ACE Prevention Briefing Paper
Ranibizumab for treatment of Age-related Macular Degeneration

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1.1 Definition of intervention

In Australia vision loss is predominantly a problem of ageing, the presence of which can significantly impact on the quality of life of older Australians. The prevalence of visual impairment in people aged 55 or greater was estimated to be 9.4% of the 4.7 million Australians in that age group in 2004. The main cause of visual impairment in this age group is refractive error, followed by cataract then age-related macular degeneration (AMD). It is estimated that 1.2% of the Australian population aged 55 or greater is blind, and the major cause of blindness in Australia is AMD. In 2004, 28,300 Australians were reported as being blind due to AMD, 50% of the older population with blindness (AIHW 2005). Legal blindness in Australia is defined as a visual acuity <6/60 (20/200) in the better eye with correction, or a visual field < 10°, or both.[1]

AMD is a progressive disease of the macula of the retina that results in loss of central vision, leaving only peripheral vision intact. It is a painless condition that leaves patients unable to read, recognise faces or drive a vehicle. There are two types of AMD, geographic AMD (dry) and exudative or neovascular (wet) form of AMD. Neovascular AMD is the more aggressive form of the disease and is estimated to comprise 67% of all AMD of which an estimated 73% are subfoveal. The latter condition is the topic of interest for this economic evaluation. Subfoveal neovascular AMD has been further categorised into predominantly classic (36%) and minimally class or occult (64%) (Access Economics 2006). This economic evaluation will evaluate the treatment of both predominantly classic or minimally classic or occult subfoveal neovascular AMD with ranibizumab against current treatment. Traditionally, these two forms of AMD have been treated separately.

Visual acuity is measured and reported using a number of interchangeable measures. For example, perfect vision can be reported as 20/20 (imperial measure), 6/6 (metric measure), 0.00 (LogMar), 1.00 (Decimal), line number 0 or by the number of letters; 20/20 vision corresponds with having 85 letters. Visual acuity is measured in the trials using the ETDRS[2] chart. Trials outcomes in age-related macular degeneration have as one of their primary outcomes the proportion of patients who lose less than 15 letters (3 lines of vision based on the ETDRS) over the course of the trial.

[1] This is the definition used in the Melbourne Vision Impairment Project (VIP) and the Blue Mountains Eye Study, both of which are based on the Australian population.

[2] The ETDRS chart is used when a well-designed standard for measuring visual acuity is required such as in clinical trials. The ETDRS chart has five letters on every line, all letters in a line have equal height and width, spaces between letters are equal to one letter width, letters are limited to the Sloan letter set, the lines progress in 0.1 logMAR steps, and every letter read counts as 0.02 of each line.

1.2 Health stages/risk factors affected by the intervention

The intervention is aimed at the Australian 2003 population, aged 50 years or greater, who have active neovascular subfoveal AMD, diagnosed by fluorescein angiography. The aim of treatment with ranibizumab is to slow the progression of the disease.

1.3 Current Practice

The current treatment for predominantly classic subfoveal AMD is photodynamic therapy with verteporfin (PDT_V). Verteporfin is injected into the peripheral bloodstream (a 10 minute infusion) where it is transported to the eye and 15 minutes later activated by light (photodynamic therapy). Light activation of verteporfin results in local damage to neovascular endothelium, resulting in vessel occlusion. Photodynamic therapy is currently listed on the Medicare Benefits Scheme (MBS) for the treatment of choridal neovascularisation. Verteporfin is listed on the Pharmaceutical Benefits Scheme (PBS) for treatment of predominantly (greater than or equal to 50%) classic, subfoveal choroidal neovascularisation (CNV) due to macular degeneration as diagnosed by fluorescein angiography in patients with a baseline visual acuity equal to or better than 6/60 (20/200). A total of 15 subsidised treatments per eye are allowed. The product information recommends that patients be re-evaluated every three months and in the event of recurrent CNV leakage, verteporfin treatment should be repeated. Traditionally there has been no subsidised treatment of minimally classic subfoveal AMD, with a small percentage of patients (around 5%) self-funding PDT ((Access Economics 2006).

As of March 2007, ranibizumab is provided on the PBS for the initial and continuing treatment by an ophthalmologist, of subfoveal choroidal neovascularisation (CNV) due to AMD, where the AMD has been diagnosed by fluorescein angiography. The recommended dosing regimen is monthly. There are no limiting criteria of minimum visual acuity as in the case of the verteporfin subsidy.

1.4 Efficacy/Effectiveness of intervention/s

Likelihood of progression in AMD is estimated from a subgroup analysis at 24 months of patients with minimally classic AMD lesions enrolled in the MARINA trial (Rosenfeld PJ, Brown DM et al. 2006) in which progression of the disease (as measured by a loss of at least 15 letters in and in some cases improvement in the disease by the gaining of at least 15 letters) was reported by baseline visual acuity ((Boyer DS, Antoszyk AN et al. 2007) and from a similar subgroup analyses at 12 months of predominantly classic AMD lesions enrolled in the ANCHOR trial (Brown DM, Kaiser PK et al. 2006) in which progression of AMD (as measured by a loss of at least 15 letters and improvement by gaining of at least 15 letters) was also reported by baseline visual acuity (Kaiser PK, Brown DM et al. 2007).

These subgroup analyses were pre-planned ad hoc categorisation analysis of gender, age, visual acuity, AMD lesion size, CNV lesion type and duration of neovascular AMD using the pre-specified primary end point of proportion of patients who lost <15 letters from baseline, secondary end points of the proportion who gain ≥15 letters and the mean change in VA score from baseline. The subgroup analysis assessed which of the covariates evaluated was the more influential predictor of VA outcome at 24 months (or 12 months for ANCHOR study). VA score was found to be the most important predictor, followed by total CNV lesion size at baseline and then age. A finding from the subgroup analysis was that patient gender had no impact on any of the three key VA end points (proportion of patients gaining at least 15 letters, proportion of patients who lost fewer than 15 letters and mean change from baseline).

The ANCHOR and MARINA trials used as their treatment regimen monthly injections of ranibizumab to treat predominantly classic and minimally classic or occult patients respectively. An alternative treatment regimen, of once monthly injections followed by three monthly injections has been trialled (PIER trial,(Regillo CD, Brown DM et al. 2008)) but this treatment regimen was rejected by the Pharmaceutical Benefits Advisory Committee for subsidisation in the treatment of AMD, because "some clinical trial evidence from the PIER trial suggests it may be associated with worse outcomes than monthly dosing"(PBAC March 2007). Therefore only a monthly treatment regimen is evaluated in this economic evaluation.

1.5 Modelling to health outcomes

Modelling has been used to extrapolate outcomes from the clinical trials and the subgroup analysis of these trials to a five year time horizon and to transform outcomes assessed in the trials, the number of patients who lost fewer than 15 letters and the number of patients who gained at least 15 letters, to a patient relevant outcome that will enable comparison of this treatment with preventive interventions being examined in the ACE Prevention project.

The economic evaluation of the cost-effectiveness of ranibizumab in the treatment of subfoveal neovascular AMD is undertaken using a Markov model. A cohort of the relevant population, those aged 50 plus with active AMD, are separated out into two arms in the model; those treated with ranibizumab or those for whom ranibizumab is unavailable. The arms of the model are then further divided into patients who have predominantly classic lesions and those who have minimally classic lesions. Those with predominantly classic disease where ranibizumab is unavailable will be treated with PDT-V and those with minimally classic will receive no treatment, (excepting that a small proportion whose lesions become predominantly classic received PDT treatment in the trial and this is replicated). There are 12 health states in each arm of the model. The structure of the model is illustrated in Attachment 1. The health states in the model are based on the visual acuity groupings used by the subgroup analysis of the MARINA and ANCHOR trials.

All subjects enter the model with active AMD. The ACE protocol has as one of its assumptions that the interventions are modelled in a steady state. Therefore each patient who enters the model is assumed to be a new incident case with early visual impairment. Each cycle of the model is a monthly cycle, in accordance with the ranibizumab treatment regimen. Patients progress through the model, from visual acuity health states (as defined by number of letters) to other visual acuity health states (as defined by number of letters) in response to their probability of losing at least 15 letters (3 lines of vision). Of these a proportion will lose at least 30 letters (as occurred in the clinical trials) and will discontinue treatment. The clinical trials reported that a proportion of patients gained at least 15 letters. Clinical trial reports and graphical representations indicate that this improvement happens very quickly after treatment initiation and then levels off. This is represented in the model as an increase of at least 15 letters (3 lines of vision) within the first month of treatment after this it is assumed no further gain in vision is possible. Patients who continue to lose letters will eventually either be not eligible for treatment (if they are legally blind and are being treated with PDT-V) or will discontinue treatment.

In the model patients are exposed to population all cause mortality risk. Excess mortality from having AMD has not been included in the model because an association reported for visual impairment and mortality reflect confounding by comorbidities, risk factors, and other factors related to susceptibility to death rather than an independent biological association of vision problems or specific eye diseases (Manickam Thiagarajan, Jennifer R. Evans et al. 2005). The age of patients entering the model is based on the age distribution of the Australian population aged 50 years and over and the prevalence of AMD in this population.

The five year time horizon chosen for this intervention differs from the lifetime horizon chosen for most of the interventions under the ACE protocol. A five year time horizon was chosen because currently there is only two year data of the clinical efficacy of ranibizumab in the treatment of minimally classic AMD and only twelve month data of the clinical efficacy of ranibizumab in the treatment of predominantly classic AMD. Extrapolation of these results to a five year time horizon was considered to be a sufficiently heroic assumption (especially given the need to continually give ranibizumab injections into the eye every month to maintain efficacy) and a time horizon beyond that was not considered to be a feasible assumption at the moment.

This evaluation has also deviated from the ACE protocol in the choice of utility weights. QALYs rather than DALYs have been chosen. The Table below compares the health states in the model (predominantly classic branch of the model) with the Dutch DALY weights and with QALY weights from a study (Brown G, Sharma S et al. 2000)) which have been used in submissions to NICE. There are two reasons for this choice. First, Patients with mild vision disorder are not included within the AMD model, therefore only two Dutch disability weights would have been available to represent the multiple health states in the model and this was considered to be insufficiently sensitive to be able to model patient's preferences. Therefore QALYs, derived from studies of patients with

AMD (using the better eye) and which more closely correlate to the health states used within the model, have been used(Brown G, Sharma S et al. 2000) to value the visual acuity health states[3]. Second, there is not a lot of difference between the DALY and QALY weights in this context[4] and we believe that the cost-effectiveness ratios using QALYs in this analysis are reasonably comparable to the cost per DALY estimates estimated for other analyses.

Table 1: Utilities and disability weights associated with visual acuity (VA) health states - predominantly classic

Visual acuity				
VA states in model (letters)°	**Brown et al QALYs VA states°**	**QALY weight**	**Dutch disability weight categories**	**QALY weight**
	20/20-20/25 6/6-6/7.5 (85-80)	0.89 (0.82-0.96)	Mild (some difficulty reading small newspaper print, no difficulty recognizing faces at 4m distance)	0.98 (0.967-0.999)
20/63 or better* 6/18.9 # (≥60)	20/30-20/50 6/10-6/15 (75-65)	0.81 (0.73-0.89)	Moderate (i.e. great difficult reading small newspaper print, some difficulty recognizing faces at 4m. distance	0.83 (0.7222-0.927)
20/80-20/100 6/24-6/30 (55-50)	20/60-20/100 6/19-6/30 (60-50)	0.57 (0.47-0.67)	Severe (i.e. unable to read small newspaper print, great difficult or unable to recognize faces at 4m distance)	0.57 (0.479-0.667)
20/125-20/200 6/37.5-6/60 (45-35)	20/200-20/400 6/60-6/120 (35-20)	0.52 (0.38-0.66)		
20/250 or worse 6/75 (≤30)	Counting fingers to light perception	0.40 (0.29-0.50)		

***imperial measure #metric measure °Best corrected visual acuity in the better eye

[3] The study by Brown et al used the time trade-off and standard gamble techniques to elicit utility values. This was a cross-sectional study in which 80 white patients with unilateral or bilateral AMD in one or both eyes, and visual loss to a minimum of the 20/40 level in at least one eye. Utility values were measured in 5 groups according to the visual acuity in the better-seeing eye. Conventionally assigned anchor points were 1.0 for perfect health and 0.0 for death.

[4] Comparisons between QALY weights and '1-DALY weights' are not always straightforward, particularly when values for health states, rather than changes in health states are being presented. In this case the comparisons are easier as the Brown et al study used eliciting techniques related to the disability of interest similar to how the DALY weights were derived for 'pure disability states' (i.e. ignoring any co-morbidity), the difference between the two methods being the choice of technique to derive utility values (time trade-off/standard gamble versus person trade-off).

Key assumptions in modelling outcomes

The key assumptions in the model are:

- The population modelled is for Australians aged 50 years or older who have active subfoveal AMD.
- The model assumes the better eye is treated and the health state utility is for the better eye. An assumption of treating one eye only does not favour ranibizumab as there is considerable wastage associated with this drug (sufficient to treat both eyes together) so there would be little additional costs involved in treating both eyes (and potentially greater benefit). However, with PDT-V, although the cost of the drug does not increase if both eyes are treated the MBS item reimbursement for the PDT procedure does increase reflecting the increase time costs of the specialist.
- The model assumes that patients are treated with PDT-V only for a period of 2 years up to a maximum of 8 treatments. The reason for this is that currently for patients to be eligible to receive treatments 5-10 the treating doctor is required to obtain permission from a review panel to which they need to send clinical notes including the patient's visual acuity. This process needs to be repeated if a patient requires further treatment of between 10-15 treatments. No further treatment beyond 15 treatments per eye is subsidised. Given the difficulty of modelling this the model assumes patients can have up to 8 treatments within the 2 years (the probability of the number of treatments is from a study by Meads (Meads C, Salas C et al. 2002) . The two year treatment with PDT-V, is assumed to slow the loss of 15 letters in the years following treatment, although the probability of losing at least 15 letters is assumed to be increasing the further away from treatment a patient is. A decay function of 50% is applied to the probability of losing at least 15 letters each year after treatment has ceased. The probability of loss of at least 15 letters by VA is varied in the sensitivity analysis.
- It is assumed that patients who have not gained any letters after one month of treatment will not gain any letters with any further treatment.
- Patients who are losing at least 15 letters will do so at the same rate as in the clinical trials. This assumption will be tested in sensitivity testing.
- Patients who lose at least 30 letters will discontinue treatment.
- Patients who have visual acuity such that the loss of at least 15 letters, leave them with few letters to lose, will also discontinue treatment in the model.
- QALYs derived using the TTO method of elicitation are used in the model.
- Benefits are discounted at 3%. This is not subject to sensitivity testing because of the short time horizon used.

1.6 Costs of interventions and offsets

All costs are in 2003 dollars as per the ACE protocol. Where necessary health costs are deflated or inflated using the health services index (AIHW 2005).

The costs of ranibuzimab intervention include:

- Monthly costs of the drug and the associated cost of administration is estimated at $1,624.57 (the cost of ranibizumab listed in the 2007 PBS, deflated to monthly $2003 adjusted for the trial average dose), $38/month associated costs for preparation of the eye (etc. antibiotic drops, sterile gloves, draps and eyelid speculum, local anaesthesia and dilating drops, using a combination of sources such as the PBS and the Australian Pharmaceutical Industry Catalogue) and the MBS item to cover the costs of administering an injection into an eye $249.00. The cost of the drug is for the entire ampoule as any remaining drug cannot be used for another patient resulting in considerable wastage.
- Medical costs included in the model are for costs associated with initial diagnosis of AMD, Fluorescein angiography and specialist visits (these costs are common to all arms of the trial) and then ongoing monitoring costs, visits every 12 months to a specialist including further angiography. MBS sources were used to estimate the cost of identification of the disease (estimated at $261) and ongoing monitoring of the disease a further $137.85 per visit.

The costs of standard care comparator for predominantly classic AMD lesions (i.e. cost of PDT-V) includes:

- The model assumes an average of 5.58 treatments per patient over 2 years. This is from a NICE report ((Meads C, Salas C et al. 2002) on the use of PDT therapy in the TAP study. The probability of patients having between 1 and 8 treatments, is reported and a weighted monthly cost of PDT-V of $561.34 used in the model. Additional costs for administration of the drug, as per ranibizumab, are also included.
- Based on the above treatment probabilities an additional $47.43 per month for specialist care and angiography is also included.
- Injection site adverse events (AE) were included in the PDT-V arm of the model. These AE's were costed as the cost of an infusion of Verteporfin but without the cost of photodynamic therapy included.
- Medical costs associated with initial diagnosis of AMD, Fluorescein angiography and specialist visits (common to all arms of the trial).

The costs of standard care comparator for minimally classic AMD lesions includes:

- Costs for the initial diagnosis of AMD and follow up specialist visits every 12 months as per the ranibizumab arm and for predominantly classic patients.

- In the MARINA trial 16% of standard care patients received PDT-V (as the lesions become predominantly classic), this cost is included in the model as 16% of one treatment only.

There are adverse events in the form of endopthalmitis and increased incidence of cataract surgery in the ranibizumab arm of the clinical trials. Management costs of these adverse events are included in the model. In the ranibuzumab arm only, the costs associated with treating endopthalmitis and cataract are included. Drug costs for treating endopthalmitis are from the PBS and medical costs associated with inserting antibiotics from the MBS (a cost of $661 is assumed for each case of endophthalmitis). The cost of cataract surgery is assumed to be $2,209 (AR-DRG Version 5).

The cost offsets of the intervention were defined as the costs associated with the community care of people with blindness, reduced incidence of admission to nursing homes, and reduced incidence of falls.

The costs of blindness are adapted from a study by Wright et al (Wright SE, Keefe JE et al. 2000) of the financial costs of blindness to the Australian government and community. Income to patients and carers, in the form of pensions and carer payments from the government, were removed from these costs (as they are not relevant to the ACE health sector perspective); as were pharmaceutical costs (to remove any chance of double counting). Costs were inflated to 2003 dollars. These costs were separated into one off-costs incurred, such as general rehabilitation, occupation therapy and provision of low vision devices and recurring costs of blindness such as travel and household concessions. The probability of nursing home admission by VA is from a study by Wang et al (2002) and the costs of a nursing home bed are from the Australian Welfare 2007 Report (AIHW 2007), which report the government expenditure and private daily fees for residential care beds, which were then deflated to 2003-04 dollars. The cost of a fall was obtained from a population based study to estimate the health system costs resulting from falls in older adults who presented to any emergency department in Western Australian in the 2001-02 financial year. A prevalence based approach was adopted to estimate the total annual burden of falls on the health system ({Hendrie D, 2004 #54}) of people who presented to an emergency department with an injury who had an admission to either a short stay or inpatient ward. A prevalence based approach calculates the total cost of injury in a given year, regardless of when the injuries were sustained. This cost was applied to an increased risk of falls by visual acuity as reported by Lotery et al ((Lotery A, Xiao Xu et al. 2008)). In the AMD group, falls were highest in those patients with severe VA and this is reflected in the model.

The cost of depression was not included in the model. Although, there is reported to be significant incidence of depression in patients with AMD ((Casten RJ, Rovner BW et al. 2004), the level of depression is correlated with the length of time since diagnosis (shorter time periods elicit greater distress) and whether patients were blind in one eye or both (those blind in one eye had greater distress because they feared losing sight in their other eye). These reports suggest an adaptive aspect to AMD, that is the longer that

people have AMD and the worse their vision (ie blind in both eyes) the less chance they will have depression associated with their disease (as distinct from depression due to other causes).

1.7 Uncertainty Analysis

To incorporate the uncertainty associated with all cost and outcome data we use Monte Carlo simulation modelling and present uncertainty ranges as well as point estimates for benefits, costs, cost offsets and cost-effectiveness ratios. Details of the parameters varied in the uncertainty analysis are presented in Table 2

Table 2: Details of uncertainty analysis

Parameter	Value	Uncertainty distribution	Source
Probability of gaining ≥15 letters	Varies by the health state	Beta distribution	(Boyer DS, Antoszyk AN et al. 2007),(Kaiser PK, Brown DM et al. 2007)
Probability of losing ≥15 letters	Varies by the health state	Beta distribution	(Boyer DS, Antoszyk AN et al. 2007),(Kaiser PK, Brown DM et al. 2007)
Utilities	Varies by Health state	Gamma distribution	(Brown G, Sharma S et al. 2000),(Sharma S, Brown GC et al. 2000 Aug)
Age	77	Custom distribution	ABS Australian population 2003,(Brown DM, Kaiser PK et al. 2006; Rosenfeld PJ, Brown DM et al. 2006)
Upfront costs of blindness	$1021	Gamma distribution	(Wright SE, Keefe JE et al. 2000)
Recurring costs of blindness	$383	Gamma distribution	(Wright SE, Keefe JE et al. 2000)

1.8 Results and sensitivity analysis

The following is the results of the probabilistic sensitivity analysis after 10,000 cohorts have been run through the model.

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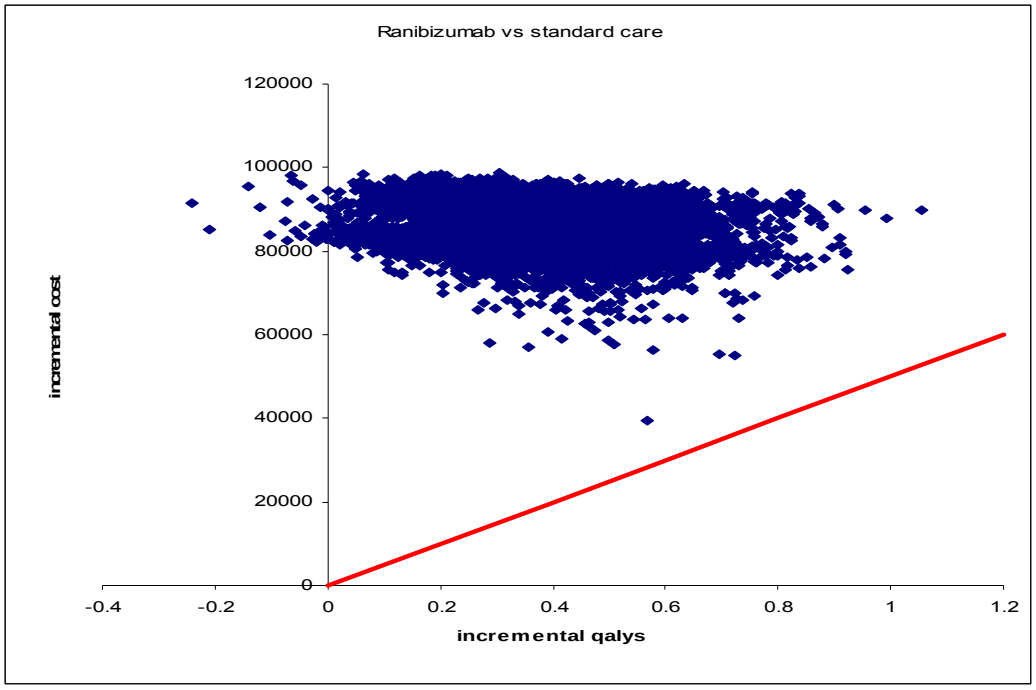
	Median	**95% uncertainty interval**
QALYs intervention	3.08	(2.72,3.60)
Costs intervention	$93,000	($92,000; $107,000)
Net costs	$82,600	($75,000; $95,000)
Incremental effects	0.352	(0.08; 0.68)
ICER with cost-offsets	$240,000	($118,000; dominated)

Figure 1: the cost effectiveness plane of the ICER with cost-offsets.



Note: The red diagonal line depicts a $50,000/QALY threshold.
Note 2: incremental costs and effects are per person

Figure 2: The cost-effectiveness acceptability curve.

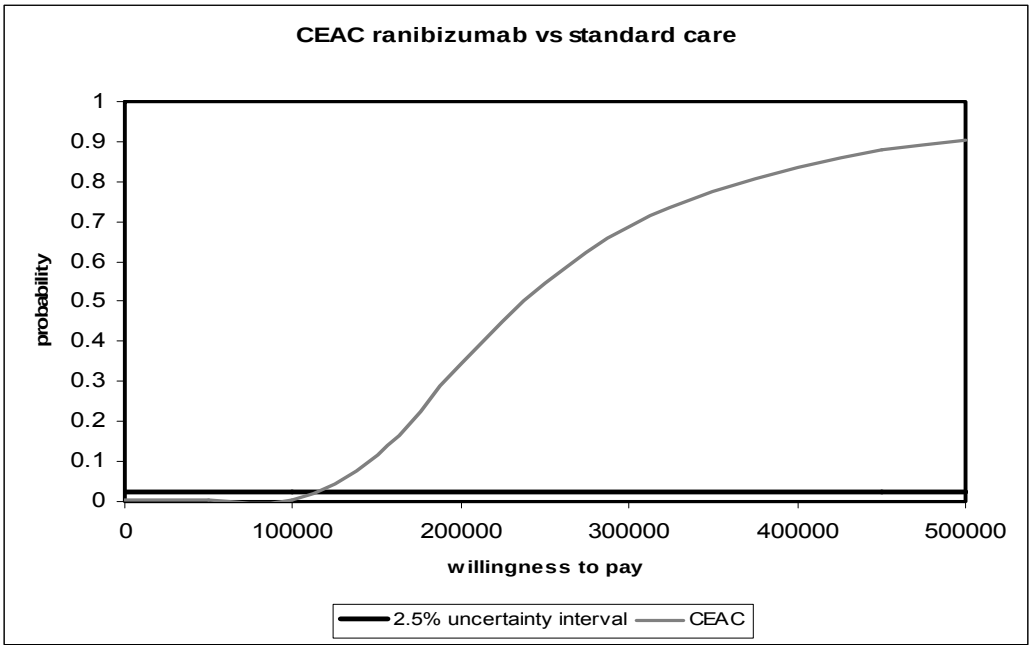


Figure 2 depicts the probability that the intervention will be cost-effective at different willingness to pay thresholds. As is demonstrated, using a patient outcome of QALYs, the intervention is significantly above the $50,000 threshold assumed in the ACE protocol.

1.9 Discussion

The results have not been presented separately for minimally classic and predominantly classic for two reasons. Firstly, there is little difference in the results of the incremental analysis if separated into the different lesion types and secondly, the introduction of ranibizumab as a clinically effective treatment of both types of AMD lesions removes the necessity of identifying the lesions type as a means of separating out the type of treatment available – that is, there has been a paradigm shift.

If the acceptable cost-effectiveness threshold is set at $50,000 per quality adjusted life year then it does not appear that ranibizumab for the treatment of subfoveal AMD provides value for money. The clinical trials provide strong evidence that ranibizumab has a statistically significant greater effectiveness and clinical effectiveness than PDT_V in the treatment of predominantly classic AMD and over standard care in the treatment of minimally classic and occult AMD. However, the cost of monthly injections of ranibizumab results in an ICER that is substantially over $50,000/QALY. In some respects, ranibizumab is a victim of its own success in treating AMD patients because

these patients require expensive ongoing treatment to significantly delay the progression of what remains a chronic progressive disease.[5]

Further, it could be argued that the utilities that have been measured for patients with AMD, and which are used in this study, may no longer be applicable. The arrival of ranibizumab has changed the prognosis for patients with wet AMD, from a relentless disease which robbed them of all sight (if in both eyes) to potentially a much milder disease, maybe similar to dry AMD, in which their vision loss is much more gradual or maintained at a constant level (expert opinion). As such, other domains associated with this disease, such as anxiety and depression, may not figure so prominently in the early health states resulting in larger preferences for these health states and a greater differential between them and the lesser visual acuity health states. If this holds then it could be expected that the resulting incremental benefit would be greater resulting in a more favourable ICER.

Time costs have not been included in the sensitivity analysis as they are more heavily incurred by patients receiving ranibizumab (these patients require monthly injections) and so are unlikely to change the overall conclusion.

Although the increased probability of having cataract surgery is costed as an adverse event the reason why there are increased numbers requiring cataract surgery in the ranibizumab arm of the trial may in fact be a positive. Surgeons are recommending patients for cataract surgery on the basis of their superior VA compared to those patients in the standard care arm of the trial.

A significant amount of costs associated with vision impairment occurs outside the health sector. These are the costs associated with income support in the form of the aged blind pension, income support to carers or carer's payment, household concessions, postal assistance, rent assistance, day centre use, access to radio, library and information services and assistance with travelling e.g. taxi vouchers. A health sector perspective does not include these costs. The largest part of these costs is pension costs.

There have been no published cost-effectiveness analyses that have compared ranibizumab to standard care by which to compare this evaluation. Currently, there is a NIHR HTA in progress in the UK in which patients with wet AMD treated with ranibizumab are being compared to patients treated with a similar but cheaper drug, Avastin (Bevacizumab). This trial is due to report in 2012.

Table 3 provides a summary of the 2nd stage filter issues. Our policy conclusion is that the lack of effective alternative treatments in the prevention of blindness from AMD

[5] A sensitivity analysis in which patients were assumed not to be treated after 2 years reduced the costs of treatment substantially and significantly reduced the ICER. This is because if comparing the two treatments after two years, patients in the ranibizumab arm have much better VA levels than the comparator arm, while incurring no further costs (these results are not presented as they are not assumed to be a realistic representation of actual treatment).

suggests that the ability of ranibizumab to significantly delay the onset of blindness (or possibly delay it permanently) and in some cases to improve sight, means that policy makers will take this into consideration, alongside the ICER, when making decisions about subsidising this drug.

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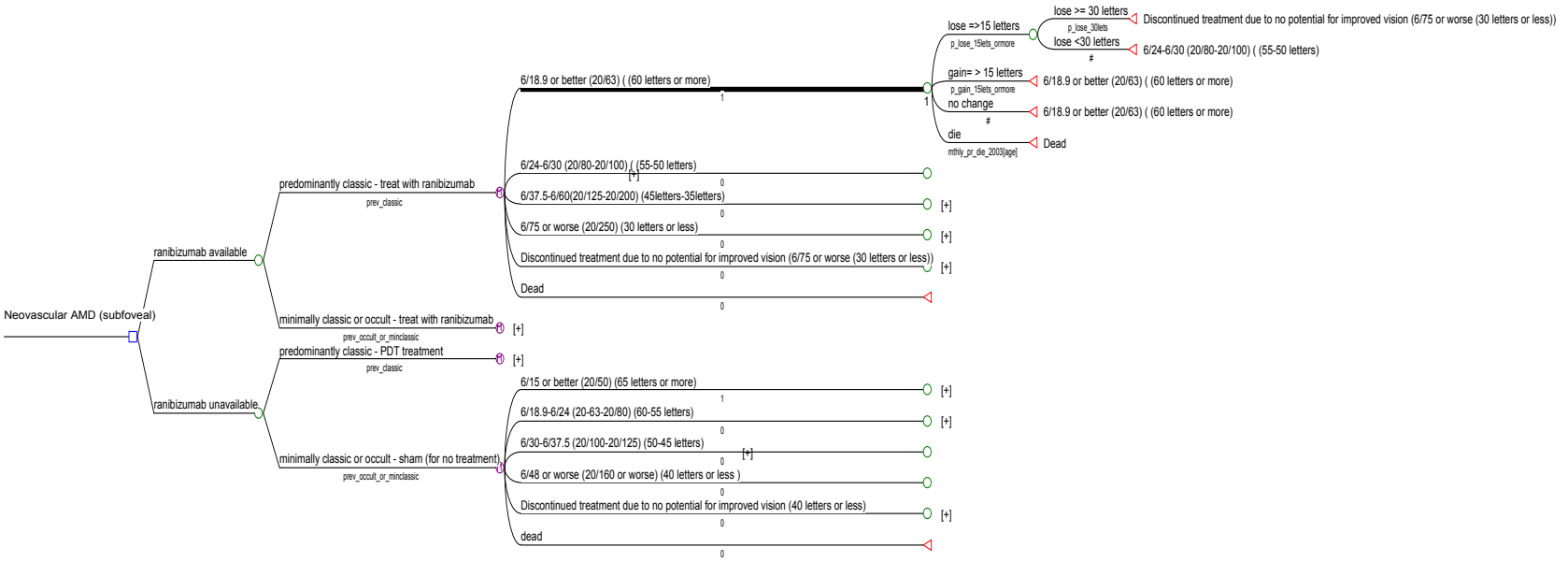

Table 3: Second stage filter summary

Cost per DALY	Strength of evidence	Equity	Acceptability	Feasibility	Sustainability	Relevance to indigenous population	'Other effects' (not captured in modelling)?
Including cost offsets: $240,000/QALY	Strong evidence of effectiveness. Well designed RCT in which patients and outcome investigators were blinded.	Subsidisation of the drug on the PBS has removed equity issues around access.	Issues around the drug delivery, intravitreal injections may be unacceptable to some. The high cost of the drug is an issue.	There are workforce issues around the supply of ophthalmologists capable of delivering this drug as required (especially in future years as the prevalent pool of people eligible to receive these injections increases).	The issue here is of cost. Requires governments to continue to provide subsidy for the drug. The increasing pool of patients who need this drug may place an unacceptable burden on the PBS budget. However, future generic copies of the drug will decrease its cost and improve the ICER.	Low in the respect that this is a disease of aging and indigenous people have lower life expectancy. However, the high levels of smoking in indigenous populations may lower the age at which AMD become an issue for indigenous people.	Positive: None identified Negative: None identified.
Decision point:	Requires ICER to be below the threshold of $50,000/DALY. Undertaking evaluation with disability weights instead of QALYs unlikely to change conclusion						

Policy Considerations: The lack of effective alternative treatments in the prevention of blindness from AMD means that the ability of ranibizumab to significantly delay the onset of blindness (or possibly delay it permanently) and in some cases to improve sight means that policy makers will take this into consideration, alongside the ICER, when making decisions about subsidising this drug.

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