RANIBIZUMAB AND PEGAPTANIB FOR AGE-RELATED MACULAR DEGENERATION

REPORT BY THE NICE DECISION SUPPORT UNIT.

24 September 2007

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CHAPTER 1: THE COST-EFFECTIVENESS OF PEGAPTANIB FOR AGE-RELATED MACULAR DEGENERATION: RE-ANALYSIS OF THE PFIZER MODEL

1. Background

Following the Appraisal Committee meeting of 8th of May 2007, a consultation document with preliminary recommendations was issued. Ranibizumab was recommended for the treatment of wet AMD for people with a confirmed diagnosis of predominantly classic lesions, only for the better-seeing of two affected eyes. Pegaptanib was not recommended for treatment of wet AMD. One of the issues raised during consultation was that pegaptanib may be more clinically and cost effective when used to treat a subgroup of patients with early stage disease. In the submission by Pfizer, the manufacturer of pegaptanib, a range of incremental cost-effectiveness ratios (ICERs) was presented, for groups of patients stratified by initial levels visual acuity. The Pfizer model is based on patient-level data and is structurally different to the Assessment Group (AG) model. The Decision Support Unit (DSU) were therefore requested to produce cost-effectiveness estimates from the Pfizer model using alternative parameter assumptions in order to enable consideration of the subgroups by initial visual acuity, but with a range of parameter assumptions consistent with those applied in the original AG model. In addition, additional analyses based on the Pfizer model were requested to match the assumptions being used in the revised analysis being undertaken by the AG.

The alternative parameter assumptions covered 4 main areas:

1. The costs of administration
2. Health utilities
3. The disease modifying effect of pegaptanib
4. The costs of blindness

2. Methods

The following work was undertaken by the DSU to address each of these respective areas:

The costs of administration

- Adjusting the costs of AMD treatment in the Pfizer model in line with changes in unit costs and resource use the Assessment Group applied in the original Assessment Report. These included:
  - OCT costs (£50.86) added to each visit
  - Optometrist assessment (£58.76) added to each visit
  - Fluoroscein angiography costs (£184.08) added every 6 months
  - Costs of injection procedure altered from extended outpatient attendance (£90.20) to day case (£395).

- Adjusting the costs of AMD treatment in the Pfizer model in line with changes in unit costs and resource use based on the Royal College of Ophthalmologists costing guidelines published in July 2007.[1] These included:
  - Replacing resource use and unit cost assumptions for pegaptanib with the (i) full assessment and treatment costs and (ii) treatment (injection only) costs reported in the Royal College costing guidelines
  - Full assessment and treatment costs were applied at the 1st attendance. For subsequent attendances the costs were based on full assessment and treatment costs and treatment (injection only) at alternate attendances (i.e. equivalent to a full assessment every 3 months).

Health utilities

- Adjusting the utility estimates in the Pfizer model based on alternative estimates reported in the Novartis submission supporting ranibizumab (CIC data) referred to as the "Brazier" utility values and estimates reported in the publication by Espallargues et al (2005).

[1] Commissioning contemporary AMD services: A guide for commissioners and clinicians (July 2007)

The disease modifying effect of pegaptanib

- Examining the impact of alternative assumptions related to the potential disease modifying effect of pegaptanib. These included:
    - (i) Lifetime effect (based on approach used in the submission by Pfizer), (ii) no continuing effect after cessation of treatment and (iii) a disease modifying effect lasting 1-year after cessation of treatment (i.e. patients reverted back to the prognosis of sham injections at year 3 in the model)

The costs of blindness

- Examining the impact of alternative assumptions related to the costs of blindness based on the additional work undertaken by the AG.

The cost-effectiveness of pegaptanib was assessed in different subgroups corresponding to the base-case population presented by Pfizer (Scenario A in the manufacturers submission with a starting visual acuity between 6/12 to 6/95) and the subgroups reported in the original Assessment Group report (Subgroup 1: 6/12 to >6/24, Subgroup 2: 6/24 to >6/60 and Subgroup 3: 6/60 to >3/60). Where feasible uncertainty around the ICER estimates was explored using probabilistic sensitivity analysis (all areas except the costs of blindness). Due to the number of potential assumptions considered related to the costs of blindness, estimates of the ICER were based on deterministic analyses only.

A total of 13 separate scenarios were considered covering these areas. The alternative assumptions employed in each individual scenario are reported in Table 1. Table 2 provides a summary of the respective ICERs from each scenario undertaken using probabilistic analysis. Full details of the probabilistic results including the probability the pegaptanib is cost-effective at alternative threshold values for the ICER (£20,000, £30,000 and £40,000 per additional QALY) are reported in full in Appendix 1. The results of the scenarios run deterministically related to the costs of blindness are reported in Table 3.

3. Results

The costs of administration

Scenarios 1-3 report the results of the ICER based on the alternative assumptions related to the costs of drug administration. Scenario 1 provides the results using the manufacturer's original costing assumptions, while Scenarios 2 and 3 are based on the costing assumptions based on the Assessment Group report and the Royal College of Ophthalmologists costs respectively. In summary, estimates of the ICER were markedly different between the manufacturer's assumptions and those employed using Scenarios 2 and 3. Estimates of the ICER using the manufacturer's estimates were below £30,000 per QALY in the base-case population (6/12 to 6/95) and Subgroups 1 (6/12 to >6/24) and 2 (6/24 to >6/60). There was a marked difference in the estimates of the ICER for the worst visual acuity group (Subgroup 3, ICER = £62,518). In contrast, estimates of the ICER in Scenarios 2 and 3 were only below £30,000 per QALY for Subgroup 1. The results using Scenarios 2 and 3 across each of the subgroups considered were broadly consistent with each other.

Given the disparity between the manufacturer's original estimates for administration costs and those employed in the Assessment Group model and by the Royal College of Ophthalmologists, subsequent scenarios were based on the costing assumptions considered by the latter 2 sources.

Health utilities

Scenarios 4 to 7 are based on alternative estimates reported in the Novartis submission supporting ranibizumab (CIC data) referred to as the "Brazier" values (Scenarios 4-5) and estimates reported in the publication by Espallargues et al (2005) (Scenarios 6-7). In summary, estimates of the ICER using the Brazier values were slightly less favourable than the estimates based on the original utility values (Brown et al 2000). In common with the results based on the original utility estimates, the ICERs based on the Brazier utility values were only below £30,000 per QALY for Subgroup 1. This was true regardless of whether the Assessment Group costs or the Royal College costs were used as the basis for costing drug administration.

In contrast, the estimates based on Espallargues et al were markedly higher, such that estimates of the ICER exceeded £50,000 per additional QALY in each of the subgroups considered.

The disease modifying effect of pegaptanib

In their original submission Pfizer used separate transition probabilities between the visual acuity states for patients post-pegaptanib (i.e. reflecting subsequent prognosis after cessation of treatment) and for those who initially received a sham procedure. This approach was used to account for the potential disease modifying effect of pegaptanib. The analysis presented by Pfizer continued to apply separate transition probabilities for the full time horizon (10-years), in effect assuming that the disease modifying effect remains for the remainder of the patient's lifetime. However, this analysis was based on only limited follow-up data and hence concerns were raised regarding the duration (if any) of the potential disease modifying effect. A series of alternative assumptions (Scenarios 8-11) were explored to examine the impact on the ICER related to the potential disease modifying effect of pegaptanib. These included:

- (i) assuming no disease modifying effect after cessation of treatment and (ii) a disease modifying effect lasting 1-year after cessation of treatment (i.e. patients reverted back to the prognosis of sham injections at year 3 in the model)

In the absence of a disease modifying effect after cessation of treatment, the ICERs increased to over £40,000 per QALY in each of the separate subgroups. Assuming that the disease modifying effect was maintained for an additional year only resulted in less favourable ICER estimates, relative to the base-case assumption (lifetime effect), although estimates of the ICER in Subgroup 1 remained below £30,000 per QALY.

The costs of blindness

A range of alternative assumptions related to the costs of blindness were examined based on additional work undertaken by the AG. Due to the number of potential scenarios considered, these analyses were based on deterministic estimates from the model. The majority of analyses made only minimal difference to the ICER estimates

based on the original assumption employed in relation to the costs of blindness. The variable which had the greatest impact on the ICER was the assumption related to the proportion of patients receiving community care services (varied between 17% and 25% compared to 6% in the base-case analysis). Due to the minimal impact of the other assumptions on the ICER, only the assumption related to the proportion of patients receiving community care services was undertaken using both the Assessment Group and the Royal College administration costs. All other analyses were only undertaken using the Assessment Group estimates as the basis for administration costs.

As previously stated, each of the individual assumptions made only a minor impact to the ICER results. As such, ICER estimates below £30,000 per QALY were only identified in Subgroup 1. When the proportion of patients receiving community care services was increased to 25%, the ICER estimates for Subgroup 1 were below £20,000 per QALY.

4. Discussion

The ICER estimates were demonstrated to be sensitive to a number of potential issues. Clearly the costs of administration are central to the cost-effectiveness results. The original estimates applied in the manufacturer's submission result in markedly more favourable ICER estimates compared to estimates provided by the AG and the Royal College of Ophthalmologists. Estimates of the ICER of pegaptanib based on the latter two sources were similar, although slightly more favourable ICERs were derived based on the original estimates provided by the AG. In contrast to the ICER estimates based on the manufacturer's assumptions related to the costs of administration, re-analysis of the Pfizer model using both the AG and Royal College costs identified that the ICER of pegaptanib was only below £30,000 per QALY in the subgroup with the best starting visual acuity (Subgroup 1: 6/12 to >6/24).

The ICER results were also demonstrated to be sensitive to the health state utility values applied to the separate visual acuity groups. Estimates using the 'Brazier' utility values resulted in slightly less favourable ICERs compared to the base-case

analysis. However, the ICER of pegaptanib in Subgroup 1 remained below £30,000 per QALY. In contrast, the ICER estimates employing the utility values reported in the study by Espallargues et al (2005) markedly increased the ICER estimates, such that the ICERs exceeded £50,000 per QALY in all subgroups considered. However, it is worth noting that the results based on the Espallargues study should be treated with some caution. In particular, the visual acuity categories reported in the Espallargues study do not appear to discriminate well between the subgroups being considered here (e.g. one of the subgroups covers patients <20/80 to 20/400. This covers about 60% of the patients in the Pfizer trials). Given the broad groupings reported, the study has important limitations for examining the impact of utility differences between the subgroups of interest. Indeed, the utility values from the Espallargues study only report a 0.02 utility difference between any of the states that patients are likely to be maintained on treatment for in the Pfizer model. This contrasts markedly with the estimates derived from the other utility studies considered. Hence, it is doubtful that the results from the Espallargues study are appropriate to represent the incremental difference in utility values between the alternative visual acuity groups considered. What they are potentially helpful for is in questioning the absolute utility values applied in the model as opposed to providing reliable estimates which discriminate well between the different acuity states. Clearly the absolute utility values from the Espallargues study are a lot lower than the other estimates. However, it is less clear whether the absolute utility estimates are central to the cost-effectiveness estimates since the ICER results will be largely driven by the incremental difference in utilities between the health states as opposed to the absolute utility values.

The assumption related to the potential disease modifying effect of pegaptanib is also central to the cost-effectiveness of pegaptanib. Assuming that there is no continuing effect of pegaptanib once treatment ceases results in ICERs in excess of £40,000 per QALY in all subgroups. However, if it assumed that pegaptanib has a disease modifying effect then the estimates of the ICER are less than £30,000 per QALY in Subgroup 1, regardless of whether this effect lasts only one additional year or for the remaining lifetime of the patient. Hence, the cost-effectiveness of pegaptanib appears to depend upon the existence of a disease modifying effect as opposed to the exact duration of this effect.

The ICER estimates based on the alternative scenarios considered relating to the costs of blindness outlined by the AG demonstrate that these appear to have only a minor impact on the cost-effectiveness results using the Pfizer model.

In addition it is evident that the starting visual acuity is a key factor in relation to the cost-effectiveness of pegaptanib. With the exception of the scenarios based on the assumption of (i) no disease modifying effect and (ii) the Espallargues et al (2005) utility values, the ICER of pegaptanib was consistently lower than £30,000 in the subgroup with the best starting visual acuity (6/12 to >6/24). In every scenario considered, based on using either the AG or the Royal College estimates for the costs of pegaptanib administration, ICER estimates were consistently above £40,000 per QALY in the two subgroups with a lower starting visual acuity (6/24 to >6/60 and 6/60 to >3/60). However, given that the ICER estimates vary markedly between Subgroup 1 and Subgroup 2, this raises an important question as to whether there are patients within Subgroup 2 for whom the ICER is less than £30,000 per QALY.

An additional set of analyses was therefore examined by the DSU in relation to the cost-effectiveness of pegaptanib in different visual acuity levels within Subgroup 2. This approach is helpful since the results could be used to establish appropriate subgroups based on cost-effectiveness considerations. The approach used was to examine the cost-effectiveness of pegaptanib in this subgroup, starting with patients with the highest visual acuity in Subgroup 2 (i.e. patient with exactly 6/24 vision) and continuing to examine successively lower acuity levels until the ICER exceeded £30,000 per QALY. The ICER results for patients with 6/24 vision are reported in Table 4 using both the AG and Royal College estimates for drug administration costs. The results demonstrate the ICER estimates for this subgroup exceed £30,000 per QALY. Consequently no additional visual acuity levels were considered within Subgroup 2 (on the basis that the ICER estimates would get progressively less favourable). In conclusion, it appears that of the different subgroups considered, the ICER for pegaptanib is only less than £30,000 per QALY in patients with a starting visual acuity of 6/12 to >6/24.

References

Brown GC et al (2000) Utility values and age-related macular degeneration. Archives of Ophthalmology. 118(1): 47-51

Espallargues M et al (2005). The impact of age-related macular degeneration on health status utility values. Investigative Opthalmology and Visual Science. 46(11): 4016-4023.

Table 1: Summary of alternative assumptions employed in each scenario

Scenario	Drug/Admin Costs	Utilities	Disease Modifying Effect	Costs of blindness
Issue 1: Costs of administration				
1	Manufacturer	Brown (TTO)	Lifetime	Manufacturer
2	Assessment Group	Brown (TTO)	Lifetime	Manufacturer
3	Royal College of Opthalmol.	Brown (TTO)	Lifetime	Manufacturer
Issue 2: Health utility estimates				
4	Assessment Group	Brazier (TTO)	Lifetime	Manufacturer
5	Royal College of Opthalmol.	Brazier (TTO)	Lifetime	Manufacturer
6	Assessment Group	Espallargues (HUI-3)	Lifetime	Manufacturer
7	Royal College of Opthalmol.	Espallargues (HUI-3)	Lifetime	Manufacturer
Issue 3: Disease modifying effect				
8	Assessment Group	Brown (TTO)	None	Manufacturer
9	Royal College of Opthalmol.	Brown (TTO)	None	Manufacturer
10	Assessment Group	Brown (TTO)	1-year (effect stopped at Year 3)	Manufacturer
11	Royal College of Opthalmol.	Brown (TTO)	1-year (effect stopped at Year 3)	Manufacturer
Issue 4: Costs of blindness				
12	Assessment Group	Brown (TTO)	Lifetime	Various
13	Royal College of Opthalmol.	Brown (TTO)	Lifetime	Various

Table 2: Summary of cost-effectiveness results for alternative scenarios (probabilistic estimates)

	Scenario	ICER estimates (Incremental cost per QALY)			
		Base-Case* (6/12-6/95)	**Subgroup 1 (6/12 to >6/24)**	**Subgroup 2 (6/24 to >6/60)**	**Subgroup 3 (6/60 to >3/60)**
	Administration costs				
1	Manufacturer's costs	£16,105	£8,829	£21,900	£62,518
2	Assessment Group costs	£35,614	£23,104	£46,588	£110,223
3	Royal College costs	£37,604	£24,036	£46,897	£109,694
	Brazier utility estimates				
4	Assessment Group costs	£38,434	£26,329	£46,302	£120,295
5	Royal College costs	£39,441	£27,159	£47,049	£123,850
	Espallargues utility estimates				
6	Assessment Group costs	£76,709	£55,541	£87,872	£235,969
7	Royal College costs	£80,188	£58,377	£90,027	£227,294
	No disease modifying effect*				
8	Assessment Group costs	£61,819	£44,894	£73,546	£138,883
9	Royal College costs	£62,213	£45,767	£75,984	£139,527
	Disease modifying effect until year 3*				
10	Assessment Group costs	£38,735	£25,583	£49,156	£112,583
11	Royal College costs	£39,015	£26,214	£48,737	£109,757

*Manufacturers base-case scenario (Scenario A)

** Assuming manufacturer's utility estimates

Table 3: Alternative assumptions related to the costs of blindness (deterministic estimates)

Scenario	Base case value	Value in sensitivity analysis	ICER Estimates			
			Base-Case (6/12-6/95)	**Subgroup 1 (6/12 to >6/24)**	**Subgroup 2 (6/24 to >6/60)**	**Subgroup 3 (6/60 to >3/60)**
Scenario 12: Assessment Group Costs						
Proportion registering blind who were previously registered partially sighted	0.00	0.45	£35,296	£22,723	£45,937	£114,816
Proportion having annual re-assessment by OT	0.00	1.00	£35,185	£22,622	£45,814	£115,685
Proportion having annual re-assessment by OT and repeat low vision rehabilitation each year	0.00 0.00	1.00 0.50	£34,850	£22,294	£45,450	£114,483
Proportion having annual re-assessment by OT and new low vision aids each year	0.00 0.00	1.00 0.50	£34,976	£22,417	£45,587	£114,559
Uptake of low vision rehabilitation	0.11	0.44	£35,285	£22,708	£45,928	£114,848
Uptake of low vision aids	0.33	0.47	£35,306	£22,737	£45,947	£114,785
Proportion receiving community care services	0.06	0.25	£32,107	£19,608	£42,475	£112,829
Proportion receiving community care services (home care)	0.06	0.17	£33,457	£20,930	£43,939	£113,644
Scenario 13: Royal College Costs – only reported for community care due to minimal impact on ICER due to other elements						
Proportion receiving community care services	0.06	0.25	£32,353	£19,803	£42,792	£113,169
Proportion receiving community care services (home care)	0.06	0.17	£33,703	£21,125	£44,257	£113,984

Table 4: Subgroup analysis of patients with starting visual acuity of 6/24

Subgroup = 6/24 (Assessment Group costs)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£25,639	3.3975	£39,444	0.03	0.18	0.525
Sham	£14,726	3.1208	NA	0.97	0.82	0.475

Subgroup = 6/24 (Royal College costs)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£24,898	3.4058	£40,613	0.03	0.17	0.49
Sham	£13,547	3.1263	NA	0.97	0.83	0.51

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APPENDIX 1: DETAILED RESULTS OF PROBABILISTIC ANALYSES

Scenario 1 – Costing assumptions based on Pfizer submission

Base Case – Scenario A (6/12 to 6/95)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£20,782	3.3189	£16,105	0.77	0.99	1
Sham	£15,999	3.0219	NA	0.23	0.01	0

Subgroup 1 (6/12 to >6/24)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£17,303	3.7946	£8,829	0.99	1	1
Sham	£13,525	3.3668	NA	0.01	0	0

Subgroup 2 (6/24 to >6/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£21,662	3.1495	£21,900	0.38	0.88	0.99
Sham	£16,315	2.9053	NA	0.62	0.12	0.01

Subgroup 3 (6/60 to >3/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£27,259	2.5604	£62,518	0	0.01	0.08
Sham	£21,623	2.4702	NA	1	0.99	0.92

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Scenario 2 – Costing assumptions based on Assessment Group report (inc costs for OCT and optometrist at each visit, flouroscein angiography every 6 months, day case costs for injection procedure)

Base Case – Scenario A (6/12 to 6/95)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£26,529	3.3202	£35,614	0.04	0.27	0.68
Sham	£15,995	3.0244	NA	0.96	0.73	0.32

Subgroup 1 (6/12 to >6/24)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£23,402	3.7897	£23,104	0.32	0.83	0.98
Sham	£13,542	3.3630	NA	0.68	0.17	0.02

Subgroup 2 (6/24 to >6/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£27,628	3.1460	£46,588	0.01	0.07	0.29
Sham	£16,324	2.9034	NA	0.99	0.93	0.71

Subgroup 3 (6/60 to >3/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£31,786	2.5717	£110,223	0	0	0
Sham	£21,650	2.4798	NA	1	1	1

Scenario 3 – Costing assumptions based on Royal College of Opthalmologists Guide (Assuming Full assessment & treatment every 3 months)

Base Case – Scenario A (6/12 to 6/95)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£25,842	3.3228	£37,604	0.01	0.21	0.60
Sham	£14,724	3.0271	NA	0.99	0.79	0.40

Subgroup 1 (6/12 to >6/24)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£22,844	3.8045	£24,036	0.26	0.80	0.97
Sham	£12,470	3.3729	NA	0.74	0.20	0.03

Subgroup 2 (6/24 to >6/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£26,541	3.1443	£46,897	0	0.05	0.26
Sham	£15,026	2.8987	NA	1	0.95	0.74

Subgroup 3 (6/60 to >3/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£30,012	2.5684	£109,694	0	0	0
Sham	£19,880	2.4760	NA	1	1	1

Scenario 4 – Costing assumptions based on Assessment Group report & Brazier utility estimates

Base Case – Scenario A (6/12 to 6/95)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£26,512	3.7555	£38,434	0.02	0.22	0.57
Sham	£16,001	3.4821	NA	0.98	0.78	0.43

Subgroup 1 (6/12 to >6/24)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£23,549	4.1021	£26,329	0.19	0.68	0.93
Sham	£13,533	3.7217	NA	0.81	0.32	0.07

Subgroup 2 (6/24 to >6/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£27,605	3.6596	£46,302	0.01	0.1	0.31
Sham	£16,324	3.4160	NA	0.99	0.9	0.69

Subgroup 3 (6/60 to >3/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£31,707	3.1203	£120,295	0	0	0
Sham	£21,641	3.0366	NA	1	1	1

Scenario 5 – Costing assumptions based on Royal College of Opthalmologists Guide & Brazier utility estimates

Base Case – Scenario A (6/12 to 6/95)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£25,555	3.7587	£39,441	0.03	0.17	0.51
Sham	£14,732	3.4843	NA	0.97	0.83	0.49

Subgroup 1 (6/12 to >6/24)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£22,846	4.0967	£27,159	0.19	0.62	0.91
Sham	£12,476	3.7149	NA	0.81	0.38	0.09

Subgroup 2 (6/24 to >6/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£26,547	3.6600	£47,049	0.01	0.07	0.28
Sham	£15,023	3.4150	NA	0.99	0.93	0.72

Subgroup 3 (6/60 to >3/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	3.1299	3.1299	£123,850	0	0	0
Sham	3.0478	3.0478	NA	1	1	1

Scenario 6 – Costing assumptions based on Assessment Group report & Espallargues utility estimates

Base Case – Scenario A (6/12 to 6/95)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£26,474	2.0055	£76,709	0.01	0.02	0.08
Sham	£16,002	1.8690	NA	0.99	0.98	0.92

Subgroup 1 (6/12 to >6/24)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£23,509	2.1528	£55,541	0.03	0.11	0.26
Sham	£13,543	1.9733	NA	0.97	0.89	0.73

Subgroup 2 (6/24 to >6/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£27,456	1.9549	£87,872	0	0.01	0.04
Sham	£16,322	1.8282	NA	1	0.99	0.96

Subgroup 3 (6/60 to >3/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£31,835	1.7006	£235,969	0	0	0
Sham	£21,630	1.6573	NA	1	1	1

Scenario 7 – Costing assumptions based on Royal College of Opthalmologists Guide & Espallargues utility estimates

Base Case – Scenario A (6/12 to 6/95)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£25,705	1.9923	£80,188	0	0.02	0.07
Sham	£14,729	1.8554	NA	1	0.98	0.93

Subgroup 1 (6/12 to >6/24)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£22,976	2.1497	£58,377	0.01	0.07	0.23
Sham	£12,484	1.9700	NA	0.99	0.93	0.77

Subgroup 2 (6/24 to >6/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£26,613	1.9537	£90,027	0	0.01	0.04
Sham	£15,026	1.8250	NA	1	0.99	0.96

Subgroup 3 (6/60 to >3/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£29,995	1.7120	£227,294	0	0	0
Sham	£19,876	1.6674	NA	1	1	1

Scenario 8 – Costing assumptions based on Assessment Group report – no disease modifying effect assumed

Base Case – Scenario A (6/12 to 6/95)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£27,823	3.2156	£61,819	0	0.01	0.05
Sham	£15,996	3.0243	NA	1	0.99	0.95

Subgroup 1 (6/12 to >6/24)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£25,469	3.6348	£44,894	0.01	0.08	0.31
Sham	£13,516	3.3685	NA	0.99	0.92	0.69

Subgroup 2 (6/24 to >6/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£28,366	3.0704	£73,546	0	0	0.01
Sham	£16,317	2.9066	NA	1	1	0.99

Subgroup 3 (6/60 to >3/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£31,740	2.5507	£138,883	0	0	0
Sham	£21,643	2.4780	NA	1	1	1

Scenario 9 – Costing assumptions based on Royal College of Opthalmologists Guide – no disease modifying effect assumed

Base Case – Scenario A (6/12 to 6/95)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£26,598	3.2164	£62,213	0	0.01	0.05
Sham	£14,727	3.0256	NA	1	0.99	0.95

Subgroup 1 (6/12 to >6/24)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£24,714	3.6395	£45,767	0	0.06	0.29
Sham	£12,488	3.3724	NA	1	0.94	0.71

Subgroup 2 (6/24 to >6/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£27,344	3.0638	£75,984	0	0	0.01
Sham	£15,021	2.9016	NA	1	1	0.99

Subgroup 3 (6/60 to >3/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£30,093	2.5552	£139,527	0	0	0
Sham	£19,886	2.4821	NA	1	1	1

Scenario 10 – Costing assumptions based on Assessment Group report – disease modifying effect until year 3 assumed

Base Case – Scenario A (6/12 to 6/95)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£26,863	3.3107	£38,735	0.02	0.16	0.56
Sham	£16,001	3.0303	NA	0.98	0.84	0.44

Subgroup 1 (6/12 to >6/24)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£23,914	3.7758	£25,583	0.19	0.73	0.97
Sham	£13,525	3.3698	NA	0.81	0.27	0.03

Subgroup 2 (6/24 to >6/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£27,700	3.1331	£49,156	0	0.05	0.21
Sham	£16,307	2.9013	NA	1	0.95	0.79

Subgroup 3 (6/60 to >3/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£31,827	2.5737	£112,583	0	0	0
Sham	£21,636	2.4832	NA	1	1	1

Scenario 11 – Costing assumptions based on Royal College of Opthalmologists Guide – disease modifying effect until year 3 assumed

Base Case – Scenario A (6/12 to 6/95)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£26,899	3.3052	£39,015	0.02	0.14	0.55
Sham	£15,999	3.0258	NA	0.98	0.86	0.45

Subgroup 1 (6/12 to >6/24)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£24,090	3.7763	£26,214	0.17	0.71	0.97
Sham	£13,529	3.3734	NA	0.83	0.29	0.03

Subgroup 2 (6/24 to >6/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£27,622	3.1321	£48,737	0	0.05	0.22
Sham	£16,321	2.9002	NA	1	0.95	0.78

Subgroup 3 (6/60 to >3/60)

Intervention	Mean Costs	Mean QALYs	ICER	Probability CE at Max WTP		
				£20,000	£30,000	£40,000
Pegaptanib	£31,630	2.5710	£109,757	0	0	0
Sham	£21,650	2.4801	NA	1	1	1

CHAPTER 2: REVIEW OF UTILITY STUDIES IN AGE-RELATED MACULAR DEGENERATION

1. Literature Search

A literature search was conducted on 17th September 2007. The aim of the search was to identify any additional literature to inform any changes/alterations necessary to the economic evaluation of treatment for age-related macular degeneration (AMD).

A search of Embase and Ovid Medline was conducted.

The search revealed a total of 117 studies, however upon removal of duplicates 100 articles were identified for possible inclusion. Appendix 1 shows the number of identified studies at each stage of the review process. Studies were rejected at title if they did not relate to AMD.

A total of 47 articles were excluded at abstract stage. Further details are shown in the table below.

Articles were rejected at abstract for the following reasons:

Reason for exclusion	**Number of articles excluded**
No specific relation to AMD	1
Review articles of AMD (searches would have been conducted within search time of existing Final Assessment Report)	15
Commentary or opinions	6
Ocular co-morbidities included, for example cataracts	3
Review of low vision services in general	2
Studies with low subject numbers	1
Studies involving other treatment	11
Other (including prevalence, questionnaire design, focus group study, diagnostic techniques)	8
TOTAL	**47**

A total of eight studies were inspected for full review. These are listed in Appendix 2.

1.1. Articles rejected following full paper review

A total of 3 studies were rejected from further data extraction. These included two studies which included data previously identified in the Final Assessment Report; and a paper relating to treatment which falls outside of the Final Assessment Report's remit.

Details are shown below.

1. **Brown GC, Brown MM, Brown HC, Kindermann S, Sharma S. A value-based medicine comparison of interventions for subfoveal neovascular macular degeneration. Ophthalmology. 2007; 114: 1170-1178**

Aim: To perform a value-based medicine analysis of clinical trials which evaluate the interventions of laser photocoagulation, intravitreal pegapnatib therapy, and photodynamic therapy (PDT) with verteporfin for the treatment of classic subfoveal choroidal neovascularisation (CNV)

Rejected from further review, as the data to inform the pegapnatib therapy is taken from a reference rejected from the Final Assessment Report (for reasons of the trial data being taken from a non-randomised controlled trial).

2. **Brown MM, Brown GC, Brown H. Value-based medicine and interventions for macular degeneration. Current Opinions in Ophthalmology. 2007; 18: 194-200**

Aim: To review the patient value conferred by interventions for neovascular macular degeneration

Rejected from further review, as the data to inform the pegapnatib therapy is taken from a reference rejected from the Final Assessment Report (for reasons of the trial data being taken from a non-randomised controlled trial). Data for ranibzumab therapy was taken from a reference used in the Final Assessment Report. Additional data was used from an abstract given by Brown on a conference.

3. **Hewitt AW, Jeganathan VS, Kidd JE, Pesudovs K, Verma N. Influence of photodynamic therapy for age related macular degeneration upon subjective vision related quality of life. Graefe's Archives of Clinical and Experimental Ophthalmology. 2006; 244: 972-977**

Aim: To investigate patient's subjective change in visual function following PDT as a treatment

Rejected from further review as PDT with verteporfin (Visudyne) was used.

1.2. Articles kept following full paper review

A total of 5 studies were identified, including one by the authors of this report . Data extraction was completed for each of the studies. These included two studies related to AMD and depression; the association of contrast sensitivity and visual acuity in AMD; HRQoL and utility using best-eye and worst-eye data; and a comparison of QoL methods used in assessing AMD.

Studies relating to AMD and depression

1. **Rovner BW, Casten RJ, Hegel MT, Tasman WS. Minimal depression and visual function in age-related macular degeneration. Ophthalmology. 2006; 113: 1743-1747**

Aim: To evaluate the impact of minimal depression on subjective and objective visual function measures in AMD

Methods:

Type of study:	Cross-sectional, prospective study
Population:	n=206, mean age 81.2 (5.8) years
Based:	USA
Inclusion:	Newly diagnosed neovascular AMD in one eye and pre-existing AMD in fellow eye Aged >64 years Neovascular AMD diagnosed within past 6 months
Exclusion:	Diagnosis of major depression Dysthymia Minor depression or other axis I psychiatric disorders Current treatment for depression Cognitive impairment Other confounding eye conditions
Measures used:	Best corrected uniocular near and distance VA Uniocular contrast sensitivity Chronic disease score Hamilton Depression Rating Scale (HDRS) NEI-VFQ-17 Melbourne Low-Vision Index Social Problem-Solving Inventory

Results:

- Average (SD) HDRS was 2.2 (2.2, range, 0-12, median 1, mode 0)
- Scores were low overall an din the normal range (HDRS ≤7) for 95.5% of sample
- Correlations of logMAR VA with the NEI-VRD-17 and HDRS were 0.5 (P<0.001) and 0.09 (P<0.22)
- Correlation between NEI-VFQ-17 and HDRS was 0.28 (P<0.001)
- Authors classified subjects with HDRS scores ≥4 as being minimally depressed (n=49) and those with lower scores as being non-depressed (n=157)

- A HDRS score of 4 corresponded to the top 25th percentile of the distribution

Comparison of minimally and non-depressed subjects

	Total n=206	High HDRS n=49	Low HDRS n=157	F score	P value
Age (yrs)*	81.2 (5.8)	79.7 (5.4)	81.6 (5.9)	4.4	0.04
Education (yrs)*	12.5 (2.9)	12.3 (2.7)	12.6 (3.0)	0.26	0.61
Best-eye distance logMAR*	0.60 (0.39)	0.65 (0.35)	0.58 (0.40)	1.10	0.30
Best-eye contrast*	0.66 (0.44)	0.71 (0.44)	0.64 (0.44)	0.83	0.37
Chronic disease score*	5.2 (3.0)	5.7 (3.6)	5.1 (2.8)	1.8	0.18
NEI-VFQ-17*	37.2 (13.3)	43.1 (11.7)	35.3 (13.2)	13.7	0.001
Performance function*	3.2 (0.95)	2.9 (1.1)	3.3 (0.87)	7.3	0.01
HDRS*	2.2 (2.2)	5.4 (1.7)	1.2 (1.1)	434.8	0.001
Problem-solving skills*	26.6 (10.3)	29.7 (10.4)	25.6 (10.1)	5.9	0.02
Female†	144 (70)	40 (82)	104 (66)	4.2	0.04
White†	203 (99)	49 (100)	154 (98)	0.95	0.62
Lives alone†	90 (44)	18(37)	72 (46)	0.25	0.25

* Mean (SD) † n (%)

- Minimally depressed subjects were slightly younger than non-depressed
- The minimally depressed group contained more females
- Subjects in the 2 groups did not differ in severity of vision loss (i.e. best-eye distance VA or CS) or general health (chronic disease score)
- Minimally depressed subjects had significantly worse vision function (reflected in higher NEI-VFQ-17 scores and lower performance-based task scores) than depressed subjects
- Hierarchical linear regressions were undertaken to identify the independent effects of HDRS classification (HDRS ≥4 vs. HDRS<4) on vision function, using NEI-VFQ-17 score and performance-based task scores as dependent measures

Regression results on the NEI-VFQ-17 and Performance Function

Variable	**ß**	**P Value**	**R^2**
NEI-VFQ-17			
Age	0	0.92	
Gender	0.01	0.85	0
Age	-0.06	0.37	
Gender	0.02	0.72	
Acuity	0.47	0.001	
Contrast	-0.12	0.07	
CDS	0.14	0.02	0.30
Age	-0.02	0.71	
Gender	0	0.87	

Acuity	0.45	0.001	
Contrast	-0.13	0.04	
CDS	0.11	0.05	
HDRS group	0.22	0.001	0.02
Performance-based visual function			
Age	-0.14	0.06	
Gender	0.06	0.39	
Age	-0.09	0.13	
Gender	0.05	0.40	
Acuity	0.49	0.001	
Contrast	0.11	0.08	
CDS	-0.09	0.14	0.32
Age	-0.12	0.05	
Gender	0.08	0.18	
Acuity	-0.47	0.001	
Contrast	0.13	0.05	
CDS	-0.07	0.25	
HDRS group	-0.18	0.01	0.35

CDS Chronic disease score

- For the regressions age and gender were entered in the first step
- Best-eye distance acuity, CS and chronic disease score were entered in the second step
- HDRS group was entered in the third step
- For NEI-VFQ-17 the first step was not significant
- R^2 was 0.30 when VA, CS and chronic disease score were entered in the model ($P<0.001$)
- R^2 increased to 0.34 when HDRS group was added ($P<0.001$)
- A similar pattern occurred for performance-based visual function
- This suggests that minimal depression exerts a small but independent adverse effect on both self-rated and performance-based visual function

Conclusions:

- Minimally depressed patients with AMD, who would not be considered depressed according to current diagnostic standards, suffer decrements in visual function that cannot be accounted for by severity of their eye disease or general medical problems

2. Sun C, Tikellis G, Klein R, Steffens DC, Marino Larson EL, Wong TY. Depressive symptoms and age-related macular degeneration in older people: The Cardiovascular Health Study. Ophthalmic Epidemiology. 2007; 14(3): 227-133

Aim: To examine the association between AMD and depressive symptoms

Methods:

Type of study: Population-based, cross-sectional, study

Population: n=2194, mean 78.4 years
Based: USA
Inclusion: Not stated
Exclusion: Not stated
Measures used: Centres for Epidemiologic Studies depression scale (CES-D)
Early AMD – soft drusen alone, REP depigmentation alone, or a combination of soft drusen with increased retinal pigment and/or depigmentation in the absence of late AMD

Results

- Of the 2194 participants included in the analysis, 338 (15.6%) had early AMD and 29 (1.3%) had late AMD
- Occurrence of depressive symptoms (defined as CES-D>9) was detected in 368 (16.8%) participants
- Mean CES-D score was 4 (0-29)
- After controlling for age, gender, race, education, systolic blood pressure, glucose, coronary heart disease, stroke, triglyceride, HDL-cholesterol, cigarette smoking and alcohol consumption, the presence of early AMD, specific early AMD signs, or late AMD was not associated with depressive symptoms
- Subsidiary analysis were performed
- Using a more severe cut-off (CES-D.10) to define depression, no association was found between early and late AMD with depressive symptoms
- Analysis stratified for race, gender, diabetes, hypertension, current cigarette smoker, and presence of cardiovascular disease, depressive symptoms was not associated with early AMD. There were too few late AMD cases to perform stratified analysis
- In the multinomial logistic models comparing the three top quartiles of CES-D score to the lowest quartile for all subjects, the presence of early or late AMD signs was not associated with increasing CES-D quartiles, with a multivariable adjusted OR of 1.06 (95% CI: 0.74-1.52) for early AMD and an OR of 1.04 (95% CI: 0.35-3.14) for late ARMD, comparing the highest quartile of CES-D with the lowest quartile
- Among the participants who took antidepressants (n=353), the CES-D score ranges from 0 to 29 with a median of 8

Conclusions:

- Depressive symptoms were not associated with early AMD or late AMD
- Including persons using antidepressants in the analysis did not alter the associations
- The study did not find an association between early AMD and depressive symptoms in older people

Relationship of AMD with depressive symptoms

	At risk (%)	Depressive symptoms* Age, sex, race OR (95% CI)†	Multivariate OR (95% CI) †	Depressive symptoms* and/or use of antidepressants At risk (%)	Multivariate OR (95% CI) †
Early AMD					
Present	338 (15.7)	0.90 (0.65-1.23)	0.97 (0.69-1.36)	366 (22.1)	0.98 (0.74-1.32)
Absent	1827 (17.0)	1.00	1.00	1964 (22.8)	1.00
Soft drusen					
Present	321 (15.9)	0.91 (0.66-1.27)	0.99 (0.70-1.40)	361 (20.8)	0.94 (0.70-1.28)
Absent	1844 (16.9)	1.00	1.00	1999 (23.0)	1.00
RPE depigmentation					
Present			1.29 (0.58-2.85)	63 (25.4)	1.49 (0.77-2.87)
Absent	45 (17.8)	1.06 (0.48-2.31)	1.00	2297 (22.6)	1.00
	2120 (16.8)	1.00			
Increased retinal pigment					
Present	127 (15.0)	0.88 (0.53-1.47)	0.91 (0.52-1.58)	165 (23.6)	1.13 (0.77-2.87)
Absent	2038 (16.9)	1.00	1.00	2195 (22.6)	1.00
Late AMD					
Present	29 (17.2)	1.03 (0.39-2.76)	1.15 (0.38-3.46)	30 (20.0)	0.97 (0.35-2.67)
Absent	1827 (17.0)	1.00	1.00	1964 (22.8)	1.00

Depressive symptoms defined as CES-D >9

†OR Odds ratio (95% CI) adjusted for age, gender and race

Additional adjustment for education, systolic blood pressure, glucose, coronary heart disease, stroke, triglyceride, HDL-cholesterol, cigarette smoking and alcohol consumption

Study examining the association of contrast sensitivity and visual acuity in AMD

3. **Bansback N, Czoski-Murray C, Carlton J, Lewis G, Hughes L, Espallargues M, Brand C, Brazier J. Determinants of health related quality of life and health state utility in patients with age related macular degeneration: the association of contrast sensitivity and visual acuity. Quality of Life Research. 2007; 16: 533-543**

Aim: To examine the contribution of contrast sensitivity (CS) in explaining HRQoL and health utilities

Methods:

Type of study: Prospective
Population: n=209, mean age 79.6 (7.5) years
Based: UK
Inclusion: Diagnosis of unilateral or bilateral AMD
Exclusion: Known ocular co-morbidities excluded
Measures used: International classification system of ARMD
Uniocular distance and logMAR VA
Binocular near logMAR VA
Binocular contrast sensitivity (CS) (using Pelli-Robson)
Time trade off (TTO)
Visual Function Index (VF-14)
Health Utilities Index mark 3 (HUI3)
EQ-5D
SF-6D

Results:

Patient Demographics

Variable	Valid N	Mean (SD) or %	Range
Socio-demographic			
Woman (%)	121	57.9	
Age	209	79.6 (7.5)	(43-96)
Currently married (%)	209	36.9	
Living alone (%)	96	46.2	
Currently employed (%)	7	3.4	
Clinical			
Months since diagnosis of AMD	204	43.9 (38.7)	(0.4-222.2)
Type of lesion (% diffuse or dry)	44	21.1	
Previous PDT (%)	19	9.3	
Chronic illness or disability (%)	170	82.9	
Limits patients activities (%)	121	71.6	
Visual			
Better-seeing eye (VA) distant logMAR	209	1.01(0.67)	(-0.08-2.86)
Worse-seeing eye (VA) distant logMAR	209	1.68 (0.75)	(0.10-2.86)
Binocular near VA (logMAR)	209	0.46 (0.88)	(-1.90-1.36)
Binocular CS	196	0.69 (0.48)	(0-1.95)

Features of scores components and distributions of HRQoL measures (% in each category, best to worst)

	Valid N	Mean (SD)	Min	Max	1	2	3	4	5	6
TTO	204	0.63 (0.31)	0	1						
VF-14	208	41.48 (28.42)	2.5	100						
Reading small print	208	4.18 (1.28)	0	4	7.7	7.7	5.3	17.8	61.5	-
Reading newspaper or book	205	4.13 (1.39)	0	4	9.8	8.8	6.3	9.3	65.9	-
Reading large print	196	3.21 (1.63)	0	4	27.6	8.7	10.7	20.9	32.1	-
Recognising people when close	208	2.53 (1.45)	0	4	37.5	13.9	19.2	16.8	12.5	-
Seeing steps, stairs, kerbs	206	2.46 (1.20)	0	4	29.6	21.4	26.7	18.5	3.9	-
Reading signs	204	3.20 (1.44)	0	4	20.1	12.3	18.6	26.0	23.0	-
With fine handwork	197	3.99 (1.22)	0	4	9.6	12.2	6.6	12.7	58.9	-
Filling out forms	203	3.49 (1.48)	0	4	17.2	10.8	11.3	26.6	34.0	-
Playing games	166	3.36 (1.64)	0	4	24.1	11.5	8.4	16.9	39.2	-
Taking part in sports	69	3.20 (1.75)	0	4	31.9	7.3	10.1	10.1	40.6	-
Cooking	191	2.45 (1.19)	0	4	28.3	23.6	28.3	14.7	5.2	-
Watching TV	207	2.92 (1.23)	0	4	18.4	16.4	28.0	29.5	7.7	-
Driving during day	88	4.11 (1.59)	0	4	17.1	4.6	3.4	0.0	75.0	-
Driving during night	86	4.36 (1.29)	0	4	7.0	9.3	1.2	5.8	76.7	-
HUI3[a]	206	0.34 (0.28)	-0.24	1.00						
Vision [b]	209	0.41 (0.30)	0	1	1.4	13.9	3.8	7.7	49.8	23.4
Hearing [b]	209	0.79 (0.29)	0	1	59.3	2.9	5.7	20.6	8.6	2.9
Speech [b]	209	0.99 (0.05)	0.67	1	97.1	1.0	1.9	0.0	0.0	-
Ambulation [b]	209	0.81 (0.23)	0.16	1	44.5	19.6	24.4	8.1	3.4	0.0
Dexterity [b]	209	0.91 (0.19)	0	1	73.7	12.4	3.8	8.6	1.0	0.5
Emotion [b]	208	0.88 (0.18)	0	1	44.2	32.2	18.3	4.3	1.0	-
Cognition [b]	207	0.89 (0.17)	0	1	55.1	19.3	4.8	16.9	3.4	0.5
Pain [b]	208	0.82 (0.24)	0	1	31.3	27.4	25.5	11.5	4.3	-

[a] Multi-attribute utility score [b] Single attribute utility score

Correlation coefficients

- For simple correlations, all variables were significantly correlated with each other, but the strength of the correlation varied
- Strong correlation existed between VA and CS
- In majority of patients deteriorating CS was matched by deteriorating VA
- A small number of patients appeared to have poor CS whilst remaining to have good VA. The converse to this (poor VA and good CS) was not seen

Pearson simple (partial) correlation between measures of HRQoL, visual function and age

	CS	**VA**	**Age**	**TTO**	**VF-14**	**HUI3**	**HUI3-V**
CS	1						
VA	-0.74** (-0.49**)	1					
Age	-0.33** (-0.06)	0.35** (0.14*)	1				
TTO	0.22** (0.02)	-0.19** (0.06)	-0.35** (-0.26**)	1			
VF-14	0.73** (0.43**)	-0.68** (-0.27**)	-0.33** (0.02)	0.28** (0.09)	1		
HUI3	0.36** (0.03*)	-0.34** (0.11)	-0.31** (-0.12)	0.34** (0.19*)	0.51** (0.33**)	1	
HUI3-V	0.59** (0.20*)	-0.57** (0.18)	-0.26** (-0.08)	0.22** (0.12)	0.80** (0.63**)	0.51** (0.41**)	1

** correlation at the 1% level * correlation at the 5% level

HUI3-v vision dimension of HUI3

Multivariate regression

- CS, VA and age are all statistically significant for all outcome measures
- The signs of Beta coefficients were as expected, with VA having a negative relationship and CS a positive relationship with HRQoL and health utilities
- Other significant variables were longstanding illness, disability or infirmity (on HUI3), marital status (on TTO) and time since diagnosis (on VF-14)
- In multivariate regression only CS, age and longstanding illness remained in the selection of variables for the HUI3
- Again, CS was significant, whilst VA was not
- For all measures of HRQoL and health utility, CS remained statistically significant no matter the number of additionally explanatory variables (age, CS and VA)
- For the different instruments, either VA or age was also statistically significant when combined with CS, but never all three together
- The addition of VA as an explanatory variables along with CS did not improve the power of explaining either the HUI3 or TTO and its improvement in the adjusted R-square was marginal for the VRF-14 and HUI3-V
- Age was a more important determinant than VA for the TTO, while the reverse was true for the VF-14 and HUI3-V

Conclusions:

- CS has significant and independent properties to VA

Predictors of health status using univariate and multivariate regression analyses

	TTO Univariate B (SE)	**TTO Multivariate* B (SE)**	**VF-14 Univariate B (SE)**	**VF-14 Multivariate* B (SE)**	**HUI3 Univariate B (SE)**	**HUI3 Multivariate* B (SE)**	**HUI3-V Univariate B (SE)**	**HUI3-V Multivariate* B (SE)**
CS	0.16 (0.05) P<0.01	0.08 (0.05) P=0.09	43.02 (2.88) P<0.01	30.74 (4.09) P<0.01	0.21 (0.04) P<0.01	0.14 (0.02) P<0.01	0.35 (0.04) P<0.01	0.25 (0.05) P<0.01
VA (BSE)	-0.10 (0.03) P<0.01		-29.96 (2.22) P<0.01	-12.71 (3.32) P<0.01	-0.14 (0.03) P<0.01		-0.25 (0.26) P<0.01	-0.12 (0.04) P<0.01
Type of AMD (wet=1)	0.06 (0.05) P=0.30		7.32 (4.85) P=0.13	7.64 (3.33) P=0.02	0.06 (0.05) P=0.25		-0.10 (0.05) P=0.06	-0.12 (0.04) P<0.01
Age (yrs)	-0.01 (0.00) P<0.01	-0.01 (0.00) P<0.01	-1.23 (0.25) P<0.01		-0.01 (0.00) P<0.01	-0.01 (0.02) P<0.01)	-0.01 (0.0) P<0.01	
Gender (Female=1)	-0.08 (0.04) P=0.08		-1.44 (4.00) P=0.72		-0.06 (0.04) P=0.01		0.0 (0.04) 1.0 P=0.98	
Longstanding illness, disability or infirmity (yes=1)	-0.08 (0.06) P=0.18		-8.42 (5.26) P=0.11		-0.22 (0.05) P<0.01	-0.21 (0.05) P<0.01	-0.09 (0.06) P=0.11	
Marital status (married=1)	0.05 (0.01) P<0.01	0.04 (0.01) P=0.07	3.01 (1.27) P=0.02		0.02 (0.01) P=0.15		-0.02 (0.01) P=0.24	
Time since diagnosis (mths)	-0.01 (0.04) P=0.62	0.62	-0.25 (0.05) P<0.01		0.02 (0.01) P=0.31		-0.00 (0.00) P<0.01	
R^2	0.15		0.58		0.25		0.39	
Adjusted R^2	0.14		0.57		0.24		0.38	

* backward stepwise regression using selection criteria of p<0.1

Study examining HRQoL and utility using best-eye and worst-eye data

4. **Sahel J-A, Bandello F, Augustin A, Maurel F, Negrini C, Berdeaux GH. Health-related quality of life and utility in patients with age-related macular degeneration. Archives of Ophthalmology. 2007; 125(7): 945-951**

Aim: To assess the impact of best-eye and worse eye visual acuity (BEVA and WEVA) on HRQoL and utility in patients with wet AMD

Methods:

Type of study: Cross-sectional, prospective, observational, multicentre study
Population: n=360, mean age 77 (8.0) years
Based: France, Germany and Italy
Inclusion: Aged >50 years and diagnosis of wet AMD
Exclusion: Dry AMD; had participated in another study; mental disability; impaired VA due to cause other than AMD
Measures used: Uniocular distance and logMAR VA
NEI-VFQ-25
MacDQoL
HUI3

Results:

Patient Characteristics

BEVA and WEVA baseline distribution (VA, severity distribution, no (%))

Eye	logMAR, mean (SD)	<20/200	≥20/200 to < 20/80	≥20/80 to <20/40	>20/40
BEVA	0.49 (0.4)	32 (8.9)	84 (23.3)	100 (27.3)	144 (40.0)
WEVA	1.01 (0.4)	138 (38.3)	151 (41.9)	62 (17.2)	9 (2.5)

NEI-VFQ-25

- Mean (SD) global score was 52.6 (22.0), which summarised a decreasing trend from patients with the least VA loss (mean (SD) QoL 67.0 (19.1)) to those with most sever moss (mean (SD) QoL 40.7 (18.1))
- No significant differences of QoL was seen between countries
- No significant interaction was observed between WEVA and BEVA
- General health was significantly affected only by WEVA

NEI-VFQ-25 least squares mean scores, adjusted for age, sex and country, by severity level of BEVA and WEVA[a]

Dimensions	No of subjects	BEVA:WEVA ≥20/40:≥20/200	BEVA:WEVA ≥20/40:<20/200	BEVA:WEVA <20/40:≥20/200	BEVA:WEVA <20/40:<20/200	R^2	P value BE	P value WE	P value Interaction
General health	354	46.0	36.4	42.0	41.0	0.07	0.89	0.02	0.06
General vision	355	58.6	55.6	42.8	37.4	0.31	<0.01	0.02	0.52
Ocular pain	356	78.3	77.8	78.3	73.9	0.07	0.47	0.36	0.50
Near vision	355	61.7	59.4	35.7	32.0	0.32	<0.01	0.24	0.79
Distance vision	355	69.4	85.8	44.7	37.3	0.35	<0.01	0.04	0.50
Social function	354	81.4	83.7	59.8	52.8	0.23	<0.01	0.46	0.13
Mental health	356	53.1	49.5	37.7	28.6	0.23	<0.01	0.02	0.31
Role difficulties	354	56.1	55.1	35.2	29.5	0.28	<0.01	0.23	0.40
Dependency	350	73.9	74.7	45.7	35.9	0.36	<0.01	0.17	0.10
Driving	190	57.9	51.0	25.7	11.5	0.38	<0.01	0.03	0.45
Colour vision	353	88.5	88.5	71.9	65.0	0.16	<0.01	0.27	0.26
Peripheral vision	353	70.1	70.5	56.9	52.5	0.15	<0.01	0.52	0.44
Global score	356	66.2	83.8	46.7	40.2	0.36	<0.01	0.09	0.31

[a] calculated using analysis of variance

MacDQoL

- Mean(SD) AWI score was -3.5 (2.01)
- Mean (SD) AWI decreased with AMD severity form -4.62 (1.81) for VECA worse than 20/40 plus WEVA worse than 20/200 to -2.68 (2.12) for a BEVA of 20/40 or better plus a WEVA of 20/200 or better
- Mean AWI values were nearly identical for the two groups with a BEVA of 20/40 or better
- Mean AWI values were similar across countries
- After adjustment for age, sex, and country, the least squares mean AWI scores among 365 patients were -2.63 for those with a BEVA of 20/40 or better and a WEVA of 20/200 or better; -2.67 for those with a BEVA of 20/40 or better and a WEVA worse than 20/200; -3.66 for those with a BEVA worse than 20/40 and a WEVA of 20/200 or better; and -4.76 for those with a BEVA worse than 20/40 and a WEVA worse than 20/200
- Both the BEVA and WEVA had a significant influence on AWI ($P<0.001$ and $P=0.007$ respectively
- A significant WEVA X BEVA interaction was observed ($P=0.01$)
- BEVA and WEVA explained 20% of the MacDQoL AWI variance ($R^2=0.20$)

HUI3 scores

- Mean HUI3 scores (SD) was 0.48 (0.29)
- Mean (SD) HUI3 scores decreased from 0.62 (0.28 for BEVA of 20/40 or better plus a WEVA of 20/200 or better, to 0.39 (0.25) for a BEVA worse than 20/40 plus a WEVA worse than 20/200
- Mean HUI3 values were nearly identical for the two groups with a BEVA of 20/40 or better and markedly different from the two groups with a BEVA worse than 20/40
- Mean HUI3 values were similar across countries

HUI3 least squares mean values adjusted for age, sex, country, by severity level of BEVA and WEVA[a]

Dimensions	No of subjects	BEVA:WEVA ≥20/40:≥20/200	BEVA:WEVA ≥20/40:<20/200	BEVA:WEVA <20/40:≥20/200	BEVA:WEVA <20/40:<20/200	R^2	P value BE	P value WE	P value Interaction
Vision	348	0.75	0.74	0.42	0.37	0.36	<0.001	0.31	0.51
Hearing	348	0.69	0.86	0.64	0.91	0.06	0.85	0.45	0.10
Speech	349	0.97	0.98	0.97	0.97	0.03	0.72	0.67	0.94
Ambulation	351	0.93	0.92	0.92	0.89	0.09	0.33	0.39	0.62
Dexterity	353	0.98	0.96	0.98	0.97	0.02	0.76	0.54	0.65
Emotion	354	0.88	0.89	0.84	0.83	0.08	0.02	0.99	0.64
Cognition	354	0.97	0.93	0.87	0.92	0.02	0.28	0.10	0.47
Pain	353	0.90	0.88	0.88	0.84	0.05	0.26	0.30	0.69
Global score	335	0.60	0.57	0.41	0.42	0.21	<0.001	0.70	0.50

[a] calculated using analysis of variance

Conclusions:

- BEVA and WEVA correlated independently with QoL
- Disease-specific measures differentiated severe AMD categories better than generic HUI3
- The HUI3 vision dimension registered the severity of VA loss
- The HUI3 emotion dimension was sensitive to VA loss
- The distribution of HUI3 utility scores was homogenous across countries
- Sensitivity of HUI3 is sufficient to capture effects of AMD as perceived by patients
- The NEI-VFQ-25 showed a decreased global score as VA decreased
- Certain dimensions were more affected by VA (driving, near vision, general vision and mental health)
- MacDQoL was sensitive to severity of AMD
- VA was found to be a major determinant of vision-related QoL for patients with wet AMD. Preservation of vision in both eyes should result in a significant improvement in vision-related QoL
- Effect of AMD on patients' loss of utility was comparable to that reported for other chronic, severe diseases

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Study examining the of QoL methods used in assessing AMD

5. **Aspinall PA, Hill AR, Dhillon B, Ambrecht AM, Nelson P, Lumsden C, Farini-Hudson E, Brice R, Vickers A, Buchholz P. Quality of life and relative importance: a comparison of time trade-off and conjoint analysis methods in patients with age-related macular degeneration. British Journal of Ophthalmology. 2007; 91: 766-772**

Aim: To investigate the relative priorities in quality of life (QoL) in patients with AMD

Methods:

Type of study: Prospective
Population: n=122, mean age 77.8 (6.7) years
Based: UK
Inclusion: Not disclosed
Exclusion: Dementia (screened with Mini-Mental State Examination Test
Measures used: International classification system of ARMD
Distance and near logMAR VA
Contrast sensitivity (CS) (using Pelli-Robson)
NEI-VFQ-25
Time trade off (TTO)
Conjoint analysis (CA)

Results:

TTO Utilities:

Effect of AMD type (i.e. wet vs. dry) on TTO utility:

- One-way ANOVA showed no significant effect of AMD type on respondent's remaining life expectancy, or on the percentage of years that respondents would trade for perfect vision ($F=1.05$, $df=1$, $p=0.31$)
- People with AMD do not discriminate between the two states of the disease, or are unaware of the more volatile effects of wet AMD on visual function and potential for further vision loss

Effect of binocular AMD severity on TTO utility:

- One-way ANOVA showed significant effect of the binocular AMD severity on the percentage of traded years as disease severity increased ($F=15.2$, $df=2$, $p=0.001$), and no effect was seen on the number of expected remaining life years
- Comparisons between the means for the 3 grades of binocular AMD severity (mild, moderate, severe) showed significant differences between mild and severe ($t=4.3$, $p=0.001$) and moderate and severe ($t=4.6$, $p=0.001$)
- No significance was found between mild and moderate states ($t=1$, $p>0.05$)

Correlations between TTO utility, visual function and AMD severity

	All patients n=115	All patients n=115	Only patients prepared to trade n=52	Only patients prepared to trade n=52
Binocular distance VA (logMAR)	0.38	<0.001		NS
Binocular near VA (logMAR)	0.35	<0.001	0.29	<0.05
Binocular CS	0.27	<0.01		NS
AMD binocular severity grade	0.49	<0.001		NS
AMD grade in the better eye	0.40	<0.001		NS
AMD grade in the worse eye	0.25	<0.01		NS
General health		NS		NS

NS non-significant

- Mean utility for all patients (including those unprepared to trade) was 0.805 (95% VI 0.56 to 1.05)
- Mean utility for those prepared to trade was 0.575 (95% CI 0.41 to 0.75)
- A significant reduction in utility was seen as VA decreased (re=-0.39, p<0.001)
- Comparisons were made with data from present study to that of Brown et al (2002 – utility values and age related macular degeneration. Arch Ophthalmol; 118: 47-81)

Choice-based CA utilities:

- Analysis of the conjoint data were based on responses to paired comparison profiles of daily living difficulties for two hypothetical people derived from five attributes of daily living, each attribute was presented at one of three levels of difficulty (no difficulties, a few difficulties, a lot of difficulties)
- Attributes of daily living were identified from previous studies as being relatively independent
- These were difficulty reading or seeing fine detail; difficulty pouring liquids and performing household chores; difficulty with glare from bright lights; difficulty getting about outside the house alone; difficulty recognising faces
- No significant relationships were found between the individual conjoint utilities for age, gender, distance binocular VA, near binocular VA, binocular CS, binocular AMD severity, AMD type or grade of AMD in the better or worse eye

Comparison of TTO with conjoint utilities:

- A comparison of the TTO utilities, conjoint utilities, visual function and AMD severity was carried out using factor analysis

	Component 1	Component 2	Component 3	Component 4
Binoc distance VA	0.894			
AMD grade in better eye	0.879			
AMD binoc severity grade	0.861			
Binoc near VA	0.848			
Binoc CS	-0.783			
AMD grade in worse eye	0.646			
TTO utility	-0.512			
Utility for difficulty reading or seeing fine detail		-0.908		
Utility for pouring liquids or household chores		0.902		
Utility for difficulty with glare from bright lights			0.872	
Utility for difficulty with getting about outside the house alone			-0.773	
Utility for recognising faces across a room				-0.800
General health				0.719

Only factor analysis loadings ≥0.5 are shown

Conclusions:

- Suggest CA offers a more relevant and discriminating measure of vision-related quality of life utilities

2. Summary

The studies identified in this updated literature search do not significantly contribute to the body of evidence identified in the original Assessment Report. Some issues arising from these studies are discussed below.

2.1 AMD and depression

The Assessment Report does document the existence of clinical depression in the presence of patients with AMD. The study conducted by Rovner et al (2006) does not conflict such emphasis. The study does have noticeable flaws, as acknowledged by the authors. They did not control for size and location of scotomas, or severity of co-morbid eye diseases which may also impair visual function. The findings of minimally depressed subjects demonstrating poor problem-solving skills prevent them from adequately compensating for their vision deficits. The authors acknowledged that low levels of such skills could represent lifelong characteristics, preclinical cognitive impairment, and/or preclinical depression. This study adds little to the information identified in the Assessment Report .

Sun et al (2007) did not find any association between early AMD and depressive symptoms in older people. A different measurement of depression was used in this study, which makes direct comparison difficult. In addition, the study has a number of weaknesses as acknowledged by the authors. The main weakness is the number of potentially eligible people participating in the Cardiovascular Health Study (52%). Non-participation was found to be associated with depression risk factors (e.g. stroke, diabetes, and coronary heart disease). More depressed people tend to stay at home, and a possible reason cited for not finding any association between AMD and depressive symptoms was that people who did participate were less likely to have depressive symptoms. The issue of long-term adjustment to various stages was also recognised, with coping mechanisms playing a possible role. The weaknesses of the population studied may justify the exclusion of this study.

2.2 The association of contrast sensitivity (CS) and visual acuity (VA) in AMD

One of the recommendations of the Assessment Report states:

> *"Further research is required into health state utilities and their relationship with visual acuity and contrast sensitivity. Further research is required to reduce uncertainty over the relationship between duration of vision loss and the quality of life and functional impact of vision loss."*

The study by Bansback et al (2007) does examine the association of CS and VA in subjects with AMD. The authors concluded that CS has significant and independent properties to VA in determining HRQoL and health utilities in patients with AMD. The results demonstrated that measurements of CS appear to be better related to a person's HRQoL and health utility. The authors acknowledged the limitations of the study relating to methodological issues. The subject selection and participation methodology meant possible selection bias could have occurred. The use of the VF-14 (an instrument specifically designed for cataract patients) could be questioned. Direct comparisons to studies utilising the NEI-VFQ-25 cannot be made (the NEI-VFQ-25 was developed with AMD in mind). Finally, it is possible that ocular co-morbidities may have developed in subjects who had not undergone ophthalmological assessment for a significant period. The authors stated that the mean HRQoL and health utility values for the AMD patients in the study are unlikely to be representative. However, the values by VA and CS group should be valid. The study provides useful evidence of the relationship between functional impact of vision loss and quality of life.

2.3 HRQoL and utility using best-eye and worst-eye visual acuity data

The Assessment Report comprehensively examines the relationship between VA and HRQoL. The single study identified in the literature search examined the impact of best-eye and worst-eye visual acuity (BEVA and WEVA) on HRQoL and utility in patients with AMD. The study by Sahel et al (2007) does not relate to the disutility associated with having not having the first or worst eye treated. Instead it confirms

that BEVA and WEVA influence vision-related quality of life independently (as assessed using NEI-VFQ-25 and MacDQoL).

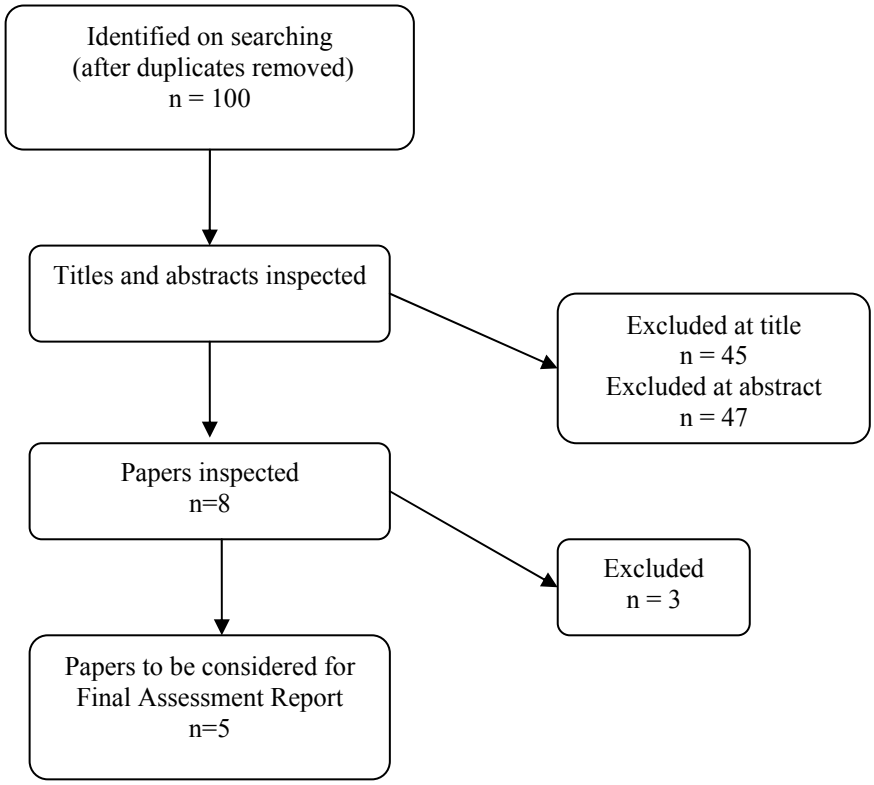
The study does have its limitations, as stated by the authors. The cross-sectional design provides only associative data. Prospective data is needed to reinforce causality. In addition, the participating centres were selected, and random selection is required for national extrapolation. However, the findings reported are homogenous among three populous European countries, and they agree with other studies published in this field.

2.4 Study examining the QoL methods used in assessing AMD

The study by Aspinall et al (2007) concludes that the methods of TTO and conjoint analysis in assessing utility are poorly related. The TTO relates moderately with visual function and disease severity, but CA does not. CA identified two different subgroups of patients: one with outdoor mobility and the other with reading as a main priority. The Assessment Report acknowledges studies which use the TTO method of utility assessment. Conjoint analysis is not discussed in any of the studies summarised in the report.

Appendix 1

Flow chart of identification of published studies for possible inclusion in the Final Assessment Report



Appendix 2 Studies identified for full review

1. Brown GC, Brown MM, Brown HC, Kindermann S, Sharma S. A value-based medicine comparison of interventions for subfoveal neovascular macular degeneration. Ophthalmology. 2007; 114: 1170-1178

2. Brown MM, Brown GC, Brown H. Value-based medicine and interventions for macular degeneration. Current Opinions in Ophthalmology. 2007; 18: 194-200

3. Hewitt AW, Jeganathan VS, Kidd JE, Pesudovs K, Verma N. Influence of photodynamic therapy for age related macular degeneration upon subjective vision related quality of life. Graefe's Archives of Clinical and Experimental Ophthalmology. 2006; 244: 972-977

4. Rovner BW, Casten RJ, Hegel MT, Tasman WS. Minimal depression and visual function in age-related macular degeneration. Ophthalmology. 2006; 113: 1743-1747

5. Sun C, Tikellis G, Klein R, Steffens DC, Marino Larson EL, Wong TY. Depressive symptoms and age-related macular degeneration in older people: The Cardiovascular Health Study. Ophthalmic Epidemiology. 2007; 14(3): 227-133

6. Bansback N, Czoski-Murray C, Carlton J, Lewis G, Hughes L, Espallargues M, Brand C, Brazier J. Determinants of health related quality of life and health state utility in patients with age related macular degeneration: the association of contrast sensitivity and visual acuity. Quality of Life Research. 2007; 16: 533-543

7. Sahel J-A, Bandello F, Augustin A, Maurel F, Negrini C, Berdeaux GH. Health-related quality of life and utility in patients with age-related macular degeneration. Archives of Ophthalmology. 2007; 125(7): 945-951

8. Aspinall PA, Hill AR, Dhillon B, Ambrecht AM, Nelson P, Lumsden C, Farini-Hudson E, Brice R, Vickers A, Buchholz P. Quality of life and relative importance: a comparison of time trade-off and conjoint analysis methods in patients with age-related macular degeneration. British Journal of Ophthalmology. 2007; 91: 766-772

Appendix 3 Studies included in full review

1. Rovner BW, Casten RJ, Hegel MT, Tasman WS. Minimal depression and visual function in age-related macular degeneration. Ophthalmology. 2006; 113: 1743-1747

2. Sun C, Tikellis G, Klein R, Steffens DC, Marino Larson EL, Wong TY. Depressive symptoms and age-related macular degeneration in older people: The Cardiovascular Health Study. Ophthalmic Epidemiology. 2007; 14(3): 227-133

3. Bansback N, Czoski-Murray C, Carlton J, Lewis G, Hughes L, Espallargues M, Brand C, Brazier J. Determinants of health related quality of life and health state utility in patients with age related macular degeneration: the association of contrast sensitivity and visual acuity. Quality of Life Research. 2007; 16: 533-543

4. Sahel J-A, Bandello F, Augustin A, Maurel F, Negrini C, Berdeaux GH. Health-related quality of life and utility in patients with age-related macular degeneration. Archives of Ophthalmology. 2007; 125(7): 945-951

5. Aspinall PA, Hill AR, Dhillon B, Ambrecht AM, Nelson P, Lumsden C, Farini-Hudson E, Brice R, Vickers A, Buchholz P. Quality of life and relative importance: a comparison of time trade-off and conjoint analysis methods in patients with age-related macular degeneration. British Journal of Ophthalmology. 2007; 91: 766-772