National Institute for Health and Clinical Excellence
Health Technology Appraisal

Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA 111)

Response to consultee and commentator comments on the draft remit and draft scope

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	British Geriatrics Society	The background section is a useful summary. The National Dementia Strategy was clear about the number of people with dementia. The recent neuropathological data show that most cases of dementia (80% at least, Schneider) show the underlying plaques and tangles associated with a diagnosis of Alzheimer's disease. I wonder therefore about the accuracy of the estimated prevalence of Alzheimer's disease from the 2002 estimate quoted. Para 4: it is correct to say that these measures can be used to assess disease severity. The severity is usually denoted by a composite eg Clinical Disease rating where cognition, function and behaviours are measured and an overall rating decided. While the statements re MMSE and cognition are correct there is a misapprehension that MMSE somehow equates with stage of the disease. I do not think there are any experts clinically who would accept that. This is particularly the case for highly educated individuals where MMSE may be a hopeless and inaccurate indicator of true cognitive impairment or disease severity. Similarly for individuals who are very elderly and who have lower levels of education, MMSE 10 may not be at all useful in consideration of severity.	Comments noted. The background of the scope has been amended to include prevalance date from 2005. The background of the scope includes a number of scales which are used to estimate the severity of Alzheimer's disease. The severity of AD by MMSE score was included as it formed the basis of evidence and recommendations of TA111. Section 1.2 of NICE Technology Appraisal 111 and section 1.6.2.2 of NICE Clinical Guideline 42 on Dementia note that the MMSE score alone may not be suitable in all situations to assess the severity of dementia.

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	West Kent PCT	In general the background information appears accurate and complete Prevalence figures in the draft scope came from 2002, and showed that 290,000 people in England and Wales had Alzheimer's disease. These figures could be extrapolated to estimate current or more recent levels of Alzheimer's. The Alzheimer's Society estimated that 416,967 people in the UK had Alzheimer's disease in a 2007 report (with AD accounting for 62% of all people with dementia). Based on their estimated figures for overall dementia in England and Wales in 2005 (574,717 in England and 36,924 in Wales) this suggests that 379,217 people had AD in these countries in 2005.	Comments noted. Comment noted. The background of the scope has been amended to include prevalance date from 2005.
	Eisai	The use of the MMSE to segregate mild, moderate and severe forms of the disease as described in the background information is an oversimplification and discriminatory. The terms 'mild', 'moderate' and 'severe' only describe symptoms of the underlying disease process. Alzheimer's disease per se is a devastating illness which significantly impacts quality of life and life expectancy. We believe the appraisal should recognise this important distinction between symptoms which may be mild and the disease process which is always serious.	Comments noted. The background of the scope includes a number of scales which are used to estimate the severity of Alzheimer's disease. The severity of AD by MMSE score was included as it formed the basis of evidence and recommendations of TA111. Section 1.2 of NICE Technology Appraisal 111 and section 1.6.2.2 of NICE Clinical Guideline 42 on Dementia note that the MMSE score alone may not be suitable in all situations to assess the severity of dementia.

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	Eisai	Defining a stage of the illness by an MMSE score alone is discriminatory. Patients with high cognitive reserve may have advanced disease yet still maintain an MMSE above 26. This appraisal when completed will be a valuable source of information for non-specialists in dementia care. It should seek to encourage a better understanding of Alzheimer's disease in line with the objectives of the National Dementia Strategy and educate against any tendency of non-specialists to consider dementia as an abnormality of MMSE.	Comment noted. See response above
	RICE – The Research Institute for the Care of Older People	The population data for England and Wales included is for 2002 and is out of date, for example the Dementia UK (2007) Study gives higher figures and is based on the 2005 Census figures. In addition, the figures quoted in the NICE Clinical Guideline (2006) would also give a higher estimate. Both figures would lead to an estimate of around 380,000 people with Alzheimer's disease in England and Wales.	Comments noted. The background of the scope has been amended to include prevalance date from 2005.
	RICE – The Research Institute for the Care of Older People	The burden on carers should be more clearly stated; it is not only when it is provided by an elderly relative where health and quality of life can be affected but this is important for all people with Alzheimer's disease whatever their age and all carers whatever their age	Comments noted. The background of the scope has been amended and includes some of the impacts of caring for a person with Alzheimer's disease.

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	RICE – The Research Institute for the Care of Older People	The Global Deterioration Scale is normally abbreviated as GDS rather than GD.	Comments noted. The background of the scope has been amended accordingly.
	RICE – The Research Institute for the Care of Older People	In the section on methods used to assess the severity of Alzheimer's disease, it is important that there is some mention of the fact that the MMSE score is not sufficient on its own to denote the severity of cognitive impairment as was illustrated during the previous Technology Appraisal. In particular it is inappropriate for example in people with learning disabilities, particularly Down's syndrome, and in people with language problems or whose first language is not English. There may be other reasons (for example, in highly intelligent people) where a Mini-Mental above 20 may still indicate moderately severe Alzheimer's disease based on other assessments of the severity of the disease.	Comments noted. The background of the scope includes a number of scales which are used to estimate the severity of Alzheimer's disease. The severity of AD by MMSE score was included as it formed the basis of evidence and recommendations of TA111. Section 1.2 of NICE Technology Appraisal 111 and section 1.6.2.2 of NICE Clinical Guideline 42 on Dementia note that the MMSE score alone may not be suitable in all situations to assess the severity of dementia.

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	RICE – The Research Institute for the Care of Older People	In the management of Alzheimer's disease it is important to mention the use of pharmacological treatment for behaviour since there is a great concern about the inappropriate use of antipsychotic medication and also one drug, risperidone, has now been licensed for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's disease dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.	Comments noted. The purpose of this scope is to provide a framework for the appraisal to review guidance TA111 on the use of AChE inhibitors and memantine for the treatment of Alzheimer's disease. The clinical guideline on treatment of dementia (No 42) provides guidance on the use of antipsychotic medication in people with Alzheimer's disease with severe non-cognitive symptoms (section 1.7.2.4 of CG42) http://guidance.nice.org.uk/CG42/Guidance/doc/English The scope has been updated and notes that if evidence allows the following subgroups will be considered. These include subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbities such as cerebrovascular disease).

Section	Consultees	Comments	Action
	CSU appraisals	In general the background information appears accurate and complete Prevalence figures in the draft scope came from 2002, and showed that 290,000 people in England and Wales had Alzheimer's disease. These figures could be extrapolated to estimate current or more recent levels of Alzheimer's. The Alzheimer's Society estimated that 416,967 people in the UK had Alzheimer's disease in a 2007 report (with AD accounting for 62% of all people with dementia). Based on their estimated figures for overall dementia in England and Wales in 2005 (574,717 in England and 36,924 in Wales) this suggests that 379,217 people had AD in these countries in 2005	Comments noted. The background of the scope has been amended to include prevalance date from 2005.
	The Royal College of Psychiatrist	Alzheimer's Disease (AD) prevalence figures from 2002 of 290,000 are low and out of date. Alzheimer's Society and more recent reports (Dementia UK, published in 2007) suggest numbers of people with dementia to be around 700,000 with around 400,000 having Alzheimer's disease in England and Wales. I suggest more updated figures are inserted here. See http://www.alzheimers.org.uk/site/scripts/documents_info.php?categoryID=200167&documentID=412	Comments noted. The background of the scope has been amended to include prevalance date from 2005.

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	The Royal College of Psychiatrist	On page 2, the methods used to assess the severity of Alzheimer's disease include a lot of scales which are only really used as a part of research studies and are not clinically applicable. For example, the CIBIC plus, global deterioration scale and progressive deterioration scale are not really used clinically. Clinical scales would include clinical global impression, clinical dementia rating (CDR), MMSE, and also scales for activity of daily living and non-cognitive symptoms. However, in practice, like many medical conditions, a lot of the assessment of severity is clinically-based rather than relying on scales.	Comments noted. The background of the scope includes a number of scales which are used to estimate the severity of Alzheimer's disease. The severity of AD by MMSE score was included as it formed the basis of evidence and recommendations of TA111.
	The Royal College of Psychiatrist	The main specialists involved with the care of people with dementia are old age psychiatrists. I would suggest that phrase in brackets is changed to: **(that is, old age psychiatrists, other psychiatrists including those specialising in learning disability, neurologists and physicians specialising in the care of the elderly).**	Comment noted. The specialists involved in the care of people with dementia is consistent with the recommendations of TA111 and CG42. The scope sets out the framework for the appraisal. Consultees are now invited to prepare submission dossiers for the review appraisal.
	Shire	The prevalence data should be brought up to date.	Comments noted. The background of the scope has been amended to include prevalance date from 2005.

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	Shire	On p2, paragraph 3, starting 'Several..', note that CGIC and CIBIC-plus are used to assess change, not severity. These facts should be corrected. On p2, paragraph 3, starting 'Several..', two important and validated instruments for functional assessment have been omitted, namely DAD (Disability Assessment for Dementia) and ADCS/ADL (Alzheimer's Disease Cooperative Study Activities for Daily Living Inventory). These instruments have been widely used in clinical studies to assess activities of daily living and should be added here for completeness	Comments noted. The background of the scope has been amended to include these additonal measures of functional ability.
	Alzheimer's Society	References are needed for prevalence and incidence figures. Also, the scope does not appear to have used the most up to date figures. Dementia UK (2007) prevalence figures were agreed by expert consensus and were applied to 2005 census figures. These figures indicate there are 379,217 people with Alzheimer's disease in England and Wales (based on 62% of total number of people with dementia). Using NICE clinical guideline figures would lead to an estimate of 380,322 people with Alzheimer's disease in England and Wales (based on 60% of total number of people with dementia in England and Wales (633,870) from MRC/CFAS and ONS 2005 figs).	Comments noted. The background of the scope has been amended to include prevalance date from 2005.

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	Alzheimer's Society	In order to better reflect reality, impact on carers should be stated more strongly than 'own health and quality of life can be affected by the burden of providing care'. Research studies have demonstrated that carers of people with dementia often experience a significant detriment to health and wellbeing. Moriarty and Webb (2000) found that over one-third of people caring for a person with dementia in the community scored six or higher on the GHQ-28, suggesting that they were likely to be experiencing symptoms associated with psychiatric illnesses such as depression and anxiety. This is particularly important given the ability of the carer to cope is a more significant factor in the shift from home to institutional care than the progress of dementia (Morris, R., Morris, L., & Britton, P. (1988). Factors affecting the emotional well being of the caregivers of dementia sufferers. British Journal of Psychiatry, 153, 147-56.)	Comments noted. The background of the scope has been amended with some of the impacts of caring for a person with Alzheimer's disease.
	Alzheimer's Society	The term 'sitter services' is now rarely used. This may be replaced by 'respite services' or 'befriending services', depending on the type of service.	Comment noted. The background of the scope has been amended accordingly.

Section	Consultees	Comments	Action
	Alzheimer's Society	The section on management of Alzheimer's disease should include pharmacological treatment for behavioural symptoms. This is particularly important given that Risperidone has been licensed specifically for the treatment of severe and persistent aggression in people with Alzheimer's disease that have not responded to other therapies. Antipsychotic prescription represents a significant proportion of all pharmacological treatment for people with dementia. IMS figures released earlier this year showed that 20 per cent of all prescriptions for dementia in the UK are for antipsychotic drugs. Alzheimer's Society would welcome an appraisal of clinical and cost effectiveness of risperidone, within its licensed indication.	Comments noted. The purpose of this scope is to review guidance TA111 on the use of AChE inhibitors and memantine for the treatment of Alzheimer's disease. The clinical guideline on treatment of dementia (No 42) provides guidance on the use of antipsychotic medication in people with Alzheimers disease with severe non-cognitive symptoms (section 1.7.2.4 of CG42) http://guidance.nice.org.uk/CG42/Guidance/doc/English The scope has been updated and notes that if evidence allows the following subgroups will be considered. These include subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbities such as cerebrovascular disease).

Section	Consultees	Comments	Action
	Alzheimer's Society	The frequency of mixed dementias should be noted in this section, as we believe it has implications for the population considered within the appraisal. Research indicates that 40% of people with Alzheimer's disease also have cerebrovascular disease and this figure is higher among older age groups, in particular people aged over 85 years old. This section should include data on younger people with dementia. Dementia UK (2007) found there were 13,322 people with dementia aged under 65. The authors note that this is likely to be an underestimate by up to three times. The proportion of younger people with dementia who have Alzheimer's disease will be different to that of over 65s. It should also note the prevalence of dementia among people with learning disabilities, particularly Down's syndrome. Figures from one study (Prasher 1995) suggest that the following percentages of people with Down's syndrome have dementia:30-39 years 2 per cent , 40-49 years 9.4 per cent ,50-59 years 36.1 per cent, 60-69 years 54.5 per cent Some studies (Cooper 1997, Lund 1985, Moss and Patel 1993) suggest that the following percentages of people with learning disabilities not due to Down's syndrome have dementia: 50 years and over: 13 per cent 65 years and over: 22 per cent. This is about four times higher than in the general population.	Comments noted. Clinical Guideline CG42 notes that people with mixed dementia be treated according to the predominant cause of dementia. The background of the scope has been amended to include prevalance date from 2005. NICE Clinical Guidelines 42 on Dementia gives guidance on the treatment of Alzheimer's disease which includes the management of people with co-morbidities such as learning disabilities including Down's Syndrome.

Section	Consultees	Comments	Action
The technology/ intervention	British Geriatrics Society	This is accurate	Comment noted
	West Kent PCT	The description of the technologies appears accurate	Comment noted.
	Eisai	The interventions within scope are appropriate	Comment noted.
	CSU appraisals	The description of the technologies appears accurate	Comment noted.
	The Royal College of Psychiatrist	Pfizer market donepezil along with Eisai.	Comment noted.
	The Royal College of Psychiatrist	The four drugs are appropriate; depending on the timescale for the appraisal (given that the previous one took several years) there may be other agents that become licensed during the process. For example, the most promising compound is Dimebon which is currently undergoing Phase III studies. NICE might wish to consider whether, should this be licensed during the course of the current appraisal, it later becomes incorporated or not.	Comment noted. The interventions included in this review appraisal are those which fall within the remit and are expected to obtain marketing authorisations within timescales that allow production of timely guidance.
	The Royal College of Psychiatrist	There are now studies on combination treatments and these should be included as part of the appraisal (particularly the combination of acetycholinesterase inhibitors and memantine).	Comment noted. The following statement has been included in the 'Other Considerations' section of the scope: If evidence allows, interventions will be compared with each other, or in sequential use, or as combination therapy, within their licensed indications.
	Shire	At the bottom of p2, the statement should be added that galantamine also acts by modulating activity at nicotinic receptors.	Comment noted. The tecnology section of the scope has been amended accordingly.

Section	Consultees	Comments	Action
Population	Welsh Assembly Government	We are pleased to see that NICE is asking about specific groups' requirements and trust that you will ensure that responses are carefully considered.	Comment noted
	British Geriatrics Society	The population is appropriately defined	Comment noted
	West Kent PCT	The footnote describing the DH remits to NICE does not identify mild Alzheimer's as a population to be assessed, but does include severe Alzheimer's as a population for assessment. This population is not included in this scope.	Comment noted As the population of this appraisal has been broadened to include all severities of Alzheimer's disease (mild to severe) the appraisal is a review of the TA111 in its entirely which is referenced in the footnote.
	West Kent PCT	Analyses could be stratified by disease severity, previous response to treatment, or presence of behavioural disturbance	Comment noted. The following statement has been added to the 'Other Considerations' section of the scope: if evidence allows the following subgroups will be considered. These include subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbities such as cerebrovascular disease).

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	Lundbeck	The population is currently defined in the draft scope as 'adults with mild to moderate Alzheimer's disease'. However the background information in the draft scope includes severe Alzheimer's disease (MMSE less than 10) and the technologies section correctly states that the UK marketing authorisation for memantine is for the treatment of people with moderate to **severe** Alzheimer's disease. The only reference to severe Alzheimer's disease in the draft scope is in the 'Notes for consultation' section which states that 'NICE will be consulting on a review proposal for appraising the clinical and cost effectiveness of memantine for the treatment of severe Alzheimer's disease'. There is no apparent reason why memantine in severe Alzheimer's disease should be reviewed separately to TA111. This approach splits the memantine UK marketing authorisation data into 2 separate appraisals for a progressive and continuous disease. Furthermore it is well documented that MMSE is not sensitive towards the lower limit of the scale and thus does not differentiate accurately between moderate and severe patients[1]. Lastly this split scope issue occurred during the last Alzheimer's HTA review in December 2004 and following the scope consultation, the separate 'mild to moderate' and 'moderate to severe' scopes were combined into one scope covering all stages of the disease. **We therefore strongly recommend that the population for TA111 is defined as adults with mild to severe Alzheimer's disease.** Reference 1. Peavy G, Salmon DP, Rice VA, et al. Neuropsychological assessment of severely demented elderly. Arch Neurol 1996; 53:367–72.	Comment noted. The population of the scope has been broadened to include all severities of Alzheimer's disease (mild to severe).

Section	Consultees	Comments	Action
	Eisai	The population is appropriate for the licensed indications of the acetyl cholinesterase inhibitors	Comment noted
	RICE – The Research Institute for the Care of Older People	This should be broadened to state 'adults with mild to moderate Alzheimer's disease or people whose dementia is considered to be predominantly Alzheimer's disease'. For example, people with mixed dementia or who may have other changes in their brain, may still potentially benefit from the treatment of the Alzheimer's component of their condition.	Comment noted. The population of the scope has been broadened to include all severities of Alzheimer's disease (mild to severe). Clinical Guideline CG42 notes that people with mixed dementia should be treated according to the predominant cause of dementia.
	CSU appraisals	The footnote describing the DH remits to NICE does not identify mild Alzheimer's as a population to be assessed, but does include severe Alzheimer's as a population for assessment. This population is not included in this scope.	Noted
		Analyses could be stratified by disease severity, previous response to treatment, or presence of behavioural disturbance	Comment noted. The following statement has been added to the 'Other Considerations' section of the scope if evidence allows the following subgroups will be considered. These include subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbities such as cerebrovascular disease).

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	The Royal College of Psychiatrist	The population should include those with severe Alzheimer's disease as well as mild to moderate. There are now quite a few studies on severe AD and performance of these agents in the severe population is clearly very relevant to some aspects of the licensed indication of mild to moderate, and moderate to severe AD. In addition, as pointed out in the scope, memantine is licensed for moderate to severe AD and so the population does need to include severe AD. Please also see comment at end about this.	Comment noted. The population of the scope has been broadened to include all severities of Alzheimer's disease (mild to severe).
	The Royal College of Psychiatrist	In terms of patients subgroups, patients with marked behavioural symptoms form a particularly challenging group (especially in view of recent guidance on avoiding antipsychotics) and some evidence exists they respond particularly well to treatment. I would suggest they are examined separately	Comment noted. The NICE clinical guideline on treatment of dementia (No 42) provides guidance on the use of antipsychotic medication in people with Alzheimers disease with severe non-cognitive symptoms (section 1.7.2.4 of CG42) http://guidance.nice.org.uk/CG42/Guidance/doc/English The following statement has been added to the 'Other Considerations' section of the scope: if evidence allows the following subgroups will be considered. These include subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbities such as cerebrovascular disease).

Section	Consultees	Comments	Action
	Shire	The population is defined appropriately according to the licensed indications. In our opinion the overall population should not be split into mild and moderate disease for the appraisal of acetylcholinesterase inhibitors, as the distinction between these two severities may be blurred for a substantial proportion of patients.	Comment noted
	Alzheimer's Society	This should state explicitly that the guidance applies to people of all ages, to make it clear that it is not just for over 65 year olds.	Comment noted. Although the background section notes the increased incidence of Alzheimer's disease in people over the age of 65 the scope is not restricted to this group.
		The scoping document for TA111 stated the population was: "People with Alzheimer's disease or people whose dementia is considered to be predominately Alzheimer's disease." Because of the high proportion of people with mixed dementia and also the difficulty in making a differential diagnosis, we believe this statement should remain in place for the review. It should be clear that the guidance will apply to people with Alzheimer's disease who also have other changes in the brain.	Comment noted. The scope of this appraisal is to review guidance on the use of AChE inhibitors, and memantine in the treatment of Alzheimer's disease (TA111). Clinical Guideline CG42 notes that people with mixed dementia should be treated according to the predominant cause of dementia.
Comparators	British Geriatrics Society	I wonder about the comparator for mild disease – memantine is not licensed for this indication so it maybe should not be included as comparator while for moderate disease treatment without memantine is a comparator	Comment noted. The scope has been amended so that it is clear that memantine is not a comparator for people with mild Alzheimer's disease.

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	West Kent PCT	The comparators are appropriate. Consideration could be given to whether combination treatments will be allowed as comparators.	Comment noted. The following statement has been included in the 'Other Considerations' section of the scope: If evidence allows, interventions will be compared with each other, or in sequential use, or as combination therapy, within their licensed indications.
	Lundbeck	Yes if the following additional comparators are included in the scope: For people with severe disease: • No pharmacological treatment (social support and assistance with day-to-day activities)	Comment noted. The scope will now include people with severe Alzheimer's disease, for whom non-pharmacological treatment is a comparator.

Section	Consultees	Comments	Action
		For people with moderate to severe Alzheimer's disease with persistent aggression: • Risperidone (indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others).	Comment noted. The appraisal objective is "To review and update as necessary guidance to the NHS in England and Wales on the clinical and cost effectiveness of donepezil, galantamine, rivastigmine and memantine within their licensed indications for the treatment of Alzheimer's disease". The NICE clinical guideline on treatment of dementia (No 42) provides guidance on the use of antipsychotic medication in people with Alzheimers disease with severe non-cognitive symptoms (section 1.7.2.4 of CG42) http://guidance.nice.org.uk/CG42/Guidance/doc/English However the statement in the "Other considerations ' section of the scope: if evidence allows the following subgroups will be considered. These include subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbities such as cerebrovascular disease).

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	Eisai	For people with mild disease the comparators should be: • Donepezil • Galantamine • Rivastigmine • Treatment without acetyl cholinesterase inhibitors There are differences in the evidence base for the cholinesterase inhibitors in patients with mild symptoms of disease.	Comment noted. The three acetylcholinesterase inhibitors are interventions in mild disease. Since NICE Technology Appraisal 111 recommends donepezil, galantamine and rivastigmine only for moderate Alzheimer's disease, treatment without acetylcholinesterase inhibitors is the comparator in mild disease. However, as noted in the 'other considerations' section of the scope, if evidence allows, interventions will be compared with each other.
	RICE – The Research Institute for the Care of Older People	We do not understand why there is a difference between the comparators for people with mild disease in comparison with moderate disease apart from the exclusion of memantine from the mild disease section.	Comment noted. Since NICE Technology Appraisal 111 recommends donepezil, galantamine and rivastigmine only for moderate Alzheimer's disease, treatment without acetylcholinesterase inhibitors is the comparator in mild disease. However, as noted in the 'other considerations' section of the scope, if evidence allows, interventions will be compared with each other.
	RICE – The Research Institute for the Care of Older People	It would be useful to allow the Appraisal to consider the combination of cholinesterase inhibitors with memantine for the treatment of mild to moderately severe Alzheimer's disease.	Comment noted The following statement has been included in the 'Other Considerations' section of the scope: If evidence allows, interventions will be compared with each other, or in sequential use, or as combination therapy, within their licensed indications.

Section	Consultees	Comments	Action
	RICE – The Research Institute for the Care of Older People	Finally it would also be useful to look at the comparison between anticholinesterase drugs and antipsychotic drugs for the treatment of behavioural symptoms. There are a number of studies that have investigated this.	Comment noted. NICE Clinical Guideline 42 on treatment of dementia (No 42) provides guidance on the use of antipsychotic medication in people with Alzheimers disease with severe non-cognitive symptoms (section 1.7.2.4 of CG42) http://guidance.nice.org.uk/CG42/Guidance/doc/English NICE Clinical Guideline 42 on Dementia states in section 1.7.2.5that people with mild, moderate, or severe Alzheimer's disease who have non-cognitive symptoms and/or behaviour that challenges, causing significant distress or potential harm to the individual, may be offered an acetylcholinesterase inhibitor if: • a non-pharmacological approach is inappropriate or has been ineffective, and • antipsychotic drugs are inappropriate or have been ineffective. The 'Other considerations' section of the scope states that if evidence allows, the following subgroups will be considered: subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbidities such as cerebrovascular disease).
	CSU appraisals	The comparators are appropriate. Consideration could be given to whether combination treatments will be allowed as comparators	Comment noted. The following statement has been included in the 'Other Considerations' section of the scope: If evidence allows, interventions will be compared with each other, or in sequential use, or as combination therapy, within their licensed indications.

Section	Consultees	Comments	Action
	The Royal College of Psychiatrist	These seem appropriate.	Comment noted
	Shire	It is unclear why the names of the three acetylcholinesterase inhibitors have been omitted for patients with mild disease, since these drugs will be appraised for mild patients just as for moderate disease. Please clarify this point.	Comment noted. The three acetylcholinesterase inhibitors are interventions in mild disease. Since NICE Technology Appraisal 111 recommends donepezil, galantamine and rivastigmine only for moderate Alzheimer's disease, treatment without acetylcholinesterase inhibitors is the comparator in mild disease. However, as noted in the 'other considerations' section of the scope, if evidence allows, interventions will be compared with each other.
	Alzheimer's Society	We are not clear why the three anticholinesterase drugs will be compared for the moderate subgroup but not the mild?	Comment noted. The three acetylcholinesterase inhibitors are interventions in mild disease. Since NICE Technology Appraisal 111 recommends donepezil, galantamine and rivastigmine only for moderate Alzheimer's disease, treatment without acetylcholinesterase inhibitors is the comparator in mild disease. However, as noted in the 'other considerations' section of the scope, if evidence allows, interventions will be compared with each other.

Section	Consultees	Comments	Action
	Alzheimer's Society	We believe a comparison between anticholinesterase drugs and antipsychotic drugs for the treatment of behavioural symptoms (or severe and persistent aggression?) would provide useful guidance on the most effective use of drug treatments.	Comment noted. NICE Clinical Guideline 42 on treatment of dementia (No 42) provides guidance on the use of antipsychotic medication in people with Alzheimers disease with severe non-cognitive symptoms (section 1.7.2.4 of CG42) http://guidance.nice.org.uk/CG42/Guidance/doc/English NICE Clinical Guideline 42 on Dementia states in section 1.7.2.5that people with mild, moderate, or severe Alzheimer's disease who have non-cognitive symptoms and/or behaviour that challenges, causing significant distress or potential harm to the individual, may be offered an acetylcholinesterase inhibitor if: • a non-pharmacological approach is inappropriate or has been ineffective, and • antipsychotic drugs are inappropriate or have been ineffective. The 'Other considerations' section of the scope states that if evidence allows, the following subgroups will be considered: subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbidities such as cerebrovascular disease).
	Alzheimer's Society	This review should allow for an appraisal of a combination of the cholinesterase inhibitors with memantine, for the treatment of mild to moderately severe Alzheimer's disease, where clinical trial evidence is available.	Comment noted. The following statement has been included in the 'Other Considerations' section of the scope: If evidence allows, interventions will be compared with each other, or in sequential use, or as combination therapy, within their licensed indications.

Section	Consultees	Comments	Action
Outcomes	British Geriatrics Society	Outcomes seem fine. I remain unsure about the validity of institutionalization as an outcome. Many studies show that issues like carer illness/bereavement and availability of care in the community as well as institutional care are the main determinants of institutionalization. These will differ across the UK.	Comment noted. This outcome is included in the scope. The scope sets out the framework for the appraisal. Consultees are now invited to prepare submission dossiers and participate in the appraisal - comments such as this on the validity of evidence are welcomed.
	West Kent PCT	The outcomes do not explicitly include activities of daily living, these could be considered for inclusion as an outcome	Comment noted. These measures will be used where appropriate to assess the outcome "ability to remain independent", which is listed in the draft scope.
	West Kent PCT	Consideration should be given to what constitutes a clinically important change in scores on the scales used	Noted
	Lundbeck	They will if the measures of severity and response to treatment also include the following methods of assessment: 1. Severe Impairment Battery (SIB) 2. Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) 3. Responder analysis based on marked clinical improvement* or any clinical improvement‡ * a decline of ≥4 points on the ADAS-cog or ≥5 points on the SIB and a decline on the CIBIC-plus and a decline on the ADL ‡ any decline on the ADAS-cog or on the SIB and a decline on the CIBIC-plus and a decline on the ADL	Comment noted The SIB and ADSC-ADL instruments have been included in the background section of the scope. The scope sets out the framework for the appraisal. The list of outcomes is not exhaustive. Several measures of disease severity are outlined in the background section of the scope. Consultees are now invited to prepare submission dossiers. The following statement has been added to the 'Other Considerations' section of the scope if evidence allows, the following subgroups will be considered: subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbidities such as cerebrovascular disease).

Section	Consultees	Comments	Action
	Lundbeck	4. We would also strongly recommend that the existing outcomes of 'ability to remain independent' and 'likelihood of admission to residential/nursing care' must not be excluded for patients with severe Alzheimer's disease as not all patients in the severe stage are dependent or in residential/nursing care.	Coment noted The rate of admission to residential/nursing care would be captured during the economic modelling of the appraisal.
	Lundbeck	5. Reduction in the inappropriate use of anti-psychotics. This is one of the key outcome measures for assessing the health related benefits for memantine and health related harms for anti-psychotics in moderate to severe Alzheimer's disease. This measure also supports the recommendation for only the appropriate use of anti-psychotic medication for people with dementia in the National Dementia Strategy.[2] Recent survey information of nurses about people with dementia in hospital wards published by the Alzheimer's Society[3] also supports the growing evidence base for the widespread inappropriate use of anti-psychotics and the need for this outcome measure in the scope. Reference 2. Living well with dementia: A National Dementia Strategy. Department of Health. Feb 2009. Reference 3. http://www.alzheimers.org.uk/site/scripts/news_article.php?newsID=547. Last accessed 16 Oct 2009.	The clinical guideline on treatment of dementia (No 42) provides guidance on the use of antipsychotic medication in people with Alzheimers disease with severe non-cognitive symptoms (section 1.7.2.4 of CG42) http://guidance.nice.org.uk/CG42/Guidance/doc/English The 'Other considerations' section of the scope states that if evidence allows, the following subgroups will be considered: subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbidities such as cerebrovascular disease). If clinically appropriate and if evidence allows, modelling of the subgroup of people with behavioural disturbance may consider concomitant use of anti-psychotic medication.

Section	Consultees	Comments	Action
	Eisai	The Gottfries-Brane-Steen (GBS) scale should be added to the list of outcome measures. This is an important measure of global function in dementia and has been used in some clinical trials as a primary endpoint.	Comment noted. The scope sets out the framework for the appraisal. The list of outcomes is not exhaustive. Several measures of disease severity are outlined in the background section of the scope. Consultees are now invited to prepare submission dossiers.
	Eisai	Measures of functional activity should be added such as basic Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL).	Comment noted. These measures will be used where appropriate to assess the outcome "ability to remain independent", which is listed in the draft scope.
	Eisai	Carer time should be added to the list of outcomes measured. Carers play a large role in the management of dementia and savings on carer time are a useful outcome of treatment with potential health benefits for the carers themselves.	Comment noted. The NICE reference case specifies that costs and benefits will be considered from a NHS and PSS perspective. The impact of the technologies under appraisal on the health-related quality of life of carers is included in the appraisal.

Section	Consultees	Comments	Action
	Eisai	Caregiver utility should be added as an outcome measure. Patient symptom severity is known to be related to carer quality of life.	Comment noted. The NICE reference case specifies that costs and benefits will be considered from a NHS and PSS perspective. The impact of the technologies under appraisal on the health-related quality of life of carers is included in the appraisal. Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained. See the Guide to the Methods of Technology Appraisal 2008, section 6.2.23.
	Eisai	Time to admission should be added to likelihood of admission to residential/nursing home care. Delaying admission (as oppose to avoiding it altogether which is frequently not possible) is an important treatment goal with health economic benefits.	Comment noted.

Section	Consultees	Comments	Action
	RICE – The Research Institute for the Care of Older People	We note that one of the outcomes to be measured is the 'ability to remain independent'. This is important but it is not clear how it is to be assessed. There is now a considerable literature demonstrating that people receiving the drugs for Alzheimer's disease show a less than expected decline in comparison with people receiving placebo or no treatment and this is an important concept that should be incorporated within the outcomes assessed and is likely to contribute to the ability to remain independent.	Comment noted
	RICE – The Research Institute for the Care of Older People	The appropriate measurement of health-related quality of life of patients and carers is difficult as has been discussed in the previous Appraisals and it is important that issues such as savings on caregiver time are also evaluated as a way of capturing potential benefit.	Comment noted. The NICE reference case specifies that costs and benefits will be considered from a NHS and PSS perspective. The impact of the technologies under appraisal on the health-related quality of life of carers is included in the appraisal. The scope sets the framework for the appraisal. Consultees are now invited to prepare submission dossiers.
	CSU appraisals	The outcomes do not explicitly include activities of daily living, these could be considered for inclusion as an outcome	Comment noted. The outcome "ability to remain independent" will be assessed during the appraisal. The measurements used will depend on evidence available. The scope sets the framework for the appraisal. Consultees are now invited to prepare submission dossiers..
	CSU appraisals	Consideration should be given to what constitutes a clinically important change in scores on the scales used	Comment noted.

Section	Consultees	Comments	Action
	The Royal College of Psychiatrist	Activities of daily living should be included as an outcome.	Comment noted. The outcome “ability to remain independent” is included in the scope.
	The Royal College of Psychiatrist	Effects on carers beyond quality of life should be considered, for example carer stress and the amount of time carers spend caring for people with Alzheimer’s disease.	Comment noted. The NICE reference case specifies that costs and benefits will be considered from a NHS and PSS perspective. The impact of the technologies under appraisal on the health-related quality of life of carers is included in the appraisal.
	Shire	We suggest rearrangement of text, in order to list items of the same status together. Therefore, 'Behavioural symptoms (eg neuropsychiatric inventory, NPI)' should appropriately be included as a sub-bullet point of the first main bullet point, not as a separate item. ‘Activities of Daily Living (eg DAD and ADCS/ADL)’ should be added as a sub-bullet point to the first bullet point here (see also ‘Background information’ above).	Comment noted.
	Alzheimer’s Society	We welcome the inclusion of **‘ability to remain independent’**. We would welcome further details of how this is to be assessed.	Comment noted. The outcome “ability to remain independent” will be assessed during the appraisal. The measurements used will depend on the evidence available. The scope sets the framework for the appraisal. Consultees are now invited to prepare submission dossiers.
	Alzheimer’s Society	We recognise that assessing **health related quality of life** for people with dementia as well as their carers is difficult in the context of these appraisals, given the lack of data. We continue to believe that data on savings to carer time should be used as an alternative to HRQL, given that there is more robust clinical trial evidence around this outcome.	Comment noted.

Section	Consultees	Comments	Action
	Alzheimer's Society	In relation to '**likelihood of admission to residential/nursing care**', if predictive models are to be used they need to be adjusted for the fact that they are unlikely to be very sensitive for people with mild dementia as this outcome is likely to occur quite some time in the future. We note that 'likelihood of admission to residential/nursing care' is used. In the previous appraisal the outcome actually used was admission to full time care, which also included full time care in a person's own home. We would welcome clarity on which will be used in this appraisal.	Comment noted. Decisions regarding how admission to residential / nursing care will be modelled will be explored during the course of the appraisal.
	Alzheimer's Society	Extent of the **use of community services** should be used as an outcome as any reduction in the use of these services is likely to represent important cost savings. This is particularly important for people with mild dementia, in light of the insensitivity of admission to residential care as an outcome. Furthermore, it is government policy to support people to remain in their own homes and to increase provision of low level services. This makes impact on use of community services particularly relevant.	Comment noted. The NICE reference case specifies that costs and benefits will be considered from a NHS and PSS perspective. Decisions regarding how admission to residential / nursing care will be modelled will be explored during the course of the appraisal.
	Alzheimer's Society	It is important that **up to date and accurate data** are used in relation to costs and usage of services for people with dementia. For example, the annually produced PSSRU reports and Laing and Buisson market surveys. 2009 data is now available	Comment noted.

Section	Consultees	Comments	Action
	Alzheimer's Society	We are concerned that the outcomes do not include a range of **outcomes frequently cited by people with dementia and their carers** as important benefits of treatment. Our 2003 survey of over 4,000 people with experience of the drug treatment asked people to list benefits of treatment. Improvements in happiness, awareness and confidence were reported more frequently than direct effects on memory or activities of daily living. Improvements in memory were reported by only 18 per cent of respondents, despite memory being the primary outcome in most clinical trials. Therefore, we urge NICE to pay particular attention to the patient evidence they will receive, as it will greatly add to their understanding of the benefits of treatment. We also suggest more flexible use of clinical trial data, for example by selecting mood items from the scales used within the trial. This would allow a focus on the outcomes of treatment most important to people with dementia and carers.	Comment noted. The Institutes also welcomes evidence from patient and carer organisations on the impact of treatment on outcomes which are important to patients. The scope sets out the framework for the appraisal. Consultees are now invited to prepare submission dossiers.
Economic analysis	British Geriatrics Society	The QALY and older people has long been the subject of debate in terms of how appropriate QALY is in this situation. For this disease it is important that any model used has the correct inputs, reflects the true course of disease and has an adequate time horizon.	Comment noted The Methods Guide for Technology Appraisals states the time horizon should be sufficiently long to reflect all important differences in the costs or outcomes of technologies being compared.

Section	Consultees	Comments	Action
	West Kent PCT	Manufacturers' models submitted as part of the original TA (TA111) used time horizons of 5-10 years; NICE's own model used a time horizon of 5 years. The 5 year time horizon was debated by consultees, with some suggesting that a longer time horizon would be more appropriate in mild Alzheimer's disease	Comment noted The Methods Guide for Technology Appraisals states the time horizon should be sufficiently long to reflect all important differences in the costs or outcomes of technologies being compared
	Lundbeck	We acknowledge that the incremental cost per QALY is the standard for NICE HTA. However it is worth noting that the QALY measure has drawbacks specifically in the elderly population[4] and therefore this should be taken into consideration by the Appraisal Committee when reviewing the cost effectiveness of the technologies. Reference 4. Donaldson C et al. QALYS and long-term care for elderly people in the UK: scales for assessment of quality of life. Age Ageing 1988 Nov;17(6):379-87	Comment noted

Section	Consultees	Comments	Action
	Eisai	Whilst Eisai understands that the remit of NICE is to undertake the economic analysis from the perspective of the NHS and Personal Social Services, Eisai believes that, given the large burden placed on carers, that the economic analysis should also consider carer costs. In general carers play a much larger role and carry a greater burden of care for longer in dementia than they do in relation to other medical conditions. This is a fundamental difference between dementia and most other illnesses and the economic analysis should recognise the costs associated with caring. These costs are well described in the report 'Dementia UK 2007' (Alzheimers Society, Kings Fund and London School of Economics) and include elements such as direct cost of payments to informal carers and opportunity cost to carers of reduced employment. The input costs in the economic analysis should recognise the consequences of generic versions of acetyl cholinesterase inhibitors being available from 2012. Treatment acquisition costs are expected to fall dramatically when this happens and the analysis should accordingly use the expected lifetime cost of treatment.	Comment noted The NICE reference case specifies that costs and benefits will be considered from a NHS and PSS perspective. The impact of the technologies under appraisal on the health-related quality of life of carers is included in the appraisal.

Section	Consultees	Comments	Action
	RICE – The Research Institute for the Care of Older People	It is important that the costs are not only considered from an NHS and personal social services perspective but that the full costs to carers including costs from effects on their own health are taken into account as far as possible. It is also important that the data used for the evaluation for the economic analysis is as recent as possible and takes into account more than just a change in residential status or mortality but captures the gradual change that takes place in people with Alzheimer's disease beginning in the mild stages and continuing through to moderate and severe dementia.	Comments noted The NICE reference case specifies that costs and benefits will be considered from a NHS and PSS perspective. The impact of the technologies under appraisal on the health-related quality of life of carers is included in the appraisal.
	CSU appraisals	Manufacturers' models submitted as part of the original TA (TA111) used time horizons of 5-10 years; NICE's own model used a time horizon of 5 years. The 5 year time horizon was debated by consultees, with some suggesting that a longer time horizon would be more appropriate in mild Alzheimer's disease	Comments noted The Methods Guide for Technology Appraisals states the time horizon should be sufficiently long to reflect all important differences in the costs or outcomes of technologies being compared

Section	Consultees	Comments	Action
	The Royal College of Psychiatrist	Costs should also be considered in terms of carer time, even though much of this is provided informally by close relatives. It has emerged very clearly during the last appraisal there are considerable difficulties in applying the quality adjusted life year incremental cost analysis to people with dementia.	Comments noted The NICE reference case specifies that costs and benefits will be considered from a NHS and PSS perspective. Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained. See the Guide to the Methods of Technology Appraisal 2008, section 6.2.23.
	Shire	1. The time horizon should be sufficiently long to recognise that the time from diagnosis to death of this chronic debilitating disease may be well over ten years. The long term effectiveness in many cases of the acetylcholinesterase inhibitors should be recognised in determining this parameter.	Comment noted.
	Shire	2. We request that the cut-off of cost per QALY be stated, above which cost-effectiveness of the drugs will not be recommended	Comment noted. Guidance on the Appraisal Committee's consideration of cost-effectiveness is provided in sections 6.2.22 to 6.2.26 of the Methods Guide.
Equality and Diversity	Welsh Assembly Government	We are pleased to see that NICE is asking about specific groups' requirements and trust that you will ensure that responses are carefully considered	Comment noted

Section	Consultees	Comments	Action
	British Geriatrics Society	The issues of language, race have been dealt with in the last guidance. These should be factored in. It is the case that very elderly people are likely to be eligible for consideration of medication – this must be factored in somehow so that they are not discriminated against.	Comment noted A number of scales are used to estimate the severity of Alzheimer's disease. The severity of AD by MMSE score was included as it formed the basis of recommendations of TA111. Section 1.2 of NICE Technology Appraisal 111 and section 1.6.2.2 of NICE Clinical Guideline 42 on Dementia note that the MMSE score alone may not be suitable in all situations to assess the severity of dementia.
	West Kent PCT	Consideration of methods of eligibility determination other then the MMSE, which may not be appropriate for all groups, as per amended TA111.	Comment noted A number of scales are used to estimate the severity of Alzheimer's disease. The severity of AD by MMSE score was included as it formed the basis of recommendations of TA111. Section 1.2 of NICE Technology Appraisal 111 and section 1.6.2.2 of NICE Clinical Guideline 42 on Dementia note that the MMSE score alone may not be suitable in all situations to assess the severity of dementia.
	Lundbeck	Please see issues raised in previous Alzheimer's HTA review.	Comment noted
	Eisai	As stated in comments on the background information the appraisal should avoid over-reliance on MMSE to guide prescribing decisions. There are well-described limitations of MMSE in assessing patients at a low educational level and whose first language is not English. In addition, sole reliance on MMSE to make diagnosis and prescribing decisions will lead to discrimination against patients with a high cognitive reserve.	Comment noted A number of scales are used to estimate the severity of Alzheimer's disease. The severity of AD by MMSE score was included as it formed the basis of recommendations of TA111. Section 1.2 of NICE Technology Appraisal 111 and section 1.6.2.2 of NICE Clinical Guideline 42 on Dementia note that the MMSE score alone may not be suitable in all situations to assess the severity of dementia.

Section	Consultees	Comments	Action
	RICE – The Research Institute for the Care of Older People	The issues of equality were widely discussed in the previous Appraisal including the judicial review of TA111. It is important to acknowledge that people of high ability may well have mild Alzheimer's disease with a Mini-Mental State Examination score of above 26 and have moderate Alzheimer's disease with a score above 20. It is even more important to acknowledge the effect on cognitive testing of issues such as pre-morbid language ability, pre-existing learning disabilities, whether the person speaks English as a first language and the impact of dementia on language.	Comment noted
	CSU appraisals	Consideration of methods of eligibility determination other then the MMSE, which may not be appropriate for all groups, as per amended TA111.	Comment noted
	The Royal College of Psychiatrist	Due consideration should be given to people who suffer from dysphasia, have low educational or learning disability or for whom English is not their main language. Similarly, consideration should be given to those of high educational/intellectual ability. All of these aforementioned groups have pre-morbid ability which affects performance on the MMSE and other cognitive tests to provide either too low or too high a score, meaning that standard cognitive tools (like the MMSE) are not reliable in these groups.	Comment noted A number of scales are used to estimate the severity of Alzheimer's disease. The severity of AD by MMSE score was included as it formed the basis of evidence and recommendations of TA111. Section 1.2 of NICE TA111 notes that the MMSE score alone may not be suitable in all situations to assess the severity of dementia.
	Shire	No further comments. These issues were addressed during the previous appeal procedures.	Comment noted

Section	Consultees	Comments	Action
	Alzheimer's Society	We are sure NICE are aware of the need to address the issues raised by the Judicial review of TA111. Specifically, the impact that characteristics such as race and culture, whether English is a first language, pre-morbid language ability and impact of dementia on language skills, and also presence of learning disability has on results of cognitive testing.	Comment noted
Other considerations	British Geriatrics Society	The availability of services throughout the UK is extremely variable. This should be reflected in the other considerations – thus there may be areas with very little support and other areas where with a high percentage of older people there has to be high levels of community provision.	Comment noted
	West Kent PCT	RCTs are currently ongoing that are assessing the use of the drugs in question in combinations with each other (e.g. donepezil plus memantine in moderate to severe AD) or other agents (e.g. memantine plus vitamin E, donepezil plus aspirin). Consideration should be given to whether combination treatments will be assessed	Comment noted. The following statement has been included in the 'Other Considerations' section of the scope: If evidence allows, interventions will be compared with each other, or in sequential use, or as combination therapy, within their licensed indications
		Different modes of delivery of the drugs could be considered, for example, transdermal patches for rivastigmine, galantamine modified release capsules,	Comment noted
		Dimebon (latrepirdine) is another drug currently undergoing testing for AD; it is not currently licensed for this indication in the UK, but could be considered for inclusion in the review	Comment noted. The interventions included in this review appraisal are those which fall within the remit and are expected to obtain marketing authorisations within timescales that allow production of timely guidance.

Section	Consultees	Comments	Action
	Eisai	Careful consideration should be given to the health economic model used to assess technologies. Health economic modelling is a developing science and there have been marked improvements in the sophistication of modelling techniques in recent times such that they are better able to reflect complex disease states. In Alzheimer's disease Eisai believe that a discrete event simulation (DES) modelling technique should be used as it better captures the variation in patient baseline characteristics and the complexities and heterogeneity of disease progression on a wide range of outcomes than a Markov cohort model. Individual-level simulation is needed to accurately capture the relationship between patient characteristics, disease progression and treatment effects. DES is well suited to this in that it can also consider these variables over time at the level of the individual, and thus provide a more accurate and meaningful assessment of initiating therapy at different stages of the disease. DES also allows for the joint consideration of multiple domains of disease severity (e.g., cognition, behaviour and function), and how these relate to outcomes. Finally, the technique allows for continuous measures of disease severity, which enables the consideration of the potential benefits across all stages of the disease, and not over aggregated disease states, where important information may be lost. Eisai would welcome an opportunity early in the appraisal process to discuss the model to be used. Health economic assessment should reflect the non-linear nature of Alzheimer's disease progression and effectiveness estimates should not be restricted to too short a time-frame particularly in mild symptomatic disease.	Comments noted. The scope sets out the framework for the appraisal. Consultees are now invited to prepare submission dossiers. See the Guide to the Methods of Technology Appraisal 2008 for the detailed information on methodology, including the NICE reference case.

Section	Consultees	Comments	Action
	RICE – The Research Institute for the Care of Older People	As previously mentioned, the concept of less than expected decline for patients receiving drugs for Alzheimer's disease in comparison with patients receiving placebo or nothing should also be evaluated.	Comment noted
	CSU appraisals	RCTs are currently ongoing that are assessing the use of the drugs in question in combinations with each other (e.g. donepezil plus memantine in moderate to severe AD) or other agents (e.g. memantine plus vitamin E, donepezil plus aspirin). Consideration should be given to whether combination treatments will be assessed	Comment noted. The following statement has been included in the 'Other Considerations' section of the scope: If evidence allows, interventions will be compared with each other, or in sequential use, or as combination therapy, within their licensed indications.
	CSU appraisals	Different modes of delivery of the drugs could be considered, for example, transdermal patches for rivastigmine, galantamine modified release capsules	Comment noted
	CSU appraisals	Dimebon (latrepirdine) is another drug currently undergoing testing for AD; it is not currently licensed for this indication in the UK, but could be considered for inclusion in the review	Comment noted. The interventions included in this review appraisal are those which fall within the remit and are expected to obtain marketing authorisations within timescales that allow production of timely guidance.
	The Royal College of Psychiatrist	As above, there are now studies on combination treatments and these should be included as part of the appraisal (particularly the combination of acetycholinesterase inhibitors and memantine).	Comment noted Comment noted. The following statement has been included in the 'Other Considerations' section of the scope: If evidence allows, interventions will be compared with each other, or in sequential use, or as combination therapy, within their licensed indications

Section	Consultees	Comments	Action
	Shire	On p5, under 'Other considerations', 3rd paragraph, 2nd sentence, it is unclear how this list of support items (information and education etc) will be applied in the appraisal. There seems to be a blurring of the distinction between this drug technology guidance and the clinical dementia guideline. Regarding clinical effectiveness, trials do not exist which compare drug treatment with such support items - and the data would not be double-blinded anyway. Perhaps the support items in this list are to be considered in the cost effectiveness analysis? If so, the health economic analysis will be complex. We ask for clarification in the Scope as to how this list of support items will be utilised in the appraisal.	Comment noted The purpose of this section of the scope is to illustrate what is included as 'treatment without AChE inhibitors'. The scope sets out the framework for the appraisal. Consultees are now invited to prepare submission dossiers. See the Guide to the Methods of Technology Appraisal 2008 for detailed information on methodology, including the NICE reference case.

Section	Consultees	Comments	Action
	Shire	It is unclear how clinical effectiveness will be assessed. Will the appraisal again choose not to recognise results from open studies? In past Scopes for this appraisal, it has been specified that open studies would be considered where appropriate. In fact, results from long term open studies were not recognised in previous appraisals of these drugs. In the preceding appraisal, it was declared that clinical effectiveness has only been demonstrated for six months and this parameter was fed into the health economic analysis. We contend that acetylcholinesterase inhibitors are effective for longer than six months in many cases and that this fact should be recognised in the appraisal. We request that reference be included to long-term open studies (under 'Other considerations'?), since this is the only way that long-term clinical activity can be demonstrated in this chronic debilitating disease.	Comment noted. The process for assembling evidence for health technology assessment needs to by systematic. These principles apply to all categories of evidence that are used to estimate clinical and cost effectiveness, evidence for which will typically be drawn from a number of sources. See the Guide to the Method of Technology Appraisals 2008, section 5.1.2.
	Alzheimer's Society	Treatment without drugs should be social support and assistance with day-to-day activities. However, the package of care described represents optimal treatment rather than usual treatment. The reality is that many people with dementia receive a very limited package of care. As noted in the National Dementia Strategy for England (DH, 2009), 'recent reports and research have highlighted the shortcomings in the current provision of dementia services in the UK.'	Comment noted. The 'other considerations' section of the scope is consistent with this.
Questions for consultation	British Geriatrics Society	It is important to examine memantine for severe dementia	Comment noted Memantine for the treatment of severe Alzheimer's disease is included in the updated scope

Section	Consultees	Comments	Action
	Lundbeck	Lundbeck expect to include submission data for a subgroup of patients with behavioural symptoms which is an outcome measure already identified in the draft scope.	Comment noted
	Eisai	A multiple technology appraisal process is appropriate.	Comment noted
	RICE – The Research Institute for the Care of Older People	We have already commented elsewhere in this document about the choice of comparators that should be included. Previous evaluations of these drugs have not adequately recognised the fact that patients who do not tolerate the drug or who do not benefit from the drug are usually withdrawn from drug therapy, often within the first 3 months of treatment. This was not properly accounted for in the economic analysis and should be dealt with more appropriately in this Appraisal.	Comment noted
	Alzheimer's Society	Q. Have the most appropriate comparators been included? A. Please see comments in 'comparators' section. Q. Are there are subgroups of patients… A. It is acknowledged that not all people with dementia benefit from these drug treatments. People who do not benefit are taken off the drug treatments. We recognise that this issue was discussed in detail during the course of the previous appraisal. However, we still believe an analysis which reflected the fact that not all will stay on the treatments would produce a more reliable estimate of clinical and cost effectiveness.	Comment noted

Section	Consultees	Comments	Action
Additional comments on the draft scope.	Welsh Assembly Government	The Minister for Health and Social Services wrote to Andrew Dillon on 30 June (copy enclosed). We would be grateful if the comments made in her letter could be taken into account when the scope of the review is finalised.	Comment noted
	Novartis	The title refers to this as a 'Part review of TA 111', but the scope appears to suggest that this will be a full review of TA 111. Please can you clarify if this is a part review by highlighting which parts of TA 111 are not in scope. If this is in fact a full review of TA 111 then we suggest the title is amended to reflect this.	Comment noted. The scope has been amended accordingly.
	Lundbeck	The 'Appraisal objective' on page 1 states 'To review and update as necessary guidance to the NHS in England and Wales on the clinical and cost effectiveness of donepezil, galantamine, rivastigmine and memantine within their licensed indications for the treatment of mild to moderate Alzheimer's disease which was issued in November 2006 (amended September 2007, August 2009)'. This is factually incorrect as the previous November 2006 guidance (subsequently amended) was for 'donepezil, galantamine, rivastigmine (review) and memantine for the **treatment of Alzheimer's disease**' i.e. all stages from mild to severe not 'mild to moderate' as now specified in the current draft scope. This is a further reason to ensure severe Alzheimer's is included in the scope population for TA111	Comment noted. In response to consultation, the scope will now include people with severe Alzheimer's disease. Therefore the scope has been amended accordingly.

Section	Consultees	Comments	Action
	RICE – The Research Institute for the Care of Older People	We are concerned that the treatment of severe dementia has not been commented already in this Appraisal although we note that NICE will be consulting on a Review Proposal for evaluating memantine for this indication. This is important because currently there are no drugs approved by NICE for use in people with severe dementia and this is the group who are most likely to receive anti-psychotic drugs inappropriately.	Comment noted Severe Alzheimer's disease has now been included in the scope of this appraisal.
	The Royal College of Psychiatrist	It would seem much more appropriate to examine memantine in terms of severe Alzheimer's disease as part of a single technology assessment, otherwise it would appear that memantine would be looked at in terms of moderate Alzheimer's disease and separately in another appraisal as part of severe Alzheimer's disease which does not make any sense at all.	Comment noted Following consultation severe Alzheimer's disease has now been included in the scope of this appraisal
	Alzheimer's Society	If Memantine for the treatment of severe dementia is not to be included within this appraisal, it is important that the review is carried out promptly. Behavioural symptoms should be included as an outcome in this review and it should also assess the effectiveness of anticholinesterase drugs in combination with memantine. Government policy now clearly states the importance of early intervention and diagnosis for people with dementia, through memory assessment services. We firmly believe this review must recognise the priority now attached to early intervention and diagnosis	Comments noted Following consultation severe Alzheimer's disease has now been included in the scope of this appraisal