7.4. Results

The full results for the cost–utility analysis of AChEIs are presented first, followed by the full results for the cost–utility of memantine. Due to the many assumptions associated with the parameter estimates in the PenTAG model, it is important to be fully aware of the full uncertainty in the model. Because of this, the first set of analyses presented in this section are those from the probabilistic sensitivity analyses of the base-case parameter values for cholinesterase inhibitors in people with mild to moderate Alzheimer's disease and memantine in people with moderate to severe Alzheimer's disease. These results are followed by the deterministic base-case results which are compared to the corresponding mean estimates from the PSA.

Note that here is a great deal of structural uncertainty in the PenTAG models which cannot be accounted for in the PSA. Deterministic sensitivity analyses have been undertaken to explore some of the structural and further parameter uncertainty.

7.4.1. Mild to moderate Alzheimer's disease: cholinesterase inhibitors (Decision problem 1a)

7.4.1.1. Probabilistic sensitivity analysis

The cost-effectiveness results of 10,000 simulations for the base-case analysis of the cost–utility of AChEIs in people with mild to moderate Alzheimer's disease are presented in *Figure 72,* showing that there exists a great deal of uncertainty. The cost-effectiveness acceptability curve shown in *Figure 73* demonstrates that there is a very low probability that best supportive care is the most cost-effective technology, regardless of the threshold willingness to pay. At a willingness to pay of £30,000 per QALY gained there is a 0.3% probability that best supportive care is the best treatment option, thus indicating that there is >99% probability that it is *not* the most cost-effective treatment option. At a willingness to pay of £30,000 and £20,000 per QALY gained, rivastigmine patches have the highest probability of being cost-effective, 32%. Donepezil has a probability of 28% of being the most cost-effective treatment option at a willingness to pay of £30,000 and 27% at a willingness to pay of £20,000.

FIGURE 72 *Base-case cost-effectiveness plane for treatment with AChEIs in people with mild to moderate Alzheimer's disease*

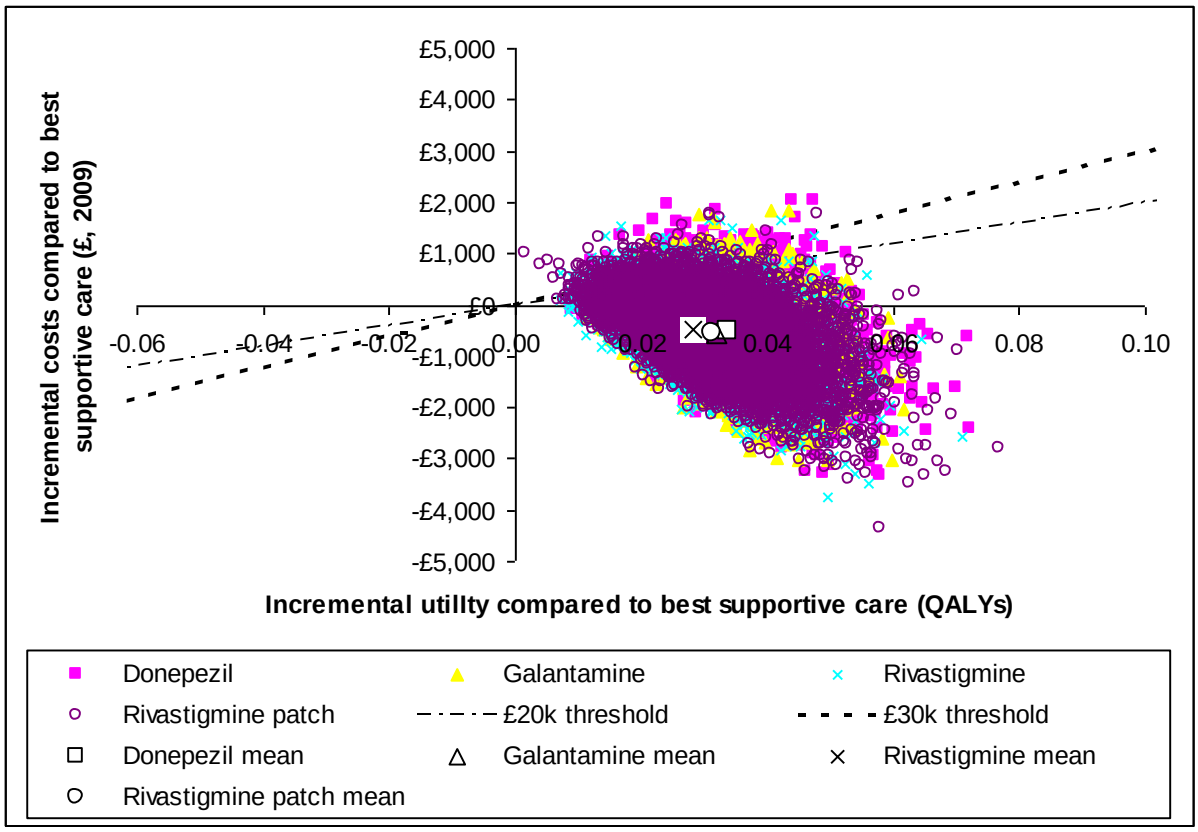
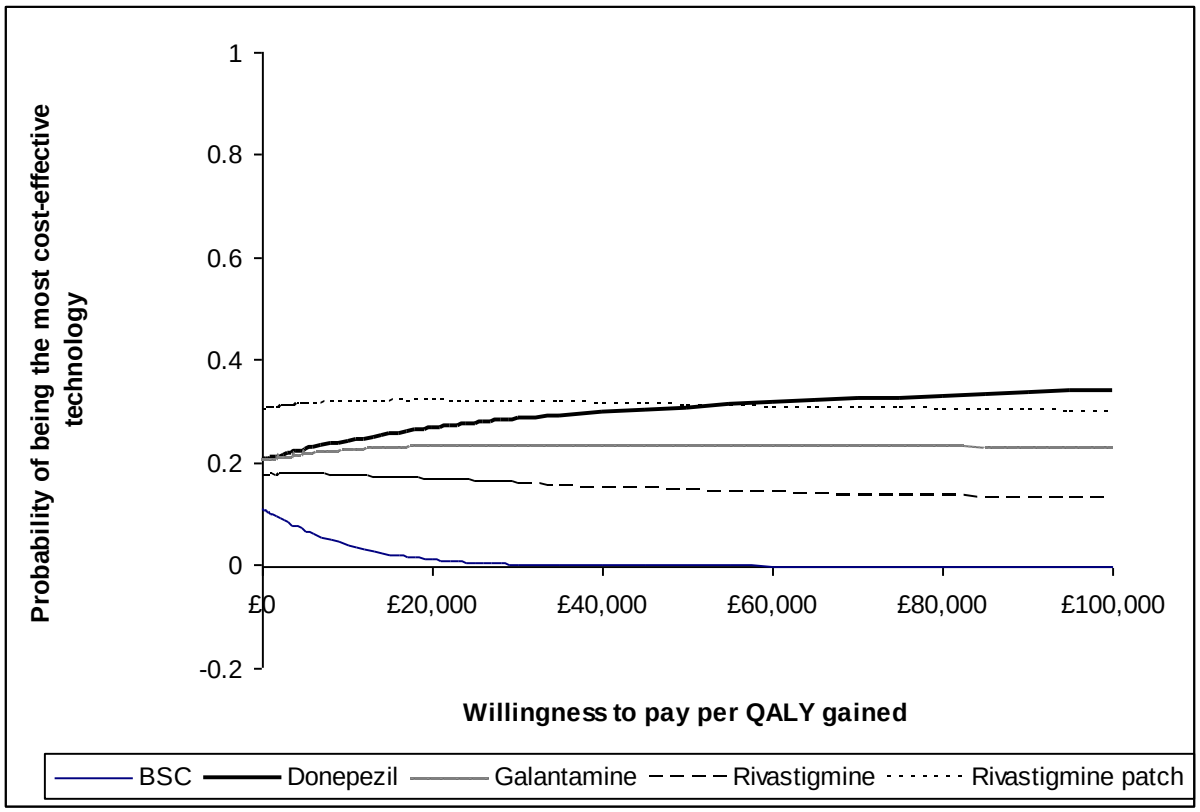


FIGURE 73 *Base-case cost-effectiveness acceptability curve for AChEIs in people with mild to moderate Alzheimer's disease*



BSC, best supportive care

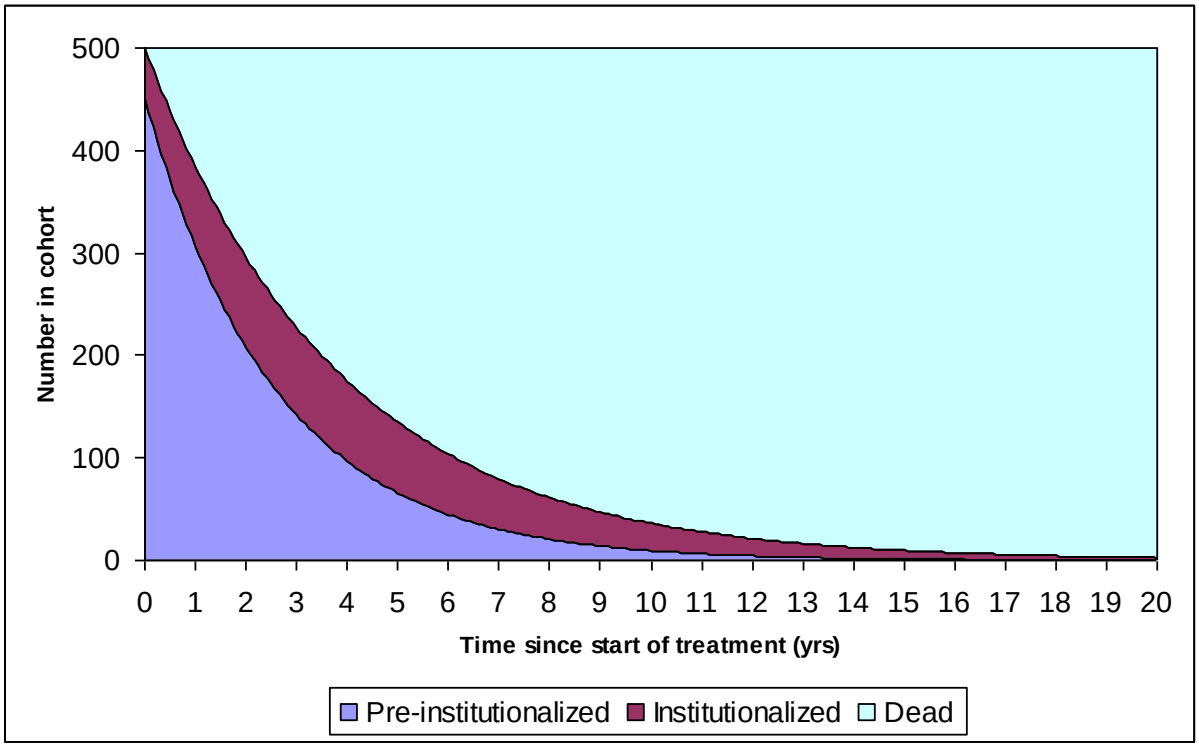
As with the ICERs from the deterministic analysis, the findings from the probabilistic sensitivity analysis (PSA) indicate that, on average, best supportive care, rivastigmine and rivastigmine patches are dominated as they are more expensive and less effective than donepezil and/or galantamine. Galantamine is estimated to be the cheapest option, but with donepezil providing the greatest QALY gains at an ICER of £23,453/QALY compared to galantamine. This ICER is greater than that from the deterministic base case analysis (£17,900/QALY) due to non-linearities in the PSA. Nevertheless, all reference to the base-case analysis will refer to the deterministic ICERs, and not the PSA ICERs.

7.4.1.2. Deterministic analysis

A graph of the progression of individuals with mild to moderate Alzheimer's disease from the best supportive care cohort through the three state Markov model is shown in *Figure 74* for the middle age group, having a mean starting age of 77 (representing 50% of the cohort). Ten percent of the cohort start the model in the institutionalized state. Across all three age

groups, the mean overall survival for the total prevalent cohort is 3.84 years. This is regardless of the treatment received since, in the base-case analysis, it is assumed that there is no treatment effect on survival. The mean time until the end of pre-institutionalization for the treated cohorts is given in *Table 116*, alongside the total cost and QALY estimates from the deterministic analysis. There is very little difference between the three cholinesterase inhibitors, as might be expected given the similar magnitude of effectiveness for MMSE and ADCS-ADL (refer back to Table 8 of main PenTAG report), with treatment leading to a mean of 1.4-1.7 months (42-51 days) delay in becoming institutionalized.

FIGURE 74 *Progression of the best supportive care cohort for the base-case analysis (mild to moderate Alzheimer's disease, age group 2)*



The base-case results for the incremental cost–utility of the AChEIs compared to the next cheapest, non-dominated technology are given in *Table 116*. It is estimated that over a patients lifetime the options of treating with best supportive care, rivastigmine and rivastigmine patches are dominated by donepezil and galantamine. Best supportive care and rivastigmine are associated with greater costs and fewer QALYs than donepezil. Rivastigmime patches are associated with greater costs and fewer QALYs compared to

galantamine. Treatment with galantamine is estimated as the cheapest option with total costs of £69,598 and total QALYs of 1.617. However, treatment with donepezil is estimated to have the most QALY gains over a patient's lifetime (1.619 QALYs) with a total cost of £69,624. Thus the ICER for donepezil compared to galantamine is £17,900 per QALY.

TABLE 116 *Results of the deterministic base-case incremental cost–utility analysis for people with mild to moderate Alzheimer's disease (MMSE 26-10)*

Treatment	Mean months to institutional care[c]	Months delay to institutional care compared to best supportive care	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[ab]
Galantamine (16-24mg)	30.4	1.6	£69,592	1.617			
Rivastigmine patch (10cm^2)	30.3	1.5	£69,598	1.616	Dominated		
Donepezil (10mg)	30.5	1.7	£69,624	1.619	£32	0.002	£17,900
Rivastigmine capsules (9-12mg)	30.2	1.4	£69,678	1.613	Dominated		
Best supportive care	28.8	NA	£70,212	1.584	Dominated		

a Cost per QALY rounded to the nearest £100

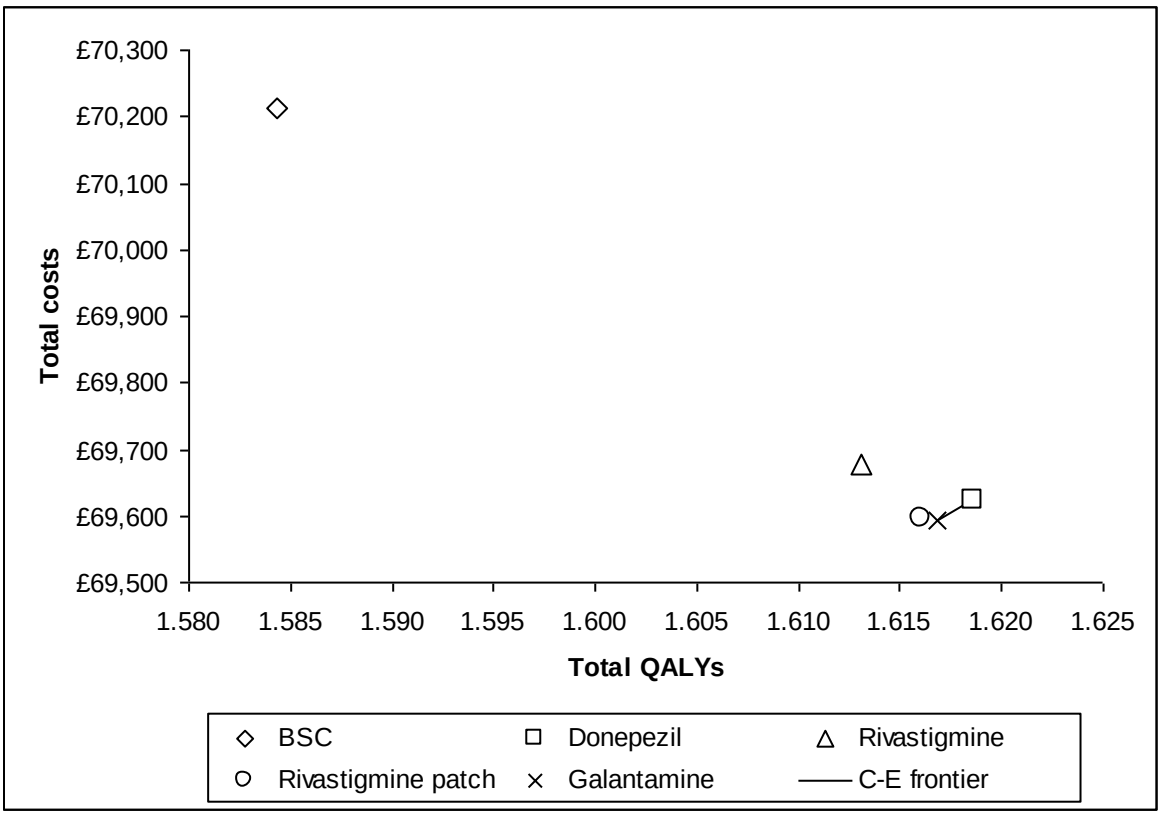
b Each technology is compared to the next cheapest non-dominated technology

c This compares to a mean time to end of pre-institutionalization for all 92 participants in the study by Wolstenholme and colleagues of 30 months. This difference arises from the Wolstenholme IPD containing all severities of Alzheimer's disease, not just those who are mild to moderate as in the above table.

The cost-effectiveness frontier is shown in *Figure 76*.

FIGURE 75 ****** removed from revised results ******

FIGURE 76 *Base-case cost-effectiveness plane for the cost–utility analysis for mild to moderate Alzheimer's disease*



The differences in the component costs between the four AChEIs when each is compared to best supportive care are shown in *Figure 77*. For all four technologies, the largest saving is for the costs associated with being in institutional care. This is as expected since the technologies are estimated to delay institutionalisation for 1.4-1.7 months. Since overall survival is not assumed to be affected by the AChEIs an individual's total time spent in institutional care is reduced by receiving treatment. The delay to institutionalization is also reflected in the higher costs incurred for the pre-institutionalized state when compared to best supportive care (*Figure 77*). The costs saved from delaying institutionalization are greater than the combined costs of the drugs, monitoring and increased costs of care in the pre-institution state when compared to best supportive care. Thus, treatment with any of the AChEIs leads to cost-savings compared to best supportive care. *Figure 77* highlights slight difference in total drug costs per patient between the AChEIs with rivastigmine capsules

being the cheapest and donepezil the most expensive. Note also that the larger cost saved in institutional care for donepezil compared to the other AChEIs is due to the greater delay to institutionalisation assumed with donepezil (1.7 months, refer back to *Table 116*).

The additional QALY gains over best supportive care for the four technologies are all in the pre-institutionalized state (see *Figure 78*). The QALYs lost in the institutionalized state with treatment with the AChEIs compared to best supportive care reflect the reduced time spent in institutionalization for those on treatment (because the base-case assumptions include no treatment effect on overall survival). The QALY gains before institutionalization are greater than the QALY losses while in the institutionalized state because the utilities before institutionalization are greater than the utility whilst institutionalized.

FIGURE 77 *Base-case cost components for the cholinesterase inhibitors compared to best supportive care for mild to moderate Alzheimer's disease*

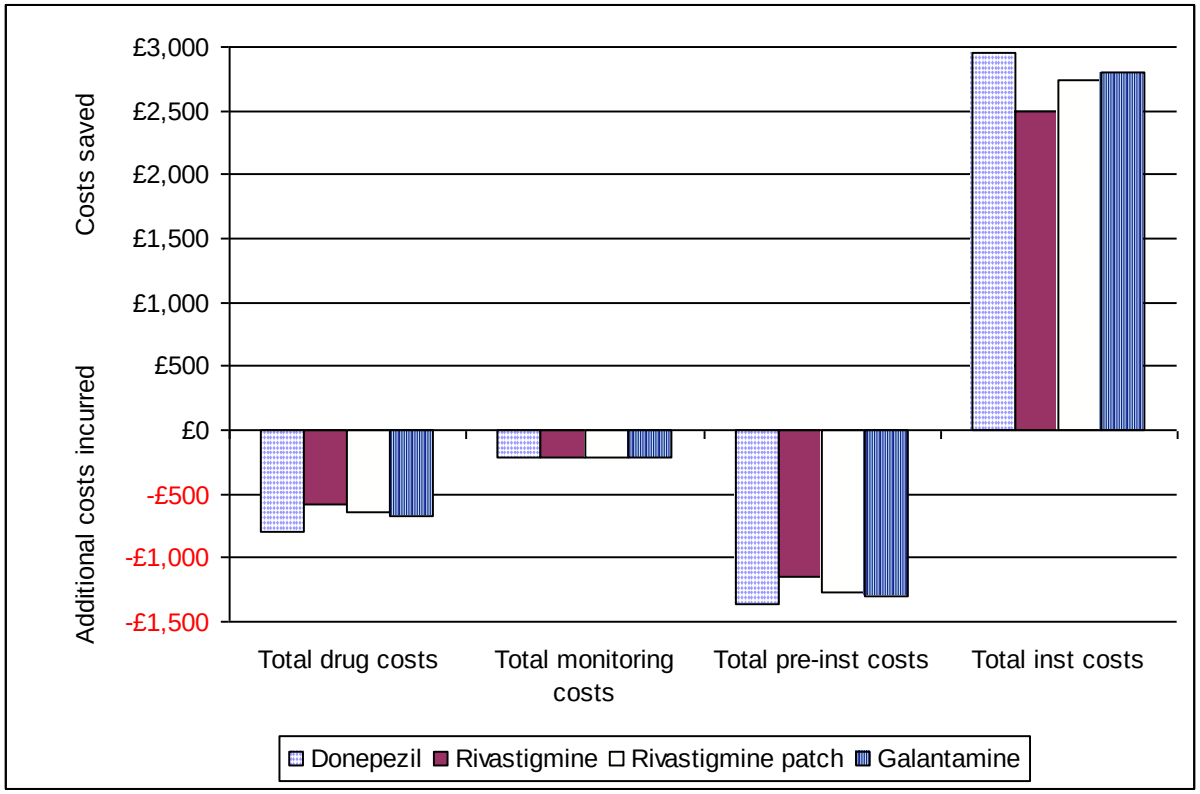
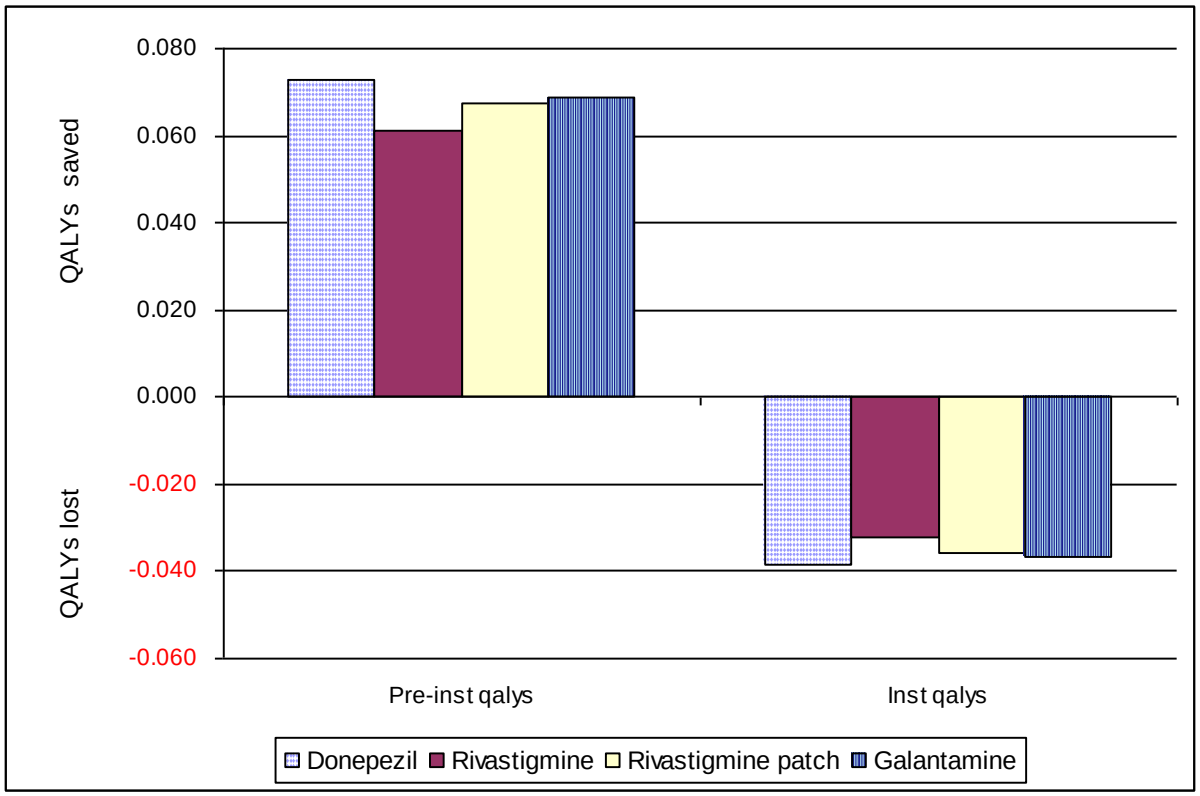


FIGURE 78 *Base-case QALY components for the cholinesterase inhibitors compared to best supportive care in mild to moderate Alzheimer's disease*



7.4.1.3. Summary of deterministic and probabilistic analyses

The PSA and the deterministic base-case analyses indicate that all AChEIs dominate best supportive care. Galantamine is associated with the least costs but donepezil is associated with the greatest QALY gains. Note that the incremental costs and QALYs between the AChEIs are very small. Furthermore, the PSA results do not indicate a particular AChEI as having a much greater probability of being cost-effective compared to any of the other AChEIs. This is the case across a range of willingness to pay values.

In *Table 117* , the deterministic and probabilistic ICERs from the PenTAG model are presented.

TABLE 117 *Base-case ICERs[a] from the PenTAG model for AChEIs in people with mild to moderate Alzheimer's disease*

	Deterministic[b]	Probabilistic[b]	Deterministic v. BSC[c]
Galantamine (16–24mg)			More effective and less costly
Rivastigmine patches (10cm^2)	Dominated	Dominated	More effective and less costly
Donepezil (10mg)	£17,900	£23,500	More effective and less costly
Rivastigmine capsules (9-12mg)	Dominated	Dominated	More effective and less costly
BSC	Dominated	Dominated	NA

a Rounded to nearest £100

b Compared to next cheapest, non-dominated treatment option

c BSC=best supportive care

7.4.1.4. One-way deterministic sensitivity analyses

Treatment effect on mortality

In the base-case analysis, it was assumed that there was no treatment effect on survival. However, analysis of the IPD from Wolstenholme and colleagues for predicting time to death in the best supportive care cohort used MMSE, Barthel ADL and age as independent variables, and the effectiveness data indicate that AChEI treatment affects MMSE and ADL. Thus, as a sensitivity analysis it is assumed that treatment effect measured by MMSE and the Barthel ADL does affect survival. The mean times to institutionalization do not change from the base-case analysis (see *Table 116*), but the mean time to death is extended and given in *Table 118* for each treatment cohort. All treatments delay death by 1.9 to 2.2 months compared to best supportive care.

The cost–utility analysis results assuming a treatment effect on survival are shown in *Table 118* for ICERs compared to the next cheapest non-dominated technology. ICERs are also presented in *Table 118a* for comparison with best supportive care demonstrating very little difference between the AChEIs.

Under the assumption of a treatment effect on mortality, greater costs and QALYs are associated with the AChEIs and but best supportive care is no longer dominated by the AChEIs. It is estimated that treatment with rivastigmine patches provides an additional 0.077 QALYs per patient over best supportive care, with additional costs of £2,840, leading to an ICER of £37,100/ QALY. Treatment with galantamine or donepezil provides additional

QALYs over rivastigmine patches but at additional costs leading to ICERs of £41,800/QALY for galantamine compared to rivastigmine patches, and £51,800/QALY for donepezil compared to galantamine. Rivastigmine capsules are extended dominated by rivastigmine patches and best supportive care.

TABLE 118 *Incremental cost–utility analysis for mild to moderate disease when survival effect of treatment is assumed*

Treatment	Mean time (months) to death[c]	Extended life (months) compared to BSC[d]	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[ab]
Best supportive care	46.0		£70,212	1.584			
Rivastigmine (9-12mg)	47.9	1.9	£72,807	1.654	Extended dominated		
Rivastigmine patch (10cm^2)	48.1	2.1	£73,052	1.661	£2,840	0.077	£37,100
Galantamine (16-24mg)	48.1	2.1	£73,129	1.663	£77	0.002	£41,800
Donepezil (10mg)	48.2	2.2	£73,346	1.667	£217	0.004	£51,800

a Cost per QALY rounded to the nearest £100

b Each technology is compared to the next cheapest non-dominated technology

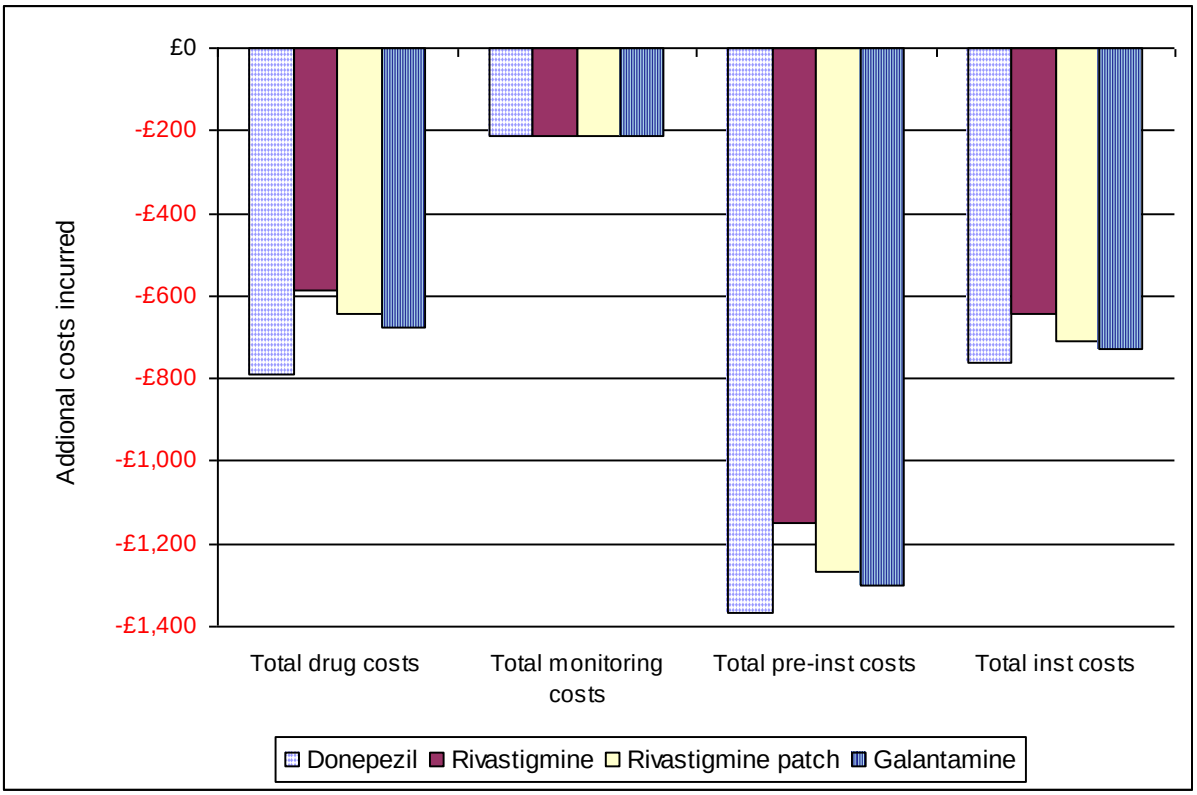
c This compares to a mean time to end of pre-institutionalization for all 92 participants in the study by Wolstenholme and colleagues of 30 months. This difference arises from the Wolstenholme IPD containing all severities of Alzheimer's disease, not just those who are mild to moderate as in the above table.

d BSC = best supportive care

TABLE 118a *Cost–utility analysis for mild to moderate disease when survival effect of treatment is assumed for AChEIs* ***compared to best supportive care***

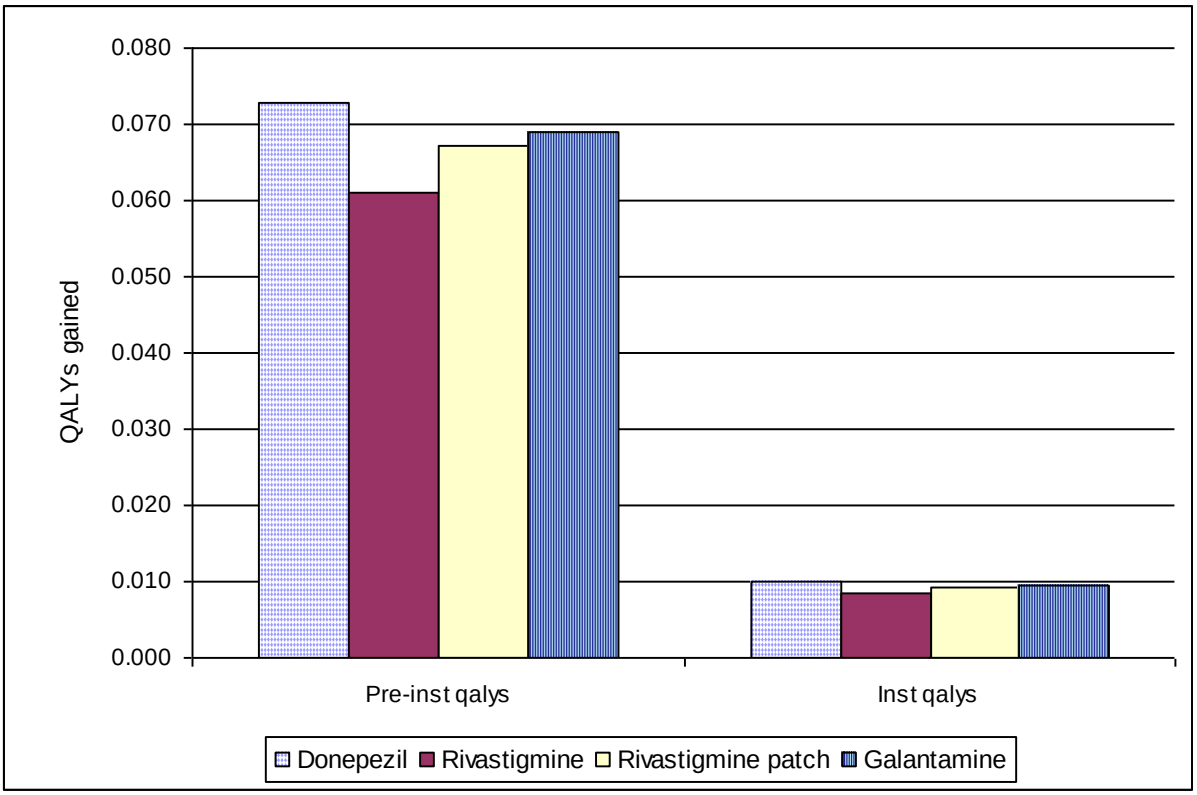
Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[ab]
Best supportive care	£70,212	1.584			
Rivastigmine (9-12mg)	£72,807	1.654	£2,595	0.069	£37,400
Rivastigmine patch (10cm^2)	£73,052	1.661	£2,840	0.077	£37,100
Galantamine (16-24mg)	£73,129	1.663	£2,917	0.078	£37,200
Donepezil (10mg)	£73,346	1.667	£3,134	0.083	£37,900

FIGURE 79 *Cost components for the cholinesterase inhibitors compared to best supportive when a treatment effect on survival is assumed*



In comparison to the base-case analysis, more QALYs are gained when a treatment effect on survival is assumed, due to additional life, but this gain is spent in a more expensive state, institutional care (see *Figure 79* and *Figure 80*). Indeed, given that institutional care is a highly cost-ineffective state, when we allow the drugs to increase overall survival, all drugs become far less cost-effective against best supportive care (*Table 118a*).

FIGURE 80 *QALY components for the cholinesterase inhibitors compared to best supportive care assuming a treatment effect on survival*



Cognitive effectiveness based on the ADAS-cog outcome

***** section removed, including *Table 119*, *Figure 81* and *Figure 82* *****

Importance of the effectiveness on MMSE

There has been debate regarding the appropriateness of the methods PenTAG have used to map ADCS-ADL to the Barthel ADL index. To assess the impact of a treatment effect on ADL in the PenTAG model for AChEIs, it was assumed that treatment only affected MMSE. In other words, the treatment effect for ADL for all drugs was set to zero. In these sensitivity analyses, the overall findings from the base case do not change: all AChEIs dominate best supportive care (see *Table 119a*). This identifies the treatment effect on MMSE is an important driver of the PenTAG model.

TABLE 119a *Incremental cost–utility analysis for mild to moderate disease when effectiveness is only assumed for MMSE*

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[ab]
Galantamine (24mg)	£69,914	1.610			
Rivastigmine patch (10cm^2)	£69,915	1.609	Dominated		
Donepezil (10mg)	£69,916	1.612	£2	0.002	£718
Rivastigmine (≤12mg)	£69,939	1.607	Dominated		
Best supportive care	£70,212	1.584	Dominated		

a Cost per QALY rounded to the nearest £100

b Each technology is compared to the next cheapest non-dominated technology

Alternatively, when it is assumed that a treatment effect only occurs on ADL (i.e. treatment effect for MMSE is set to zero), none of the AChEIs dominates best supportive care (see *Table 119b*). In fact, donepezil is dominated by galantamine, and rivastigmine capsules are dominated by rivastigmine patches and best supportive care. Rivastigmine patches give additional gains of 0.007 QALYs over best supportive care, but at an additional cost of £532 leading to an ICER of £78,024/QALY. An additional QALY gain of <0.001 is provided by galantamine compared to rivastigmine patches but at a cost that leads to an ICER of £247,800/QALY for galantamine compared to rivastigmine patches.

TABLE 119b *Incremental cost–utility analysis for mild to moderate disease when effectiveness is only assumed for ADL*

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[ab]
Best supportive care	£70,212	1.584			
Rivastigmine (≤12mg)	£70,743	1.590	Dominated		
Rivastigmine patch (10cm^2)	£70,745	1.591	£532	0.007	£78,000
Galantamine (24mg)	£70,770	1.591	£25	<0.001	£247,800
Donepezil (10mg)	£70,912	1.591	Dominated		

a Cost per QALY rounded to the nearest £100

b Each technology is compared to the next cheapest non-dominated technology

Further one-way sensitivity analyses

The parameter values and assumptions explored in the following one-way sensitivity analyses are shown in *Table 120*. Analyses are presented as incremental net monetary benefits at a willingness to pay of £30,000 per QALY for donepezil compared to

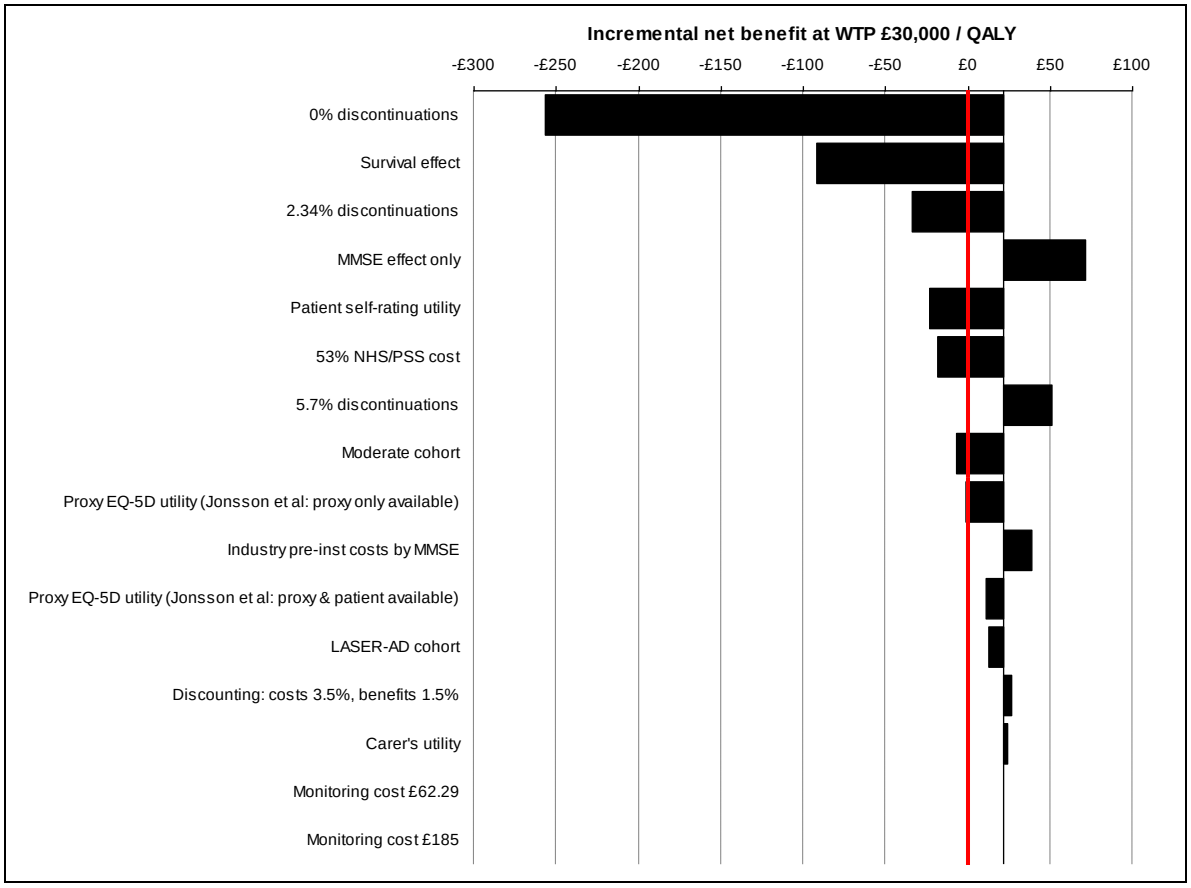
galantamine (see *Figure 83*), the next cheapest non-dominated technology (as in the above analyses) and for donepezil compared to best supportive care (see *Figure 84*). In the majority of one-way sensitivity analyses, rivastigmine patches and capsules and best supportive care were dominated by donepezil and/or galantamine, therefore no tornado plots are shown for the incremental net monetary benefits of these treatment options over the next cheapest non-dominated technology. Tornado plots for galantamine, rivastigmine patches and capsules compared to best supportive care are in the Appendix, and follow the same general trend as for donepezil compared to best supportive care (see *Figure 84*).

TABLE 120 *Parameter and assumption changes for deterministic sensitivity analyses for base-case analysis of AChEIs for mild to moderate Alzheimer's disease*

Parameter/ assumption	Base-case	Deterministic sensitivity analysis	Reference in tornado plots
Survival effect	Independent of treatment	Depends on treatment	Survival effect
Drug costs	See Table 113 in main PenTAG report	Industry cost for donepezil; 9mg cost for rivastigmine capsules; 16mg cost for galantamine; 24mg cost for galantamine	Drug cost
Cost in institutional care	£2,941 per month estimated from Wolstenholme IPD	£3267 from Lundbeck submission; £2801 from Eisai submission	Inst cost £
% institutional costs NHS/PSS	0.72	0.53 & 0.906	% NHS/PSS cost
Treatment discontinuations	4% of the total cohort per month	The maximum (5.7%) and minimum (2.34%) from the RCTs discontinue each month	% discontinuations
Cost in pre-institution state	Based on relationship from Wolstenholme IPD	Transformed industry pre-inst costs by MMSE to time to inst	Industry pre-inst costs by MMSE
Population characteristics	Based on Wolstenholme IPD	Based on LASER-AD IPD	LASER-AD cohort
Severity of cohort	Mild to moderate	Mild or moderate	Cohort severity
% cohort start in institutional care	10%	20%	% start inst
Monitoring costs	From National Schedule Reference Costs, £158 per visit	£185, upper value of interquartile range from National Schedule Reference Costs; £62.29,	Monitoring cost £

Parameter/ assumption	Base-case	Deterministic sensitivity analysis	Reference in tornado plots
		Lundbeck estimate of subsequent out-patient visit	
Patient utility weights	Average of EQ-5D, VAS & QoL-AD carer-proxy utilities	Patient self-rated EQ-5D utility and of carer-proxy EQ-5D utility	Patient self-rated utility; Carer-proxy utility (patient and proxy available; only proxy available)
Carer utility weights	Not included	HUI:2	Carer utility

FIGURE 83 *One-way sensitivity analyses for the incremental net monetary benefit of donepezil compared to galantamine for mild to moderate Alzheimer's disease*

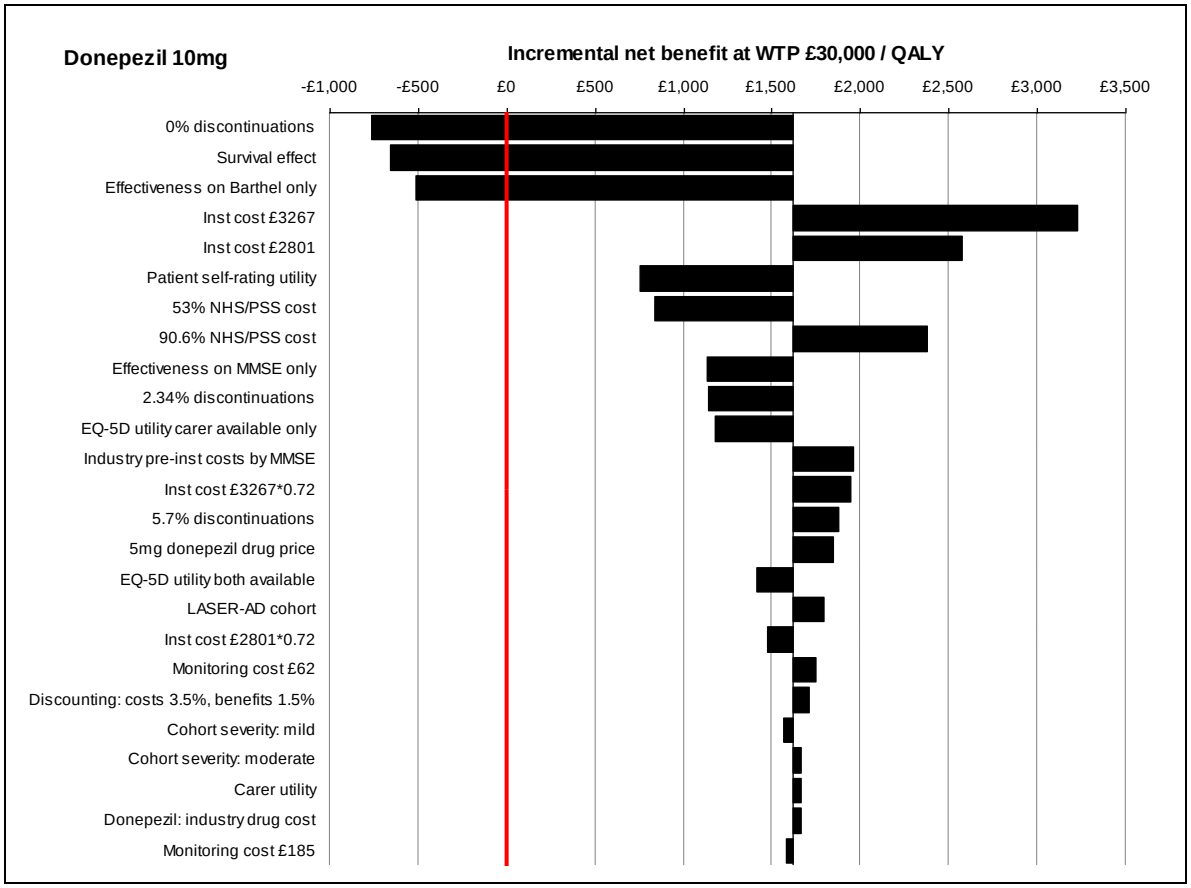


See *Table 120* for a description of the individual sensitivity analyses undertaken.

Note that there is no comparison for the mild cohort as donepezil dominates galantamine. At a willingness to pay of £30,000 per QALY gained, donepezil has an

incremental net benefit of £22 compared to galantamine. Galantamine dominates best supportive care, rivastigmine capsules and patches.

FIGURE 84 *One-way sensitivity analyses for the incremental net monetary benefit of donepezil compared to best supportive care*



[a] Compared to best supportive care, the next cheapest non-dominated treatment option
See *Table 120* for explanation of description of individual sensitivity analyses undertaken

At a willingness to pay of £30,000 per QALY, donepezil has an incremental net benefit of £1,616 compared to best supportive care. The assumption having the largest impact on the net benefit of donepezil compared to galantamine (*Figure 83*) and for donepezil compared to best supportive care (*Figure 84*) is the assumption that all patients continue treatment until they enter institutional care (0% discontinuations assumed). As pointed out in Section 7.3.7.2 of main PenTAG report, we assume that a discontinuation rate for treatment only affects the costs associated with treatment, not the effectiveness, since it is assumed that the effect estimates are based on an ITT analysis. Therefore, lower estimates of this percentage lead to greater treatment and monitoring costs, resulting in

a negative net benefit for the AChEIs. Higher estimates (such as 5.7% as shown in *Figure 83* and *Figure 84*) lead to fewer costs and greater net benefit associated with the AChEIs.

As discussed above, the assumption of a treatment effect on survival leads to the AChEIs having a larger cost per QALY gained than in the base-case analysis and no longer dominating best supportive care.

Assumptions on the costs of care in the institutionalized state have a large impact on the results as would be expected. Since it is assumed that the AChEIs delay and therefore, in the base-case analysis, reduce time spent in institutionalized care, this cost is important. Assuming a lower cost for institutional care compared to pre-institutional care leads to fewer costs saved by the treatments. This is demonstrated in *Figure 83* where lower costs in institutionalized care (either by assuming a lower total cost or by decreasing the percentage of institutionalized costs funded by NHS/PSS to 53%) lead to smaller net benefit at a willingness to pay of £30,000 per QALY gained.

There is also some uncertainty as to the utility estimates used. Alternative estimates of carer-proxy utility also led to lower estimates of net benefit since these estimates provide less of a change in utilities as the disease progresses. This is especially the case for the EQ-5D utilities from Jonsson et al where only proxy utilities are available. Therefore, buy delaying disease progression, a greater utility gain is obtained when there is a larger difference between utility for mild disease compared to severe disease. The estimates used in the base-case analysis span a large range of utility weights across severity, from 0.69 for MMSE>25 to 0.33 for MMSE<10. These utility estimates are therefore more favourable to the AChEIs in the PenTAG model since a delay to more severe stages of AD leads to a bigger gain in utility than would be obtained using alternative care-proxy estimates having a narrower range of values across severity. Use of patient's self-rated quality of life lead to lower estimates of net benefit for the AChEIs since even for the most severe state a utility of 0.78 was reported compared to 0.84 for MMSE of 26-30. Thus, fewer QALY gains by delaying entry into institutional care are obtained when assuming patient rated quality of life estimates. This is not a surprising result since the most severe state was estimated to have greater utility by patients than the adjacent less severe state (refer back to Section 7.3.9 of main PenTAG report).

Inclusion of carer's own quality of life estimates led to a very small increase in the net benefit of the AChEIs. This is as expected given that these estimates are based on data indicating that there is very little change in carer's quality of life as the disease progresses.

7.4.1.5. Summary of one-way sensitivity analyses

In *Table 121* the degree of uncertainty in the decision model and the impact of these parameters on the cost-effectiveness of the AChE inhibitors is presented for people with mild to moderate Alzheimer's disease. The most important items are those discussed above, the mains one being whether a treatment effect on survival is assumed and the rate at which patients discontinue treatment.

TABLE 121 *Degree of uncertainty in model assumptions and impact on the cost-effectiveness of the AChEIs*

Issue	Evidence source	Level of uncertainty in data	Impact of uncertainty in model	Overall rating of importance in cost-effectiveness results
Assuming a treatment effect on survival	No published RCT or epidemiological evidence. Survival prediction allows treatment survival effect	High	High	Very important
Treatment discontinuations	Final time-point data from RCTs	High	High	Very important
Costs in institutional care	Inflated 20-year old estimates from 92 individuals	High	Moderate	Important
Effectiveness evidence	Mix of different quality RCTs	Moderate	Low	Moderate
Patient's health state utility	Proxy respondents or self-rated from published literature	Moderate	Moderate	Important
Carer's health state utility	Poor published evidence	High	Low	Moderate
% of costs in institutional care funded by NHS/PSS	Poor published evidence plus expert opinion	High	Moderate	Moderate
Costs in pre-institutional state	Inflated 11- to 20-year old estimates from 92 individuals	High	Moderate	Moderate
Cost of treatment monitoring visit	National Schedule Reference Costs	Low	Low	Low
% starting model in institutional care	Published epidemiological study and author assumption	High	Low	Not important
Baseline characteristics	Statistical analysis of 92 individuals	Low	Low	Not important
Cost of drugs	BNF compared to some poor reporting of doses used in RCTs	Moderate	Moderate	Moderate

7.4.2. Moderate to severe Alzheimer's disease: memantine (Decision problem 2a)

7.4.2.1. Probabilistic sensitivity analysis

There is a great deal of uncertainty associated with estimation of the costs and QALYs of treatment with memantine compared to best supportive for people with moderate to severe Alzheimer's disease (see *Figure 85*). The cost-effectiveness acceptability curve (*Figure 86*) indicates that memantine would be the most cost-effective option when

compared to best supportive care, for a willingness to pay per QALY gained greater than £44,000. There is 38% probability that memantine is the most cost-effective treatment at a willingness to pay threshold of £30,000 per QALY. At a willingness to pay of £20,000 per QALY gained, memantine has a probability of 28% of being the most cost-effective treatment option. The ICER from the PSA for memantine compared to best supportive care is £36,900/ QALY.

FIGURE 85 *Base-case cost-effectiveness plane for memantine in people with moderate to severe Alzheimer's disease*

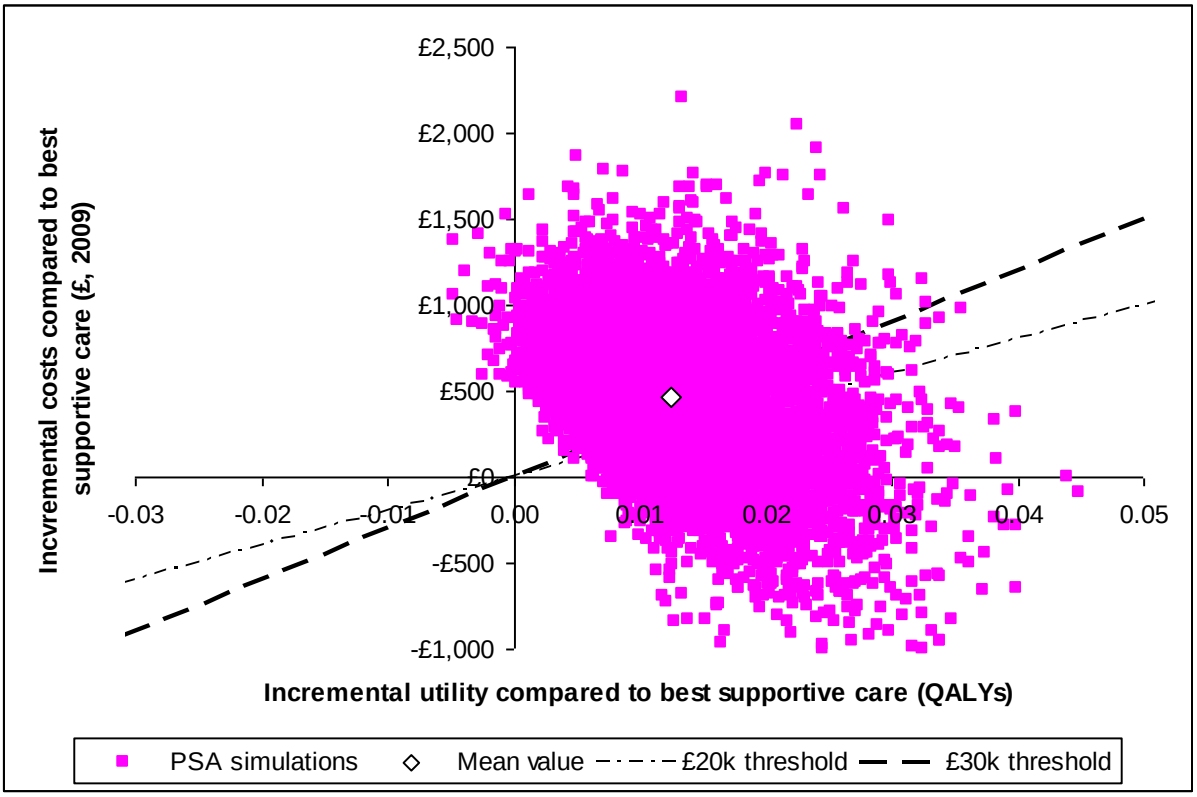
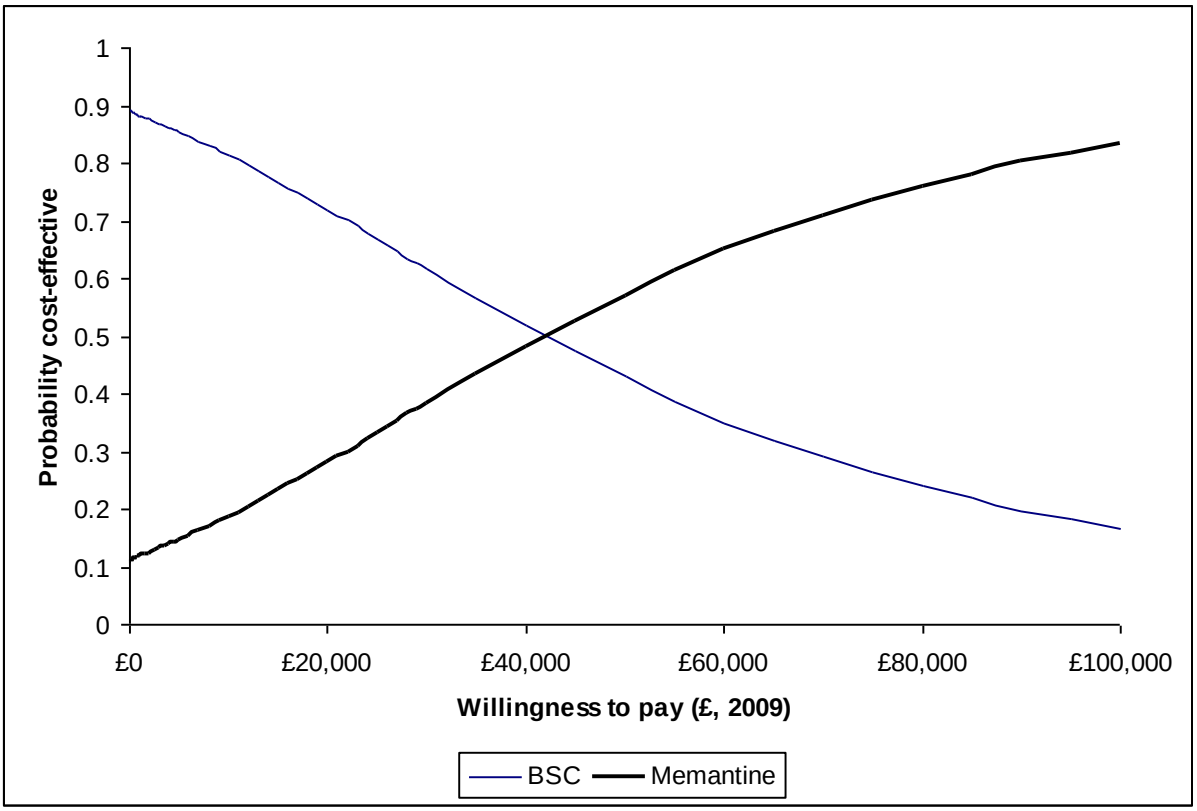


FIGURE 86 *Base-case cost-effectiveness acceptability curve for memantine in people with moderate to severe Alzheimer's disease*



7.4.2.2. Deterministic analysis

The progression of a proportion of the moderate to severe cohort on best supportive care through the model is represented graphically in *Figure 87* as an example of the time spent within each state of the model. *Figure 87* is based on data for individuals with a mean starting age of 78 (representing 50% of the cohort). Forty percent of the cohort are assumed to be in institutional care at the start of the model. The mean overall survival across all three age cohorts for moderate to severe Alzheimer's disease is 42.1 months. The mean time to institutionalization for the best supportive care cohort is 17.7 months, while for the memantine cohort this is 18.5 months, a delay to institutionalization of 0.8 months (about 23 days).

FIGURE 87 *Progression of the best supportive care cohort in the base-case (moderate to severe Alzheimer's disease, age group 2)*

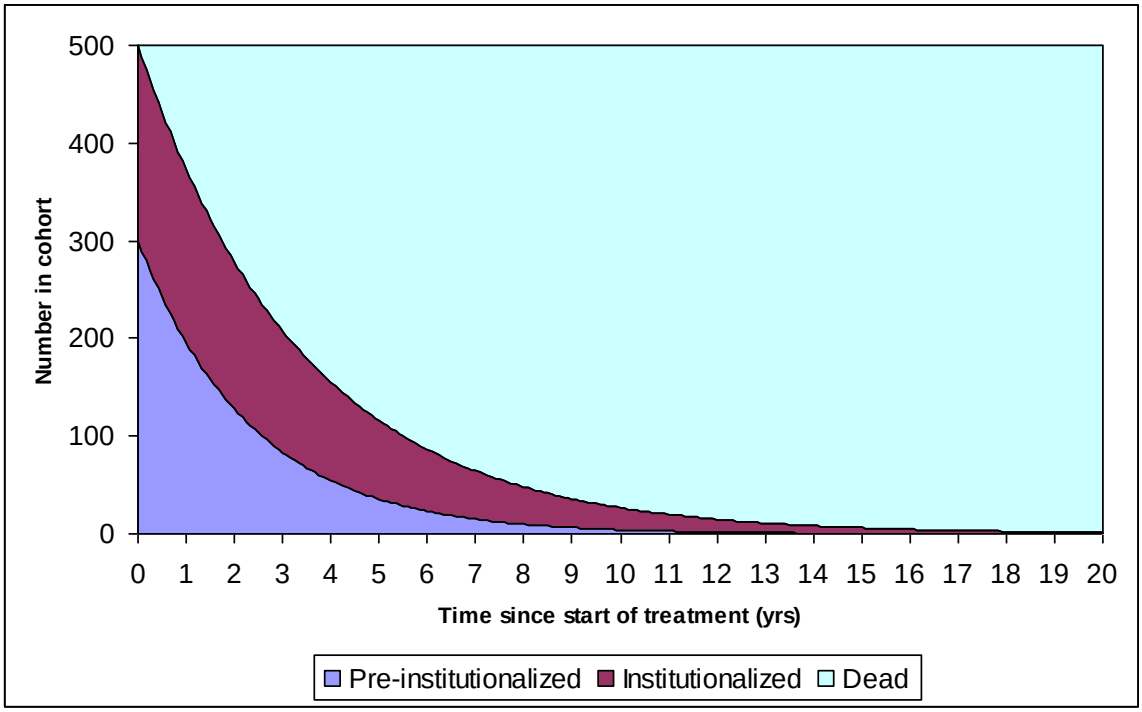


TABLE 122 *Results of the base-case deterministic analysis for people with moderate to severe Alzheimer's disease (MMSE 20-0)*

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[a]
Best supportive care	£78,123	1.215			
Memantine (20mg)	£78,528	1.227	£405	0.013	£32,100

a Cost per QALY rounded to the nearest £100

FIGURE 88 * removed from revised results *****

The base-case cost–utility analysis result for memantine compared to best supportive care for people with moderate to severe Alzheimer's disease (MMSE 20-0) is given in *Table 122*. For a gain of 0.013 QALYs over a patient's lifetime when treated with memantine compared to best supportive care, the extra cost is £405, leading to an estimated cost per QALY of £32,100 from the deterministic base-case analysis. The cost components detailed in *Figure 89* demonstrate that, as with the AChEIs, the cost savings of treatment with memantine occur while the individual is in institutionalized

care. However, the drug, monitoring and incremental pre-institutionalized costs combined are greater than the incremental institutionalisation costs leading to memantine being more costly than best supportive care. The gains in QALYs with memantine over best supportive care (see *Figure 90*) are seen in the pre-institutionalised state, since longer time is spent in this state for memantine-treated individuals.

FIGURE 89 *Base-case cost components for memantine compared to best supportive care for moderate to severe Alzheimer's disease*

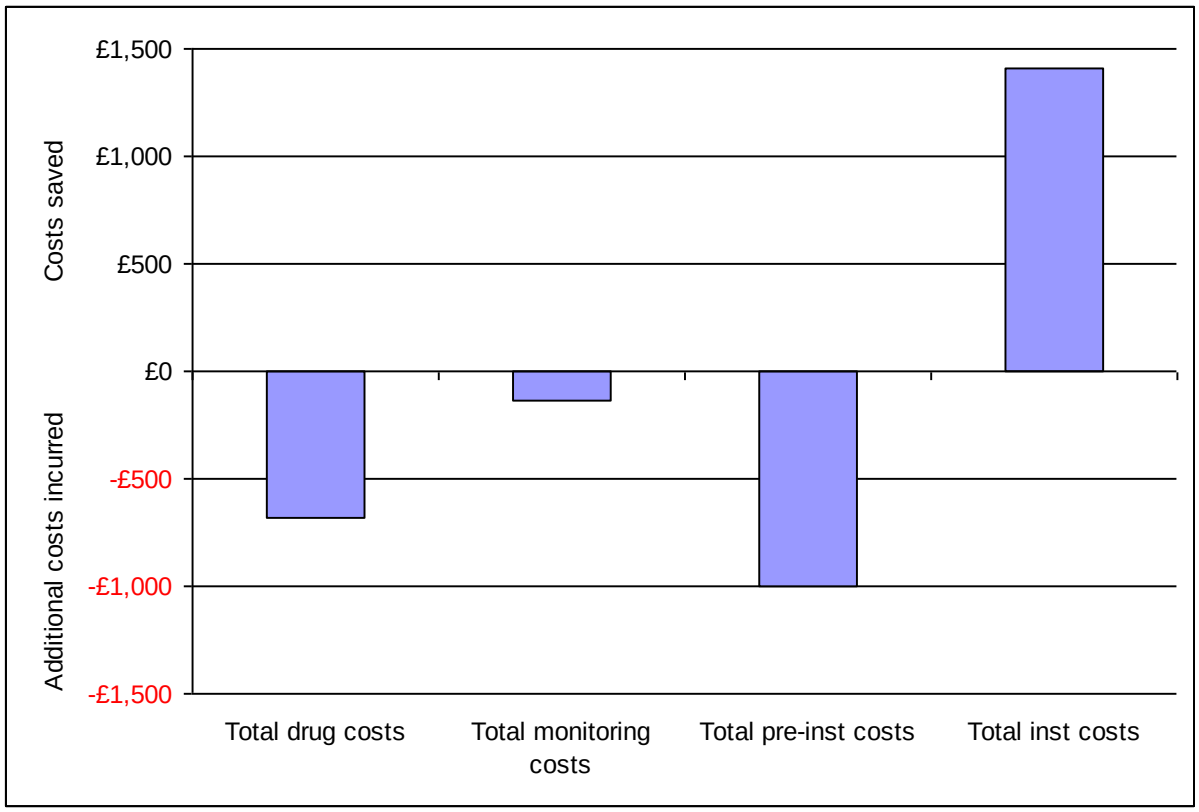
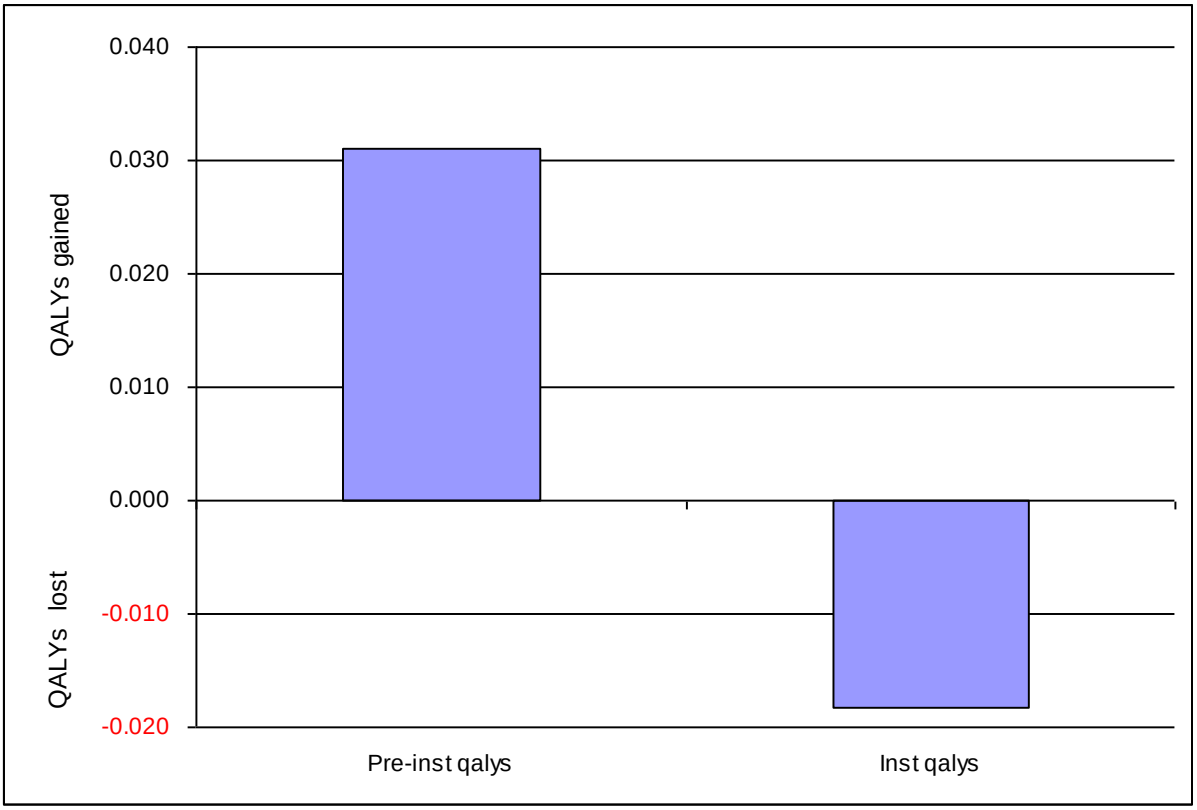


FIGURE 90 *Base-case QALY components of memantine compared to best supportive care for moderate to severe Alzheimer's disease*



7.4.2.3. Summary of probabilistic sensitivity and deterministic analysis

As with the AChEIs, there is a great deal of parameter uncertainty in the cost–utility of memantine compared to best supportive care. However, at a willingness to pay of £30,000/ QALY memantine has a 38% probability of being cost-effective. This increase to >50% with willingness to pay thresholds greater than £44,000/ QALY.

7.4.2.4. One-way sensitivity analysis

Treatment effect on mortality

Assuming a treatment effect on survival leads to a mean estimate of overall survival of 42.1 months for best supportive care and 43.7 months for treatment with memantine: an additional 1.7 months of life. It is estimated that treatment with memantine provides an

additional 0.049 QALYS compared to best supportive care over a patient's lifetime when a treatment effect on survival is assumed. However, these QALY gains cost an additional £3,235 leading to a cost per QALY of £65,600 for memantine compared to best supportive care (see *Table 123*).

TABLE 123 *Incremental cost–utility analysis for moderate to severe Alzheimer's disease when a treatment effect on survival is assumed*

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[a]
Best supportive care	£78,123	1.215			
Memantine (20mg)	£81,358	1.264	£3,235	0.049	£65,619

a Cost per QALY rounded to the nearest £100

The assumption of a treatment effect on survival leads to a larger cost per QALY than the base-case analysis (ICER of £32,100/ QALY). Examination of the cost components in *Figure 91* reveals that there are no cost savings associated with memantine over best supportive care. However, *Figure 92* demonstrates that there are QALY gains in both states, pre-institutionalized and institutionalized. This is in contrast to QALY losses in the institutionalized state in the base-case analysis (refer back to *Figure 90*), since longer time is spent in the institutionalized state when a treatment effect on survival is assumed.

FIGURE 91 *Cost components for memantine compared to best supportive care assuming a treatment effect on survival*

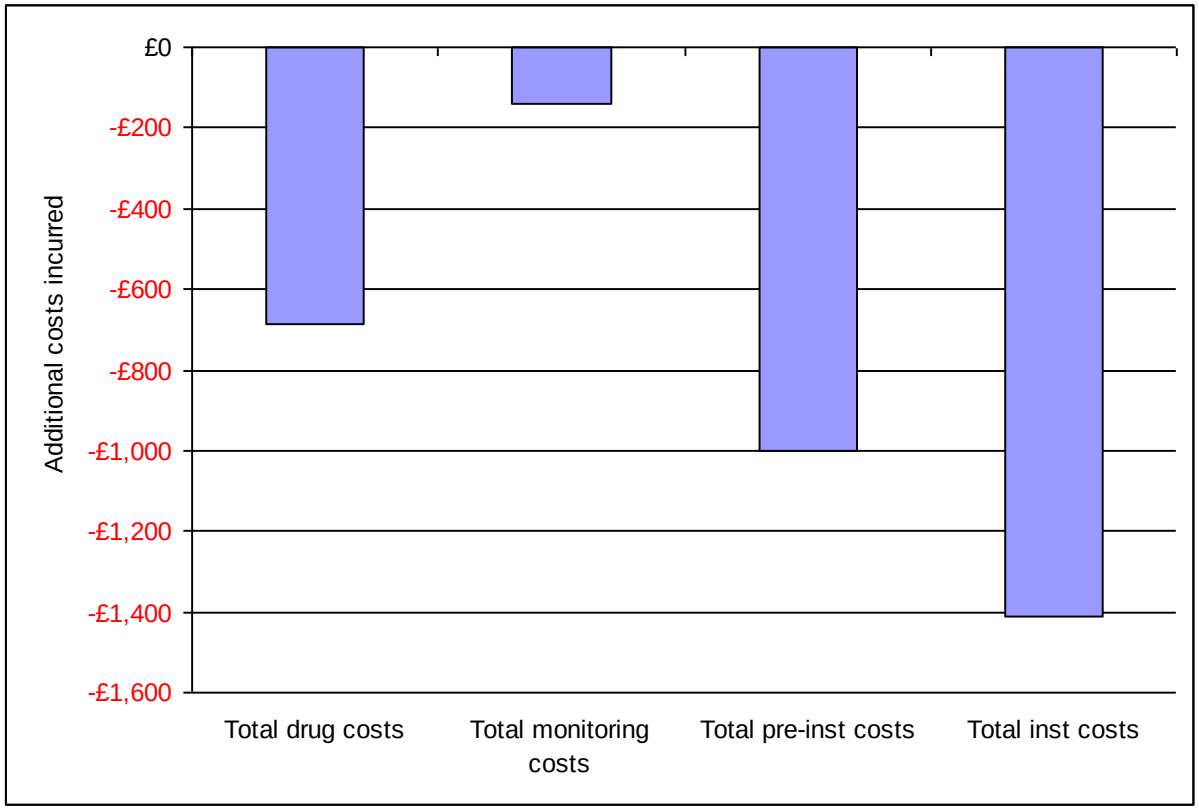
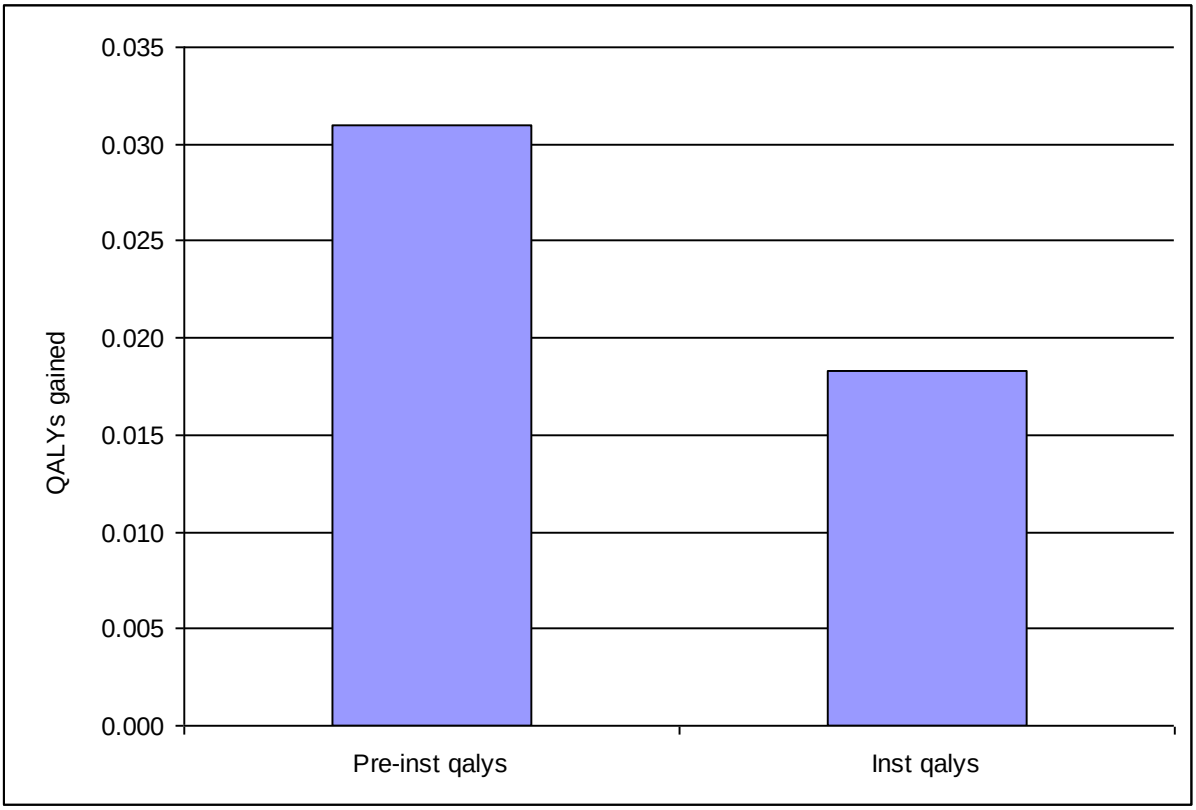


FIGURE 92 *QALY components for memantine compared to best supportive care assuming a treatment effect on survival*



Importance of MMSE effectiveness

As with the AChEIs, an assumption that the only effectiveness observed is on MMSE was made. This lead to an ICER of £79,600/ QALY for memantine compared to best supportive care. Thus, the effectiveness for MMSE is particularly important in the cost-effectiveness of memantine.

TABLE 123a *Incremental cost–utility analysis for moderate to severe Alzheimer's disease when a smaller treatment effect on memantine is assumed*

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[a]
Best supportive care	£78,123	1.215			
Memantine (20mg)	£78,703	1.222	£579	0.007	£79,600

a Cost per QALY rounded to the nearest £100

Assuming no treatment effect on MMSE, only an effect on Barthel, gives a much larger ICER for memantine, £122,200/ QALY. Thus, the impact of MMSE on the resultant ICERs is very important. An additional issue to bear in mind is that the estimate of effectiveness used in this decision model for MMSE in patients treated with memantine is based on just one study, Reisberg et al, as the other available study reporting an effect on MMSE included patients who had been treated with AChEIs as well as memantine. However, inclusion of the data from this study reduces the overall effectiveness of memantine on MMSE from 0.7 to 0.5 (See Figure 53 in the Appendices), and increases the ICER to £45,000 (see *Table 123b*).

TABLE 123b *Incremental cost–utility analysis for moderate to severe Alzheimer's disease when a smaller treatment effect on memantine is assumed*

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[a]
Best supportive care	£78,123	1.215			
Memantine (20mg)	£78,597	1.225	£474	0.011	£45,000

a Cost per QALY rounded to the nearest £100

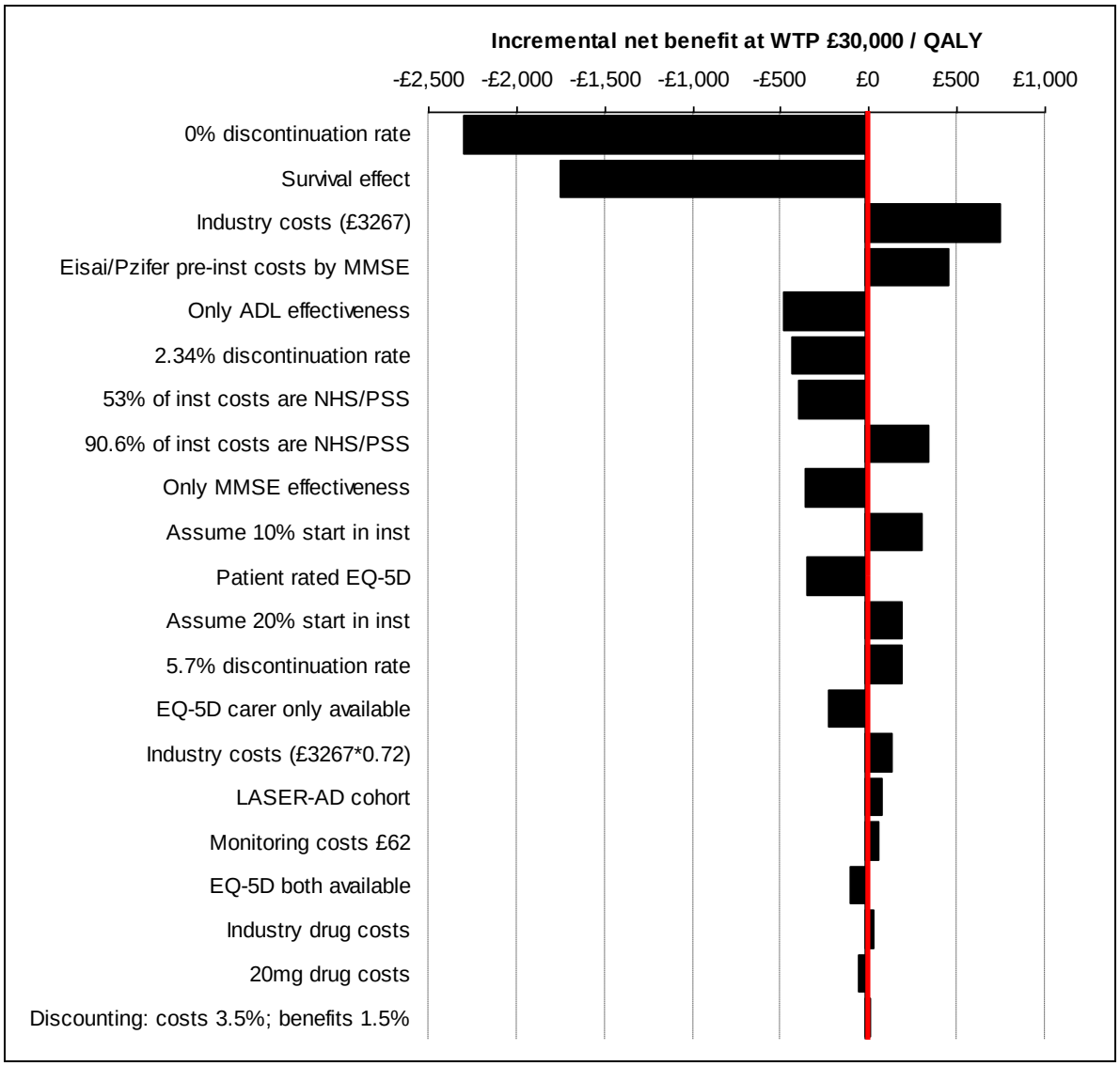
Further one-way sensitivity analyses

As with the cholinesterase inhibitors, a number of one-way sensitivity analyses have been undertaken to assess important assumptions and parameters in the model. The same assumptions as those outlined in *Table 120* above are applied to the memantine dataset, with additional sensitivity analyses outlined in *Table 124*. A tornado plot showing the impact on the cost-effectiveness of changing individual parameters and assumptions is given in *Figure 93*. Assessment of the cost-effectiveness of memantine for different severity cohorts is described and discussed in Section 7.4.3.

TABLE 124 *Additional parameter and assumption changes for deterministic sensitivity analyses for base-case analysis of memantine with moderate to severe Alzheimer's disease*

Parameter/ assumption	Base-case	Deterministic sensitivity analysis	Reference in tornado plots
Drug costs	See Table 113 of main report	Industry cost for memantine; 20mg cost for memantine	Drug cost
% start in institutional care	40%	20%	% start inst

FIGURE 93 *One-way sensitivity analyses for the incremental net benefit of memantine compared to best supportive care*



For the base case, memantine has a negative net benefit (-£26) compared to best supportive care at a willingness to pay of £30,000/ QALY. As with the AChEIs, assuming all patients remain on treatment or assuming a survival effect has the largest impact on the net benefit of memantine compared to best supportive care. Furthermore, the assumption that 2.34% of the total cohort discontinue treatment each month leads to a larger negative net benefit (as estimated in the base case analysis) for memantine compared to best supportive care.

Using proxy EQ-5D utilities or patient EQ-5D utilities from Jonsson et al, rather than the average EQ-5D, VAS and QoL-AD utilities used in the base case, leads to larger negative net benefits associated with memantine treatment.

7.4.2.5. Summary of one-way sensitivity analysis

There are many uncertainties in the PenTAG model for treatment with memantine in people with Alzheimer's disease. Note that although many of the one-way sensitivity analyses shown in *Figure 93* lead to positive net benefits for memantine compared to best supportive care, a number do lead to negative net benefits. These are

- The utility values used
- The estimate of effectiveness on MMSE
- The assumption of the rate of discontinuations
- A possible survival effect from treatment.

The assumption of a survival effect with treatment has one of the largest impacts on the cost-effectiveness findings. As noted above, there is no direct evidence from RCTs that memantine extends survival, however memantine does influence the covariates explaining some of the variation in overall survival.

7.4.3. Exploratory subgroup cost–utility analyses

Exploratory subgroup analyses were undertaken to assess

- Decision problem 1b (in Table 103 of main report): treatment of mild Alzheimer's disease with AChEIs
- Decision problem 1c (in Table 103 of main report): treatment of moderate Alzheimer's disease with AChEIs
- Decision problem 2a (in Table 103 of main report): treatment of moderate Alzheimer's disease with memantine

- Decision problem 3 in (Table 103 of main report):: treatment of moderate Alzheimer's disease with AChEIs or memantine

Caution should be used in the interpretation of these results as the effectiveness estimates used are not restricted to the severities assessed. That is, they have not been derived from trials which have recruited patients of that disease severity or from trial sub-group analyses. Therefore, the main differences between these analyses and the base-case analyses are the baseline population characteristics. Furthermore, the methods mapping Barthel ADL to ADCS-ADL are dependent upon baseline Barthel, therefore differences in Barthel ADL effectiveness can be seen for different severity cohorts, given the same treatment effect on ADCS-ADL. Additionally, the methods used to incorporate the treatment effects into the decision model induce an effect by severity. As severity increases, the MMSE coefficient for delaying time to institutionalisation decreases, while the Barthel coefficient increases. This explains why there are changes in the ranking of the AChEIs for the mild and moderate subgroups. This is because, for instance, donepezil has the greater treatment effect on MMSE whereas galantamine has the greatest treatment effect for ADL. This also explains the finding that treatment with memantine in the moderate to severe cohort has a larger ICER than treatment of a moderate cohort or a severe cohort.

7.4.3.1. Treatment of mild Alzheimer's disease (Decision problem 1b)

The results of an explorative cost–utility analysis of AChEIs for a cohort of people starting the model with mild Alzheimer's disease are presented in *Table 125*. Donepezil dominates all other treatment options, including best supportive care. Furthermore, all drugs dominate best supportive care.

TABLE 125 *Cost–utility results of AChEI use in people with mild Alzheimer's disease*

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[ab]
Donepezil (10mg)	£74,919	1.784			
Galantamine (16-24mg)	£74,922	1.781	Dominated		
Rivastigmine patch (10cm2)	£74,928	1.780	Dominated		
Rivastigmine capsules (9-12mg)	£74,979	1.778	Dominated		
Best supportive care	£75,470	1.750	Dominated		

a Rounded to nearest £100

b Compared to next cheapest, non-dominated technology

7.4.3.2. Treatment of moderate Alzheimer's disease (Decision problems 1c and 3)

The results of an explorative cost–utility analysis of AChEIs or memantine for a cohort of people starting the model with moderate Alzheimer's disease are presented in *Table 126.* In this analysis it is assumed that 10% of the cohort start in institutional care and that treatment with all drugs stops once patients enter institutional care or discontinue for other reasons. Memantine is dominated and so the results presented in *Table 126* address both decision problem 1c and 3. All treatment options are dominated by donepezil. Total costs and QALYs are also smaller for the moderate than the mild group as survival is lower and disease severity is greater. Furthermore, all drugs dominate best supportive care.

TABLE 126 *Cost–utility results of treatment in people with moderate Alzheimer's disease*

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[ab]
Galantamine (16-24mg)	£66,847	1.533			
Rivastigmine patch (10cm2)	£66,853	1.533	Dominated		
Donepezil (10mg)	£66,896	1.535	£49	0.001	£35,300
Rivastigmine	£66,948	1.529	Dominated		
Memantine (15-20mg)	£67,249	1.523	Dominated		
Best supportive care	£67,517	1.500	Dominated		

a Rounded to nearest £100

b Compared to next cheapest, non-dominated technology

7.4.3.3. Treatment of severe Alzheimer's disease (decision problem 2b)

The results of an explorative cost–utility analysis of memantine for a cohort of people starting the model with severe Alzheimer's disease are presented in *Table 127*. The resultant ICER of £26,500 per QALY is slightly lower than that for the cohort of people with moderate to severe Alzheimer's disease. This is because there are lower incremental costs associated with treatment with memantine in the severe cohort than in the moderate to severe cohort, but the QALYs gained are the same (0.013). The lower costs associated with the severe cohort are a factor of the methods used to incorporate a treatment effect which lead to differences in effectiveness depending on severity. The data informing the effectiveness of memantine in this severe cohort is from a trial where the participant population ranged from moderate to severe Alzheimer's disease. Therefore, these results should be treated with caution, as with the results presented above in *Table 125* and *Table 126.*

TABLE 127 *Cost–utility results of memantine in people with severe Alzheimer's disease*

Treatment	Costs	QALYs	Incremental costs	Incremental QALYs	ICER[a]
Best supportive care	£67,988	1.012			
Memantine (15-20mg)	£68,342	1.025	£354	0.013	£26,500

a Rounded to the nearest £100

7.5. Summary of cost-effectiveness findings

FIGURE 94 *** not yet updated ***

The cost–utility results for AChEIs in people with mild to moderate Alzheimer's disease (Section *7.4.1*) and memantine in people with moderate to severe Alzheimer's disease (Section *7.4.2*) indicate a great deal of uncertainty, only some of which is expressed in the PSA. Nevertheless, when considering the AChEIs, there is > 99% probability that best supportive care is *not* the most cost-effective treatment option at a willingness to pay of £30,000 per QALY for the base case analysis. However, this analysis does not account for uncertainty as to whether treatment impacts upon the survival of AD patients. If this is assumed, the AChEIs no longer dominate best supportive care and ICERs for the AChEIs are approximately £37,000.

The probability that memantine is cost-effective in a moderate to severe cohort compared to best supportive care (Section *7.4.2*) at a willingness to pay of £30,000 per QALY is 38% (and 28% at a WTP of £20,000 per QALY). Above a willingness to pay of around £44,000/QALY the probability of memantine being more cost-effective than best supportive care is >50% and this increase as the willingness to pay threshold increases.

Base-case deterministic and probabilistic ICERs for treating mild to moderate and moderate to severe Alzheimer's disease are presented in *Table 128.*

TABLE 128 *Base-case deterministic and probabilistic ICERs for treatment of mild to moderate and moderate to severe Alzheimer's disease*

	Mild to moderate AD		Moderate to severe AD	
	Deterministic	**Probabilistic**	**Deterministic**	**Probabilistic**
Galantamine (16–24mg)	Dominated	Dominated	NA	NA
Rivastigmine patches (10cm^2)			NA	NA
Donepezil (10mg)	£17,900 [a]	£23,500 [a]	NA	NA
Rivastigmine capsules (9-12mg)	Dominated	Dominated	NA	NA
BSC	Dominated	Dominated		
Memantine (15-20mg)	NA	NA	£32,100	£36,900

[a] Compared to galantamine, the next cheapest non-dominated technology

7.6. *** section not yet updated ***

7.7. Comparison of PenTAG model with industry models

7.7.1. Eisai/Pfizer v. PenTAG: donepezil

TABLE 133 *Outputs from PenTAG and Eisai/Pfizer models for donepezil (moderate cohort)*[a]

		Model outputs		Incremental values	
Output	**Treatment**	**Eisai/Pfizer**	**PenTAG**	**Eisai/Pfizer**	**PenTAG**
ICER		Donepezil dominates	Donepezil dominates		
Total costs	Donepezil	£102,086	£66,896		
	No treatment	£103,969	£67,517	-£1,883	-£621
Total QALYs	Donepezil	4.353 (patient + carer)[b]	1.535		
	No treatment	4.245 (patient + carer)[b]	1.500	0.108	0.035
Undiscounted total life years		4.603	3.633		
Undiscounted life years in community	Donepezil	1.852	2.418		
	No treatment	1.685	2.276	0.167	0.142
Undiscounted years in institutional care	Donepezil	2.751	1.215		
	No treatment	2.918	1.357	-0.167	-0.142
Mean treatment duration (years)		1.89	0.67		
Total drug costs		£1,973	£780		
Total monitoring costs	Donepezil	£208	£212		
	No treatment	£0	£0	£208	£212
Total pre-inst costs	Donepezil	£39,201	£40,135		
	No treatment	£37,413	£38,690	£1,788	£1,445
Total inst costs	Donepezil	£60,705	£25,769		
	No treatment	£66,556	£28,827	-£5,851	-£3,058

a All costs and QALYs discounted

b Eisai/Pfizer base-case includes carer QALYs, therefore total QALYs = patient QALYs + carer QALYs. Donepezil total QALYs = 1.332 + 3.021; No treatment total QALYS = 1.234 + 3.011

TABLE 134 *Outputs from PenTAG and Eisai/Pfizer models for donepezil (mild cohort)*[a]

		Model outputs		Incremental values	
Output	**Treatment**	**Eisai/Pfizer**	**PenTAG**	**Eisai/Pfizer**	**PenTAG**
ICER		Donepezil dominates	Donepezil dominates		
Total costs	Donepezil	£79,023	£74,919		
	No treatment	£82,409	£75,470	-£3,386	-£552
Total QALYs	Donepezil	4.267 (patient + carer)[b]	1.784		
	No treatment	4.120 (patient + carer)[b]	1.750	0.147	0.034
Undiscounted total life years		4.110	4.243		
Undiscounted life years in community	Donepezil	2.161	2.777		
	No treatment	1.926	2.642	0.235	0.135
Undiscounted years in institutional care	Donepezil	1.949	1.466		
	No treatment	2.184	1.600	-0.235	-0.135
Mean treatment duration (years)		2.23	0.69		
Total drug costs		£2,281	£807		
Total monitoring costs	Donepezil	£240	£220		
	No treatment	£0	£0	£240	£220
Total pre-inst costs	Donepezil	£37,938	£43,427		
	No treatment	£37,128	£42,160	£810	£1,267
Total inst costs	Donepezil	£38,564	£30,465		
	No treatment	£45,282	£33,310	-£6,718	-£2,845

a All costs and QALYs discounted

b Eisai/Pfizer base-case includes carer QALYs, therefore total QALYs = patient QALYs + carer QALYs. Donepezil total QALYs = 1.502 + 2.765; No treatment total QALYS = 1.370 + 2.750

7.7.2. Lundbeck v. PenTAG: memantine

TABLE 135 *** removed from revised results ***

TABLE 136 *Comparison of outputs from PenTAG (moderate to severe cohort) and Lundbeck (moderate cohort) models for memantine compared to best supportive care[a]*

		Model outputs		Incremental values	
Output	**Treatment**	**Lundbeck**	**PenTAG**	**Lundbeck**	**PenTAG**
ICER		Memantine dominates	£32,084		
Total costs	Memantine	£93,076	£78,528		
	No treatment	£94,787	£78,123	-£1,711	£405
Total QALYs	Memantine	1.533	1.227		
	No treatment	1.502	1.215	0.031	0.013
Total pre-inst/FTC QALYs	Memantine	0.870	0.665		
	No treatment	0.813	0.634	0.057	0.031
Total inst/FTC QALYs	Memantine	0.661	0.562		
	No treatment	0.690	0.581	-0.029	-0.018
Expected overall survival (years)		3.7	3.5		
Expected time to FTC/ institutional care (years)	Memantine	1.73	1.538		
	No treatment	1.65	1.473	0.08	0.065
Time in FTC/institutional care	Memantine	1.97	1.966		
	No treatment	2.05	2.032	-0.08	-0.065
Mean treatment duration		1.73	0.79		
Total drug costs		£1,348	£678		
Total monitoring costs	Memantine	£106	£140		
	No treatment	£0	£0	£106	£140
Total pre-inst costs	Memantine	£16,642	£34,413		
	No treatment	£14,324	£33,414	£2,318	£999
Total inst costs	Memantine	£77,133	£43,298		
	No treatment	£80,464	£44,710	-£3,331	-£1,412

a All costs and QALYs discounted

Appendix: One-way sensitivity analyses for mild to moderate cohort

FIGURE A *Rivastigmine capsules compared to best supportive care*

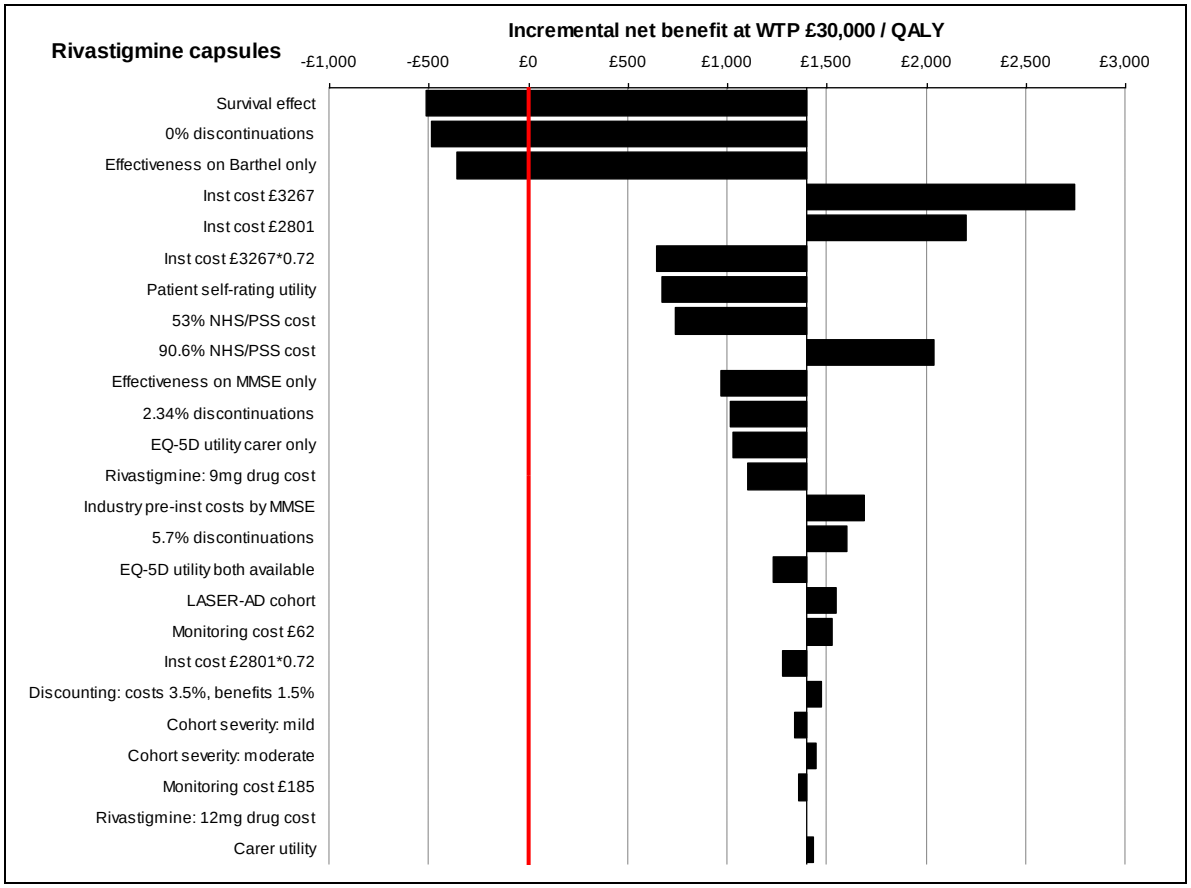


FIGURE B *Rivastigmine patches compared to best supportive care*

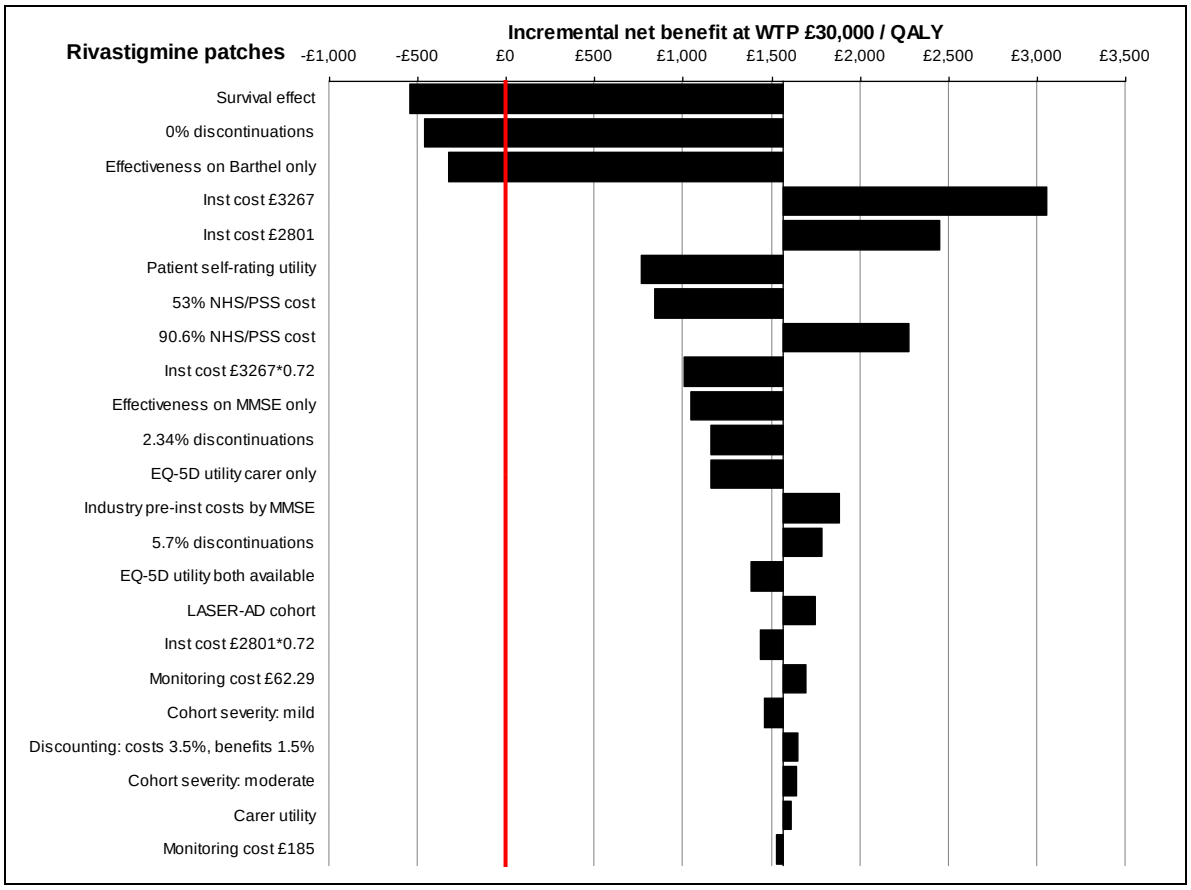


FIGURE C *Galantamine compared to best supportive care*