not shown for the analysis from a health and social care perspective. Probability cost-effective is 29.4% at a £30,000 per additional QALY threshold.

Population: Adult carers of people with primary progressive dementia living in the community. Intervention: Befriending carers by trained lay workers, compared with usual care. UK setting.	Costs: Resource use from study RCT (retrospective interview based on Client Service Receipt Inventory, Caregiver Time Questionnaire and Caregiver Activity Schedule). Unit costs were from NHS and national sources (BNF; NHS RefCosts). £2005 Utilities: EQ-5D conducted in study RCT. Societal weights from a UK sample.	A societal analysis perspective is taken, followed by a health and social care perspective secondary analysis.					Deterministic scenario analyses conducted from societal perspective only, which includes cost of informal carer time. Extending the time horizon made the intervention less cost-effective from this perspective. Including QALYs of the PWD made the intervention 9.2% more likely to be cost-effective.

Directly applicable							
Potentially serious limitations [b, c, d]							

a. Carer QALYs only.
b. Time horizon of 15 months means the analysis is shorter than the expected lifetime of a person with dementia (mean age of person with dementia in the study is 78.2 years).
c. The applicability of estimates of baseline data, intervention effects and resource use are from 1 RCT.
d. Extensive scenario analysis was not conducted from the perspective that is appropriate for decision making (health and social care).

Multicomponent interventions

Study, population, country and quality	Data sources	Other comments	Incremental (Family intervention vs. Control group)			Conclusions	Uncertainty
			Cost	**Effect**	**ICER**		
Martikainen et al., (2004)	Effects: Effect of intervention informed by a RR of nursing home admission: 0.65 (95% CI: 0.45-0.94), based on 1 study (US RCT, n=206).	The model adopted a Markov structure with 7 health states: mild, moderate and severe disease, each either living at home or in a nursing home, and death. A 5-year time horizon was adopted.	Carer QALYs only			'The [intervention] is a potentially cost-saving option and it has the highest probability of being optimal.'	CEACs and likelihood of being cost-effective only appears to have been generated only for analyses of the person with Alzheimer's disease. These analyses suggest that the intervention is over 90% likely to be cost-effective compared with current practice, but appears to exclude carer outcomes.
			€-2,992 [a]	-0.01 QALYs	€299,200 /QALY [b]		
			Combined carer and person with Alzheimer's disease QALYs				
			€-2,992 [a]	0.00 QALYs [c]	Intervention dominates usual care		

Population: Informal carers of people with Alzheimer's disease. Intervention: Cognitive-behavioural family meetings including psychological, educational and counselling support for carer, compared with	Costs: Resource use included for the person with Alzheimer's disease only, estimated by from two municipal health centres. Unit costs were from the list of health service costs in Finland. Intervention cost estimated by providing centre. Price-year is unclear. Utilities: Utility weight of persons with Alzheimer's disease and carers obtained from published HUI-2 values (US). Carer utility dependent on	Cost-effectiveness results are reported using outcomes associated with the person with Alzheimer's disease. Carer QALYs are also reported, such that an ICER can be estimated (using costs associated with the care of the person with Alzheimer's disease), subject to rounding error.					

current practice. Finland setting.	disease severity and location of person with Alzheimer's disease.						
Partially applicable							
Very serious limitations [d, e, f, g]							

a. Incremental costs for resource use associated with the person with Alzheimer's disease only.
b. This ICER reflects the incremental cost of every 1 QALY lost. Here, this means a cost saving of € 299,200 per each carer QALY lost.
c. Subject to rounding error. Incremental QALYs for person with Alzheimer's disease reported as +0.01.
d. The applicability of estimates of intervention effects are from 1 RCT from the US, and all resource use inputs are relevant to the Finnish setting.
e. Utility weights were obtained from a study that used the Health Utilities Index Mark 2, rather than the EQ-5D, in the US.
f. Probabilistic sensitivity analysis appears to have been conducted for a patient outcomes only (therefore excluding carer QALYs). No deterministic sensitivity analysis reported.

Study, population, country and quality	Data sources	Other comments	Incremental (Carer support intervention vs. Control group)			Conclusions	Uncertainty
			Cost	Effect	ICER		
Drummond et al., (1991)	Effects: Caregiver	6-month time horizon as per	$2,204	0.11 QALYs	$20,036 /QALY	'This study alone cannot	No probabilistic or deterministic

	Quality of Life Instrument (CQLI) profiles collected at baseline, 3 and 6 months (Canadian RCT, n=60 [1:1]). Trial-based analysis (no extrapolation). <u>Costs:</u> Resource use from study RCT (interviews with carers) and health records. Unit costs were from Canadian national health and social care sources and the carer. CAD1988 <u>Utilities:</u> CQLI profiles converted to utilities by time trade-off technique.	the RCT primary analysis endpoint. The analysis used carer outcomes only.				demonstrate that caregiver support programs represent good value for the money. It does show that [the ICER] compares favourably with other health care interventions.'	sensitivity analyses were conducted.
Population: Family principal carers of a relative with dementia (moderate to severe; unlikely to be placed in a long-term care setting within 6 months). Intervention: Carer support nurses (weekly visits); 4-hour weekly respite care; education							

about dementia and caregiving; monthly family support meetings. Canadian setting.	-						
Partially applicable							
Very serious limitations [a, b, c, d, e]							

a. Time horizon of 6 months means the analysis is shorter than the expected lifetime of the study population (mean age of carer in the study is 66.1-69.4 years).
b. The applicability of estimates of baseline data, intervention effects and resource use are from 1 RCT, and all resource use inputs are relevant to the Canadian setting.
c. Utility weights were obtained from the CQLI, rather than the EQ-5D, in Canada.
d. No sensitivity analysis was conducted.
e. Study published in 1991 and is based on 1988 prices, which is a significant limitation for the purpose of current decision-making.

M.12 Cholinesterase inhibitors and memantine for dementia

M.12.1 Pharmacological management of Parkinson's disease dementia

Review question

- What is the comparative effectiveness of donepezil, galantamine, memantine and rivastigmine for cognitive enhancement in dementia associated with Parkinson's disease?

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Gustavsson et al., (2009) DLB (PDD excluded) UK perspective	Effects: MMSE for AChEIs from UK observational audit for 4-mo treatment effect; MMSE for controls assumed. Extrapolated to 5 years using Scandinavian longitudinal study in AD. Additional noncognitive symptoms (extra-pyramidal and psychosis) assumed for DLB. Costs: Largely based on SHTAC AD model £2005; not specified which AChEIs are assumed (cost appears to relate to donepezil) Utilities: based on SHTAC AD model (MMSE-based in models 2 & 3)	5-yr time horizon Model 1 was a reconstruction of SHTAC AD model Model 2 was a micro-simulation model Model 3 was a Markov model with 4 MMSE states	**All cases; model 1:**			'The cost per QALY gained of cholinesterase treatment of all patients with DLB… is comparable to that of patients with moderate AD, and is probably cost saving.'	No deterministic or probabilistic sensitivity analysis undertaken.
			£461	0.170 QALYs	£2,706 /QALY		
			All cases; model 2:				
			£1,845	0.039 QALYs	£46,794 /QALY		
			All cases; model 3:				
			£2,766	0.077 QALYs	£35,922 /QALY		
			Moderate dementia; model 1:				
			£−7,722	0.392 QALYs	Dominant		
			Moderate dementia; model 2:				
			£−39	0.085 QALYs	Dominant		
			NICE £2016[f]; all cases; model 1:				
			£−4,681	0.170 QALYs	Dominant		
			NICE £2016[f]; all cases; model 2:				
			£−1,098	0.039 QALYs	Dominant		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
			NICE £2016[f]; all cases; model 3:				
			£−1,338	0.077 QALYs	Dominant		
Partially applicable[c,g,h]			**NICE £2016[f]; moderate; model 1:**				
			£−14,556	0.392 QALYs	Dominant		
Very serious limitations [i,j,k]			**NICE £2016[f]; moderate; model 2:**				
			£−3,192	0.085 QALYs	Dominant		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Willan et al., 2006 PDD (PD + MMSE 20–24) Multinational evidence; UK perspective	Effects: MMSE from EXPRESS RCT (Emre et al. 2004); IPD assuming linear progression from baseline to 24wk. Costs: Resource use from EXPRESS; unit costs from experts (BNF; NHS RefCosts; PSSRU). £2003–04 Utilities: mapped from MMSE to EQ-5D (using Scandinavian mapping study)	24-wk time horizon	**Authors' results:**			'Although no between-treatment differences in cost were seen, the small sample size and highly variable cost distributions prevent us from making strong conclusions with regard to the effect of rivastigmine on total costs and, by inference, on cost effectiveness.'	PSA: 55% probability cost effective at £20,000/QALY; 59% probability cost effective at £40,000/QALY
			−£26.18	+0.0077	Dominant		
			Excluding patient/carer costs:				
			+£451.17	+0.0077	£58,642		
			NICE £2016 approximation[a]:				
			+£124.45	+0.0077	£16,176		
Partially applicable[b,c]							
Very serious limitations[d,e]							

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
[a] approximation removes costs borne by patients and caregivers; reestimates rivastigmine drug cost assuming it is proportional to change in price of 28x3mg pack (£2004=£34.02 [BNF 47]; £2016=£2.57 [NHS Drug Tariff Feb 2016]; reduction of 92.4%); inflates all other costs from £2004/05 to £2015/16 using PSSRU hospital & community health services inflators							
[b] includes costs borne by patients and caregivers (can be removed from some analyses but not PSA, etc.)							
[c] utility valuation via mapping algorithm with only one dimension (MMSE) estimated in Scandinavian population							
[d] short time horizon, in context of chronic condition with potential long-term effects (e.g. requirement for full-time care; possible survival impact)							
[e] potential conflict of interest							
[f] approximation reestimates AChEI drug cost assuming original model used cost of donepezil 10mg daily and 2 monitoring visits per year, and that drug costs are proportional to change in price of 28x10mg pack (£2005=£89.06 [BNF 49]; £2016=£1.45 [NHS Drug Tariff Feb 2016]; reduction of 98.4%); inflates all other costs from £2005/06 to £2015/16 using PSSRU hospital & community health services inflators							
[g] PDD specifically excluded from effectiveness data							
[h] discounted at 6% / 1.5%							
[i] primary effectiveness data (MMSE) drawn from uncontrolled observational evidence							
[j] evidence used to extrapolate long-term effects drawn from AD populations							
[k] no consideration of uncertainty							

M.13 Managing non-cognitive symptoms

M.13.1 Interventions for treating illness emergent non-cognitive symptoms in people living with dementia

Review questions

- What are the most effective pharmacological interventions for managing illness emergent non-cognitive symptoms, such as psychosis, depression, behavioural changes in people living with dementia?

- What are the most effective non-pharmacological interventions for managing illness emergent non-cognitive symptoms, such as psychosis, depression, behavioural changes in people living with dementia?

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Banerjee et al., (2013) [a] People diagnosed with Alzheimer's disease with depression for ≥4 weeks prior; UK health and social care perspective. **Directly applicable** **Very serious limitations**[b,c,d]	Effects: EQ-5D for antidepressants and placebo obtained from HTA-SADD (39-week UK RCT, n=326 [1:1:1]). Trial-based analysis (no extrapolation). Costs: Resource use from HTA-SADD (retrospective questionnaire for prior 3-6 months). Unit costs from experts (BNF; NHS RefCosts; PSSRU). £2009-10 Utilities: EQ-5D conducted in HTA-SADD. Societal weights NR	39-week time horizon as per the RCT duration. Analysis perspective of health and social care and informal carers is presented in alongside health and social care perspective.	**Sertraline vs. Placebo**			'There were non-significant pair-wise differences in costs or outcomes (QALY gains) between sertraline, mirtazapine and placebo.' 'This study finds no evidence to support … antidepressants as a first-line treatment for people with depression in AD who are referred to old-age psychiatry services.'	CEACs produced by non-parametric bootstrapping of incremental costs and QALY outcomes. Mirtazapine <30% probability cost-effective vs. placebo at £30,000/QALY. Mirtazapine >90% probability cost-effective at all standard threshold values vs. Sertraline.
			£693	0.03 QALYs	£23,100 /QALY		
			Mirtazapine vs. Placebo				
			£404	0.05 QALYs	£8,080 /QALY		
			Mirtazapine vs. Sertraline				
			£289	0.02 QALYs	£14,450 /QALY Mirtazapine dominant		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
a. Same analysis reported in Romeo et al. (2013), *Br J Psych*, with additional cost-effectiveness acceptability curve presented. b. Limited exploration of uncertainty, except for a deterministic analysis of different informal care costing assumptions (informal care analyses are not appropriate for the NICE reference case). c. Cost-effectiveness acceptability analysis not presented for sertraline vs. placebo. d. Analysis time horizon is 39 weeks.							

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Kirbach et al., (2008) US adults of 65 years or over with diagnosed with Alzheimer's disease. **Partially applicable** [a] **Very serious limitations**	Effects: Olanzapine effectiveness estimates were taken from the Clinical Antipsychotics Trial of Intervention Effectiveness-AD trial (CATIE-AD). (9 months, US RCT, n=421 [2:2:2:3]) Costs: Resource use from Jonsson et al., (2006) Unit costs from Murman and Colenda (2005). £2006	Model horizon over 13 years. Both costs and QALYS were discounted at 3% [c]. Direct and indirect costs considered [a]. Costs may have been considered that are beyond the reference case but no way to ascertain this.	**Olanzapine vs. No Treatment**			This analysis suggests that Olanzapine compared with no treatment is cost-effective for agitation and psychosis related to Alzheimer's disease at the $50,000 ICER threshold.	Uncertainly analyses were conducted by increasing and decreasing the treatment effect, costs and transition probabilities to the model health state Nursing Home (NH) resulting in a range of ICERS from $31,336 per QALY to $42,039 per QALY. As these are below
			$3,060	0.15 QALYs	$37,104 /QALY		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
	Utilities: Utility weights used to estimate QALYs were provided by Murman and Colenda (2005).	Model contains health states including Mild AD, Moderate AD, Severe AD, Nursing Home and Death.					$50,000 per QALY, these would be considered cost-effective. [b]

a. Analysis perspective is not clearly stated.
b. Parameter values with distributions used in the probabilistic analyses are not included.
c. Discount rate as recommended by the Panel on Cost-Effectiveness in Health and Medicine.

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Livingstone et al., (2014) Adults diagnosed with dementia in the UK.	Effects: Intervention effects taken from Fischer-Terworth and Probst (2011) . Costs: Resource use and unit costs from LASER-AD longitudinal study (n=224). Cost year £2011	One year time horizon as no evidence of effect of interventions was found to last beyond this. The study took a UK National health Service	**Non-pharmacological intervention[a] vs. Usual Care**			The savings associated with the non-pharmacological intervention were due to the reduction in the costs of managing agitation, which more than offset the intervention costs.	The probabilistic results were broadly the same as the deterministic results (0.005829 QALYs gained, -£716 incremental cost).
			£-711	0.005949 QALYs	**Dominant**		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Directly applicable **Very serious limitations** [d, c]	Utilities: DEMQOL system from the LASER-AD longitudinal study (n=224) were converted to QALYs.	(NHS) and Personal Social Services (PPS) perspective.				Monetary net benefit (MNB) at £20,000 and £30,000 per QALY threshold was £820 and £889 respectively.	One way sensitivity analysis on key parameters did not result in the MNB becoming negative at any point [b].

a. The non-pharmacological intervention included
- music-based group therapy once per week for 26 weeks for 45 minutes with a mean group size of seven participants,
- structured teaching with a therapist once per week for 26 weeks for 45 minutes with a mean group size of seven participants,
- psychoeducational staff training by a psychologist through a programme of 12 lessons,
- intensive family member–staff communication comprising provision of basic information about dementia to family members, everyday availability of professional caregivers to answer family members' questions, and a 1-hour session of psychoeducational counselling by a psychologist to a close family member of each participant.

b. The cost-effectiveness acceptability curve shows that the intervention had an 82.2% probability of being cost effective at a maximum willingness to pay for a QALY of £20.000 and an 83.18% probability at a value of £30,000.

c. The trial from which the effects were taken was not randomised.

d. Utility not derived from the EQ-5D as per the NICE reference case.

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Rosenheck et al., (2007)	Effects: Quality adjusted life years (QALYs) for all interventions were	9-months' time horizon as per the RCT duration.	**Olanzapine vs. Placebo**			'There were no significant differences across the	Net health benefit analysis at $50,000 per QALY
			$1,557	-0.02 QALYs	**Dominated**		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
People diagnosed with Alzheimer's disease (DSM-IV) living at home or assisted living in the United States. [a] **Partly applicable** [b]	assessed using the Health Utilities Index Mark 3 in the Clinical Antipsychotics Trial of Intervention Effectiveness-AD trial (CATIE-AD). (9 months, US RCT, n=421 [2:2:2:3]). Trial-based analysis (no extrapolation). Costs: Unit costs of services were estimated from published reports and administrative datasets. Antipsychotic medication cost were based on published wholesale prices for the specific capsule strengths used in CATIE-AD, adjusted downwards for discounts and rebates affecting patients whose medication costs would	Analysis perspective addressed comprehensive health care costs (American Health services). Study acknowledges increased risk of cerebrovascular adverse events and death but this is not accounted for in the outcomes.	**Risperidone vs. Placebo**			treatment groups in QALYs.' Olanzapine was worse than placebo, producing fewer QALYs whilst Risperidone and Quetiapine were not cost-effective at the $100,000 per QALY threshold.	were conducted for treatments and were reported with a range of probabilities of being superior. However, no details of input parameters, distributions chosen or of how the analysis was done were reported. 'While there were no significant differences between treatments with regard to net health benefits at the conventional 95% probability standard, placebo was most often superior to the
			$5,292	0.02 QALYs	$264,000 /QALY		
			Quetiapine vs. Sertraline				
			$2,916	0.01 QALYs	$291,000 /QALY		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Potentially serious limitations [c, d]	have been paid by Medicaid. Utilities: Quality adjusted life years (QALYs) were assessed using the Health Utilities Index Mark 3.						SGAs on net health benefit analysis, with probabilities ranging from 50% to 90%.'

a. This economic evaluation is cost-benefit component of the CATIE-AD trial.
b. The study was conducted in the US in a population of ambulatory outpatients living at home or in assisted living.
c. The lead study author has received research support and acted as a consultant to the pharmaceutical companies who manufacture the drugs under research.
d. QALYs were generated in a way not consistend with the NICE reference case.

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Zwijsen et al., (2016) People diagnosed with dementia living in dementia special care	Effects: EQ-5D administered during a cluster randomised controlled trial (Zwijsen et al., 2011, n=652) [c].	On five different occasions, each 4 months apart, challenging behaviour and QOL of residents was assessed at all DSCUs. [a]	**GRIP vs. Placebo**			'GRIP was not considered cost-effective in comparison with usual care with regard to challenging behaviours, sickness absence, QALYs or all but one QALIDEM subscale.'	'The CEA curve for the QALY analysis showed that the probability of GRIP being cost-effective in comparison for usual care was
			€276	-0.02	€-3,353 /QALY[b] Usual care dominant		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
units (DSCUs) in the Netherlands from a societal perspective. **Partially applicable** **Potentially serious limitations** [a,b,c,d]	Costs: Resource use from Royal Dutch Society for Pharmacy (Z-index, 2006). Involvement of physicians and psychologists at DSCUs were estimated using prospective 1-monthy diaries provided to each professional. Utilities: EQ-5D to assess health related quality of life using the Dutch EQ-5D tariffs.						zero for all possible ceiling ratios.'

a. Time horizon not clearly reported.
b. ICER not clearly reported. If reverse calculated, assuming that the QALY change is correct, the cost should be €67.06.
c. Lots of missing data due to design of the study. When one DSCU resident died or left, he/she was replaced by another.
d. QALYs generated in a way that is not consisend with the NICE refence case (as used Dutch tarrifs).

M.14 Staff training

M.14.1 Staff training

- What effect does training for staff working with people living with dementia have upon the experiences of people living with dementia in their care?

No health economic evidence

M.15 Needs of younger people living with dementia

M.15.1 Needs of younger people living with dementia

- What are the specific needs of younger people living with dementia?

No health economic evidence

M.16 Assessing and managing comorbidities

M.16.1 Assessing and treating intercurrent illness in people living with dementia

- Are there effective methods for assessing intercurrent illness in people living with dementia that are different from those already in use for people who do not have dementia?
- Are there effective methods for treating intercurrent illness in people living with dementia that are different from those already in use for people who do not have dementia?

No health economic evidence

M.16.2 Management strategies for people living with dementia and co-existing physical long term conditions

- What are the optimal management strategies (including treatments) for people living with dementia with co-existing physical long term conditions?

No health economic evidence

M.16.3 Managing mental health conditions alongside dementia

- What are the optimal management strategies (including treatments) for people with dementia and an enduring mental health condition?

No health economic evidence

M.17 Palliative care

M.17.1 Palliative care

- What models of palliative care are effective for people with dementia?

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Goldfeld et al., (2013) Nursing home residents with advanced dementia who participated in the CASCADE study **Partially applicable** [a] **Potentially serious limitations** [b,c,d]	Effects: Choices, Attitudes, and Strategies for Care of Advanced Dementia at the End-of-Life (CASCADE study), a prospective cohort study conducted between 2003 and 2009 in the US. (non-RCT, n=268 [1:1]). Trial-based analysis (no extrapolation). Costs: Medicare expenditures attributable to services utilised were determined using publicly available sources and based on nationally representative rates from 2007 in U.S. dollars ($). Utilities: The study mapped the Symptom Management at the End-of-Life in Dementia Scale and Comfort Assessment in Dying with Dementia Scale to the Health Utility Index Mark 2 (HUI2).[b]	Medicare expenditures, and incremental net benefits (INBs) over 15 months. The terms 'Usual hospitalisation practice' and the 'No DNH Order' are used in this table synonymously. Do Not Hospitalise (DNH) Orders are not currently routinely used in the UK.	**Usual hospitalisation practice vs DNH order**			'This study found that more aggressive treatment strategies leading to hospitalisation are not cost effective for nursing home residents with advanced dementia compared with approaches that avoid hospitalization.'	'Taken together, at levels of WTP less than $150,000 and unmeasured confounding with respect to quality-adjusted survival limited to 30%, not having a DNH order does not appear to be cost-effective.' 'The sensitivity analyses suggest that hospitalization for pneumonia remains not cost effective. For all WTP levels, and all levels of unmeasured confounding related to expenditures and quality-adjusted survival, hospitalization was not cost effective (i.e., <90% of INBs were positive).'
			$5,972	+3.7 QALD	$1,614 /QALD $589,130 /QALY		
			Hospitalisation for suspected pneumonia vs no hospitalisation for suspected pneumonia				
			$3,697	-9.7 QALD	Dominated		

Study, population, country and quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
a. US study. b. For each follow-up period, the resident's HUI2 score was multiplied by the number of days in the period to derive quality-adjusted Life-days (QALD) for that period. Total quality-adjusted survival was estimated by summing the QALD for each period (quality adjusted life years [QALY] = QALD/365) c. This study was not a randomised controlled trial. HRQoL is mapped HUI2 – a tool not in the NICE reference case.							

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