Valuation of Health States Associated with Age-related Macular Degeneration

Thomas James Butt

Institute of Ophthalmology, UCL

A Thesis Submitted in Fulfilment of the Degree of Doctor of Philosophy (Ph.D.)

I, Thomas James Butt confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Economic evaluation of health technology using cost-utility analysis (CUA) normally applies an extra-welfarist framework in which health, the unit of effectiveness, is maximised. Typically, health status is measured by health-related quality of life (HRQoL) questionnaires to define health states. Preferences for health states are valued on a utility scale and combined with the time spent in the state to calculate quality-adjusted life years (QALYs).

This thesis develops methods for measuring and valuing health using the case of age-related macular degeneration (AMD), where there are limitations with current methods for calculating QALYs.

How do widely used methods for deriving health state utility values in AMD perform and how can these methods be improved?
In order to estimate utility, preferences for health states must be elicited. This is generally conducted from a personal *ex ante* perspective, in a representative sample of the public. However, limitations with the descriptive aspects of HRQoL questionnaires mean that the public valuers may lack information to express informed preferences.

This thesis investigates the performance of questionnaires and addresses the impact of informing the public when valuing health states.

Are non-health attributes important in AMD and how can they be incorporated into the cost-utility economic evaluation framework?
The objective of maximising health can be at odds with some of the broader aims of health care systems such as promoting equity or improving the process of care.

This thesis develops weightings for health state utilities that represent a broader utility function incorporating preferences for non-health attributes and investigates the impact of perspective when valuing these attributes. It also develops a conceptual framework for assessing the economic value of decision aids.

How is visual function associated with utility in AMD and how can the association be applied to economic evaluation?

For economic evaluation, the long-term impact of a treatment generally requires health states from clinical trials to be extended using modelling techniques. In AMD, health states are normally defined by levels of visual acuity (VA).

This thesis finds that the association between VA and utility is weak, demonstrates impact of an alternative visual function measure on CUA and develops a mapping algorithm from visual function to utility.

What is the economic impact of treating AMD patients with good starting vision?

Initiating treatment in patients with early AMD is shown to be cost-effective compared with current practice using an economic model based on real world outcomes.

Acknowledgements

Support also came from the UCL health economists for discussions on several working papers and from the UK Health Economist Study Group (HESG) for feedback on a paper on informed valuations; particularly Dr Annie Hawton of Exeter University for acting as HESG discussant.

Personal thanks go to my family and friends who have supported me through the endeavour: My parents who taught me the value of education; James Milner for ensuring it is always the year of action; Oliver Wharton as part of SLRC; and 刘伟 for setting me off on the journey.

Thomas Butt

Brussels, September 2014.

Table of Contents

List of Figures

List of Tables

Acronyms and Abbreviations

Abbreviation	Full term
ABC	Avastin (bevacizumab) for neovascular age-related macular degeneration (trial)
AMD	Age-related macular degeneration
ANOVA	Analysis of variance
ARVO	Association for Research in Vision and Ophthalmology
BNF	British National Formulary
CEA	Cost-effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CLAD	Censored least absolute deviation
CNV	Choroidal neovascularisation
CRD	Centre for Reviews and Dissemination (York)
CS	Contrast sensitivity
CBA	Cost-benefit analysis
CTTO	Consultation time trade-off
CUA	Cost-utility analysis
DALY	Disability-adjusted life year
DCE	Discrete choice experiment
DMO	Diabetic macular oedema
EC	European Commission
EFFECT	Eccentric Fixation from Enhanced Clinical Training (trial)
GALI	General Activity Limitation Indicator
HESG	Health Economists' Study Group
HRQoL	Health-related quality of life
HTA	Health technology assessment

HUI-3	Health Utilities Index mark 3
HYE	Healthy year equivalent
ICER	Incremental cost effectiveness ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LCM	Latent class model
NEI-VFQ	National Eye Institute Visual Function Questionnaire
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OCT	Optical coherence tomography
OLS	Ordinary least squares
ONS	Office for National Statistics
PAS	Patient Access Scheme
PDT	Photodynamic therapy
PICO	Population, Intervention, Comparaison, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient-reported outcome measure
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
REC	Research ethics committee
SF-36	Short form-36
SG	Standard gamble
TPM	Two-part model
TTO	Time trade-off

UCL	University College London	
UK	United Kingdom of Great Britain and Northern Ireland	
VBP	Value-based pricing	
VA	Visual acuity	
VAS	Visual analogue scale	
VEGF	Vascular endothelial growth factor	
VF	Visual function	
vN-M	von Neumann-Morgenstern (utility theory)	
WHO	World Health Organization	
WTP	Willingness to pay	
YLD	Years of life lost	
YLD	Years lost due to disability	

Ethical approval

In relation to **Chapter 3**, full NHS National Research Ethics Service ethical approval for the study titled "Placing a Value on Good Health: A Pilot Study in Patients with Age-related Macular Degeneration (AMD)" was granted on 30th September 2011 The Research Ethics Committee (REC) reference number is 11/LO/1247.

Also in relation to **Chapter 3**, UCL Research Ethics Committee approval was received for the study "Creating a simulation of Macular Degeneration" on 22nd January 2013. The reference number is 3626/002.

In relation to **Chapter 6**, full NHS National Research Ethics Service ethical approval for the study titled "Eccentric Fixation From Enhanced Clinical Training (EFFECT): A Randomised Clinical Trial for Patients with AMD" was granted on 27th April 2011. The REC reference number is 11/EE/0061.

1. Introduction

This chapter introduces the background to economic evaluation. Specific emphasis is placed on the calculation of quality-adjusted life years (QALYs) for use in cost-utility analysis (CUA) including the stages in health state measurement and valuation required to calculate QALYs. The chapter also describes age-related macular degeneration (AMD) as a disease and the current treatment option available to patients with AMD.

1.1. Economic evaluation of health technology

1.1.1. Cost-utility analysis

In order to determine whether to fund a healthcare programme, health systems require a methodology for comparing the relative value for money of interventions. Within the budget constraint of a single-payer system such as the UK (United Kingdom) National Health Service (NHS), the payer must decide which services offer the greatest benefit relative to cost. This often involves making choices between funding interventions for different conditions that generate outcomes that are not directly comparable. For example, a drug for cancer patients, which reduces pain and extends life or cataract surgery, which improves vision.

Health care decision makers within the NHS are increasingly employing CUA. The CUA approach aims to maximise health outcomes thereby takes an extra-welfarist approach to economic evaluation. It may be considered a specific form of cost-effectiveness analysis (CEA) where the measure of effectiveness

incorporates preferences for health. Outcomes are generic and incorporate the notion of value so facilitate comparisons across healthcare programmes. The QALY, which combines the quality and length of life into a single unit, is the most commonly used unit of health outcome.(1)

The National Institute for Health and Care Excellence (NICE) has published guidelines on health technology assessment (HTA) in which it recommends CUA for the economic evaluation of new interventions. It recommends that QALYs should be calculated from health state utility values derived from a generic preference based health-related quality of life (HRQoL) questionnaire that has been valued in the UK general population.(2) Such an approach allows outcomes across conditions to be compared on a common scale reflecting societal preferences.

1.1.2. Quality-adjusted life years

QALYs combine the value of quality of life and length of life into a single score that may be used in CUA. The demand to use a scale that is comparable across diseases is driven by policymakers who wish to allocate resources according to the wishes of stakeholders within a resource-constrained health care system.(1)

To calculate a QALY, a quality weight is applied to the duration of time spent in a health state: QALY= duration*quality of life weight. For example, one year spent in perfect health (or full health) would accrue 1 QALY (1*1=1).

Figure 1.1 illustrates this using a simple example. In the example, remaining length of survival is 5 years, at a decreasing level of quality of life. In the first year quality of life is valued at 0.7 (i.e. 70% of perfect health), 0.6 in years 2 and

3, and 0.4 in the final two years of life. The total QALYs in this case would be 2.7

QALYs [(0.7*1) + (0.6*2) + (0.4*2)= 2.7 QALYs.] The quality of life 'weights' used

in the calculation of QALYs are utility values described in **Section 1**.
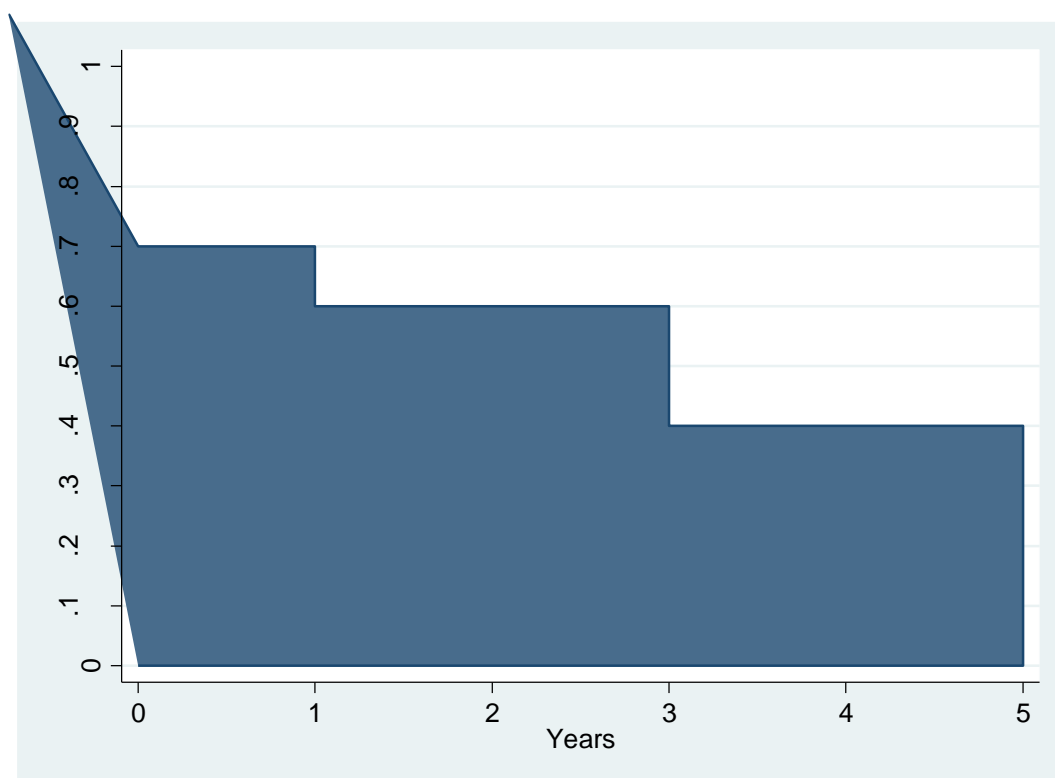
Figure 1.1. Plot of a QALY.

1.1.3. Utility

The quality component of the QALY requires that preferences for health states

are measured on a utility scale anchored by perfect health at 1 and death at

0.(3) This calculation is particularly important for vision disorders, which have

a major impact on quality of life, but, in general, a more minor impact on length

of life.

Utility values used in CUA are based on von Nuemann-Morgenstern (vN-M) utility theory: a representation of how a rational individual should behave. According to vN-M utility theory, scores represent the strength of an individual's preference, under uncertainty, for a described health state.

There are a number of conditions that utilities should meet, and although the definition of health state utility is a normative one, it should somewhat reflect the way individuals make decisions when faced with uncertainty (although empirical evidence has suggested that these conditions may be more often violated than met).(4, 5)

vN-M utility theory also assumes that utility scores are cardinal in that individuals are able to quantify the extent to which they prefer one health state to another. This is as opposed to scores being ordinal, individuals are only able to order health states in terms of preference. Theoretically, utility scores that form the basis of QALYs are meant to have these qualities, making them as close as possible to the utility scores in vN-M utility theory. The term "utility" in vN-M utility theory and in the calculation of QALYs therefore has a different definition and use to the term utility in welfare economic theory and Pareto optimisation.(4)

The source of these utilities requires a decision on who is best placed to value health states and whose preferences should count.(6) HTA bodies such as NICE in England and Wales recommend that public preferences be used in the economic evaluation of health technologies.(2) As payers in a tax-funded health system, it is considered right that the public's preferences are taken into account when allocating health care resources. Furthermore, the public offers

an unbiased view of health states, unaffected by the condition they are valuing.(7) They express their preferences from behind a "veil of ignorance". Consequently the Washington Panel on Cost Effectiveness in Health and Medicine recommended that "*weights for QALYs should be based on community preferences rather than those of patients, providers or investigators*".(8)

The standard technique for public preferences to be taken into account is for patients to answer a HRQoL questionnaire to classify their health state into a profile. A sample of the general public generates a value anchored by 0 as dead and 1 as perfect health for each health state profile. These data are used to create a tariff for converting patient scores onto a scale of health state utility values.

Critics of this procedure point out that members of the public are unlikely to have all of the information required to provide informed preferences for life in a health state.

1.1.4. Alternatives to the QALY

There are various alternatives to the use of QALYs to capture the value of health impacts. Monetary measures are commonly used in economic evaluations and methods are described in the Treasury Green Book.(9) Although less common than QALYs for valuing health interventions in the UK, monetary measures have been used in health economic evaluations. In addition QALYs may be converted to monetary values for the purpose of calculating the net benefit of an intervention. Typically the value of £20,000 per additional QALY gained is used

as the value reflecting the lower bound of the NICE cost-effectiveness threshold; however higher thresholds of £30,000 and £50,000 may be used depending on the nature of the condition and intervention.(2)

The healthy year equivalent (HYE) metric was originally proposed in the late 1960s.(10) One of the key differences between HYEs and QALYs is that the HYE values a profile of health over time, whereas in the QALY each health state is valued independently and then summed to form a profile. The advantage of the HYE is therefore that it is able to capture different values for ill health depending on when they occur in the overall profile of health; however, partly owing to complexities of valuation and calculation, HYEs are not routinely used for the evaluation of health interventions.

Disability adjusted life years (DALYs) are also used to capture the health of populations and is the preferred measure of the World Health Organisation (WHO).(11) DALYs are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population with the condition of interest and the sum of the Years Lost due to Disability (YLD) for people living with the condition. The quality weight, YLD, is calculated as the number of incident cases multiplied by a disability weight and the average duration. Amendments were made to the methodology of DALY weighting in 2010.(12) The updated disability weights were based on data from household surveys conducted in five countries (Bangladesh, Indonesia, Peru, the United Republic of Tanzania and the United States of America) and a web-based survey. DALYs currently remain, however, more frequently used in evaluations of health in developing countries and for comparing population health internationally, than for economic

evaluations of health interventions in single-payer health care systems such as the UK.

The European Commission (EC) has developed an indicator referred to as Healthy Life Years (HLY). These reflect the number of years a person can expect to live without disability, adjusted for their age. There are two components to the HLY: mortality which is assessed through national life tables and data on activity limitation. The data on activity limitation are obtained from the General Activity Limitation Indicator (GALI) included within an EU survey (Eurostat);(13) however as this measure is not preference-based it does not reflect 'value' as usually required for economic evaluations.

1.2. Measurement of health benefits

1.2.1. Health state classification systems

The general approach to measuring health states for CUA is to obtain patient reported description of health status across relevant dimensions using a validated HRQoL instrument.

NICE recommends the EQ-5D for measuring and valuing health states for CUA. However, there is evidence that generic health-related quality of life questionnaires such as the EQ-5D with just 5 questions and, until recently, 3 levels are not sufficiently sensitive to capture changes in health status in vision and other diseases that primarily affect function.(14) Condition-specific measures may be more sensitive, but suffer from a lack of comparability across diseases. The lack of comparability can even apply to condition-specific preference scales used in CUA.(15)

1.2.2. Generic HRQoL

Generic preference-based HRQoL questionnaires are a frequently used method for estimating health state utilities for economic evaluation. These questionnaires consist of a descriptive system that cover HRQoL and is therefore relevant to all health conditions.

Measures tend to focus on how does one's health impact on how one feels and how well one is able to do the things in life that make a life go better or worse. Questionnaires use a number of general domains that measure health across all conditions. Scores on these domains must then be aggregated to provide an overall health-state classification.

Which set of domains is to be used in measuring HRQoL remains an area of research and can have considerable impact on the results obtained. A comparison of the EQ-5D and SF-6D across different patient groups found significant differences in agreement across the groups and across severity levels.(16)

The reasons for selecting one health state classification system over another can range from philosophical concerns about what ought to matter when evaluating health, to psychometric issues concerning how responses to items on domains should or should not be correlated. To provide an idea of what the different health state classification systems focus on in terms of what is important in HRQoL, below are the domains used by the three most prominent systems currently used for generating utilities for health economic evaluation: the EQ-5D, the SF-6D, and the Health Utilities Index 3 (HUI-3):

- EQ-5D: anxiety/depression; pain/discomfort; usual activities; self-care; mobility.

- SF-6D: physical functioning; role limitations; social functioning; pain; mental health; vitality.

- HUI-3: vision; hearing; speech; ambulation; dexterity; emotion; cognition; pain.

Preferences for different health states described by responses to the questionnaire have been valued separately. For example, the EQ-5D UK value set was derived from a sample of UK general public. When a patient responds to a questionnaire, it is possible to assign a preference value to their health state using this valuation tariff. This procedure is described in **Section 1.3**.

1.2.2.1. EQ-5D

The EQ-5D is a generic instrument for the measurement and valuation of health status.(17) It was developed by the EuroQoL Group; a multi-national and multi-disciplinary group of researchers. Although originally developed and tested for use in Europe, its use has expanded internationally and there are currently 141 official language versions of the three-level version of the instrument.

The EQ-5D consists of a descriptive system and a visual analogue scale (VAS). Respondents are requested to complete both parts of the questionnaire with regard to their own health 'today'. The descriptive system includes five dimensions of health: mobility; self-care; ability to carry out usual activities; pain and discomfort; and anxiety and depression. In the EQ-5D-3L, each

dimension is described in terms of three levels of severity, although a five level version has been recently developed and is now increasingly used. The three-level version describes 243 unique health states, and the five-level version describes 3125 possible health states.

Value sets have been developed by the EuroQol Group to enable each health state described by the EQ-5D to be assigned a utility value. The original EQ value set was developed for the general population of England, funded by the Department of Health.(18) These were obtained from a representative sample of 3395 members of the English general population through face-to-face interviews.(19) These people were asked to consider a selection of health states described by the EQ-5D and then to value them using the time-trade off method. A value set for the EQ-5D-5L version for England is expected to be published soon and an interim method for deriving utilities via a cross-walk has been published for use in the meantime. Value sets are currently available for 13 other countries for the EQ-5D-3L.(20)

The EQ-5D has been validated in many different conditions and settings, and is the commonly used measure of health outcomes in economic evaluations of health technologies.(21) In the UK, it is recommended by NICE as the preferred instrument for measuring health status for QALY calculations.(2) It has also been used in large general population surveys including Health Survey for England and Understanding Society.(22, 23) The EQ-5D has also been adopted by the Department of Health as part of its Patient-Reported Outcome Measures (PROMS) programme to routinely measure changes in the health of all patients undergoing selected health interventions.(24)

Utility scores derived from the EQ-5D have a number of distribution issues. In addition to having the qualities of a maximum value of 1 and minimum value of - 0.594, EQ-5D utility scores tend to be positively skewed with an identifiable ceiling effect, meaning that EQ-5D data sets often have a large number of respondents reporting full health with an EQ-5D value of 1.(16)

1.2.3. Condition-specific HRQoL

While vision-specific questionnaires such as the NEI VFQ-25 may be developed with a more substantial descriptive system,(25) they often do not capture comorbidities and side effects of new treatments, and hence are not directly comparable to generic HRQoL measures when used to estimate QALYs.(15)

There has been research into the use of condition specific questionnaires to generate health state utilities. In vision, the VisQol was developed as a preference-based scale for a vision-specific HRQoL questionnaire.(26, 27)

Utilities to calculate QALYs require that health states are measured on a preference scale bounded by death at 0 and perfect health at 1. The construct of HRQoL is used to describe health states.

It remains to be established whether preferences for condition-specific health states, which may not mention other dimensions of health that are not relevant to the condition, are equivalent to preferences for generic HRQoL states.(28) Furthermore, the interaction of dimensions of HRQoL mean that preference scales tend to be non-linear, so a movement on a condition-specific utility scale

can be expected to be different from the change on a generic HRQoL utility

scale.(29, 30)

PROM	Example instrument
Vision-specific functioning	MAI (Massof Activity Inventory)
Condition-specific QoL	MacDQoL
Vision-specific QoL	NEI-VFQ 25
Generic HRQoL	EQ-5D

Table 1.1. Hierarchy of PROMs.

Adapted from Fenwick et al. (31)

PROMs can be viewed in a hierarchy of specificity to generalizability (**Table 1.1**). A model linking physiological variables, symptom states, functional health, general health perceptions and overall quality of life in a hierarchical pathway suggests that items further along the pathway will correlate more closely with quality of life (**Figure 2.2**).(32) Consequently it can be hypothesized that PROMs will correlate more closely with the quality of life of AMD patients than visual function measures.

Figure 2.2. Wilson and Cleary's quality of life scheme.

Choosing between generic and condition-specific PROMs is a trade-off. Condition-specific measures can be more relevant and sensitive to things that

matter to a patient with the condition. However, they can suffer from disadvantages of excluding side effects of treatment, distortions created by focusing effects and the potential loss of comparability from preference interactions with dimensions not covered by the specific measure.(33)

1.2.4. Mapping

Mapping scores from a non-preference-based questionnaire to a preference-based questionnaire expands the evidence on cost effectiveness by allowing the retrospective incorporation of trials that did not include an outcome measure suitable for calculating QALYs, therefore increasing the volume of cost effectiveness evidence available.(34)

Dakin identified 121 mapping algorithms from 80 instruments to the EQ-5D in a systematic review published in 2013. (35) A database of these mapping algorithms is maintained by researchers at the University of Oxford.

In order to create a mapping algorithm, the two questionnaires must be administered in the same sample of patients and a statistical model fitted to the scores.

Ordinary least squares (OLS), Tobit and censored least absolute deviation (CLAD) models, two-part models (TPMs), and latent class models (LCMs) have been applied. A review of mapping studies found considerable variability in performance of mapping functions in terms of model fit and predictive ability.(33) Ideally the datasets used to derive the algorithm and the datasets where the model is subsequently applied should be similar in terms of socio-demographic characteristics and severity of the condition. Furthermore, the

performance of the algorithm will be less than or equal to the performance of the least sensitive instrument in the mapping (normally the target preference-based questionnaire).(33)

1.3. Valuation of health benefits

1.3.1. Direct utility elicitation

Direct elicitation of utilities involves asking people to consider their own health status, usually at the time of asking, and for them to value their health status using one of a range of valuation techniques. Currently the most common methods used to value health status are VAS, the time trade-off (TTO) method and the standard gamble (SG) method.

The VAS method is arguably the simplest of the measurement techniques. Respondents are presented with a vertical or horizontal scale, and requested to indicate how they value their health state on that scale. VAS can differ in terms of the presentation of the scale, the numerical values attached to the scale, the definitions of the 'anchors' or limits at the top and bottom of the scale, and the wording of the question posed to respondents, including the recall period over which the respondent should consider their health. In order to be used in QALY calculations, respondents must also value a state of 'dead' on the VAS in order to be converted to the QALY scale on which 0 represents 'dead'. Even then, VAS scores are a measurable value function representing the strength of preferences under certainty so do not meet the conditions of von Neumann-Morgenstern

utilities. In contrast, a utility function, such as that measured by the SG or TTO technique, represents the strength of preferences under uncertainty. (36)

One commonly used example of a VAS is the EQ-VAS which is part of the EQ-5D questionnaire. This is a 20cm vertical 0 to 100 scale, presented in the form of a thermometer. The anchor at the top of the scale represents the 'best imaginable' health states (value = 100) and the anchor at the bottom of the scale represents 'worst imaginable' health (value = 0). Respondents are asked to mark on the scale the value that best indicates their 'current health today' on the scale. The standard version of the EQ-VAS does not include a question requesting the valuation of the state 'dead' and therefore, it is argued, cannot be used to estimate utilities for the calculation of QALYs; however valuation surveys may include additional questions to anchor on the QALY scale.

The SG method of valuation incorporates elements of valuation under uncertainty and trade-offs between uncertain states of health. Respondents are asked to consider spending a specified amount of time, t, in their current health state. They are then asked to make a hypothetical choice of remaining in that health state or accepting a risky treatment, which could lead to either perfect health or immediate death. The utility or value attached to their health state is then obtained by varying the chance or probability of the perfect health and death until the respondent considers the risky option to be equivalent to the certain option of their current health state. Essentially this approach is asking people their maximum risk of death that they would be prepared to accept in return for the chance of a cure for their condition.

The TTO method has been frequently used in health state valuation as it embodies the notion of sacrifice between quality of life and length of life, and therefore intuitively reflects the trade-off encapsulated in the QALY. Respondents are asked to choose between two certain options: (i) a specified time period (e.g. remaining life expectancy) in their current health state and (ii) a shorter period of time in 'full' health. The time spent in perfect health is then varied until the respondent thinks both options are similarly desirable and a utility is calculated anchored by death (0) and perfect health (1).

The TTO method was developed specifically for use in health care and has been validated against the SG for states better than death.(36). However, a review of the TTO literature concluded that the methodology is far from standardised.(37)

There are advantages and disadvantages associated with all three methods. The method of elicitation has also been shown to impact on the utilities derived, with the VAS tending to generate lower values than the SG.(38)

The VAS method is arguably the simplest to conduct and can be self-completed using online or postal surveys quickly and inexpensively. However it has been criticised by economists for a lack of theoretical foundation for eliciting preferences due to a lack of explicit trade-off.(39) The standard gamble and TTO methods are more commonly used by economists; however these are more difficult for respondents to complete, and in particular methods are being developed to make the TTO more amenable to valuing states worse than death and address issues of time-preference.(40, 41)

1.3.2. Discrete choice experiment

While the TTO is the most widely used valuation technique for eliciting health state utility values,(38) it may not provide consistent preferences in AMD patients.(42) Ordinal methods such as rank or discrete choice experiment (DCE) avoid the key concerns of the TTO in AMD – namely an unwillingness to trade any years for an improvement in vision and the cognitive challenges of the question in elderly patients. Furthermore, the DCE method is well grounded in utility theory.(43) Respondents are required to simultaneously consider several attributes of the good being valued therefore the method can be considered a specific form of conjoint analysis.

DCEs are particularly attractive as a method for eliciting preferences for non-market goods such as the environment and healthcare where it is not possible to observe revealed preferences.(44) The original interest in DCEs in health economics was due to their flexibility to include non-health benefits such as utility derived from the process of care, reassurance or anxiety (compared with the SG and TTO which were specifically designed to capture health outcome benefits only). In healthcare, DCEs have been used to value patient experience such as waiting time, quality of care and health outcomes.(45) The flexibility of the valuation task to not be valued against perfect health and death (like the TTO and SG) may draw more reliable preferences since aspects of vision may be considered to fall outside of health and may include the process in which care is delivered.(46)

1.3.3. Choice of preferences

Patients can express preferences for their own health state via the direct elicitation methods described above. Patients may represent suitable candidates for valuing their health due to their knowledge of the condition, removing the need to elicit a health state and conduct a valuation in the public who may only be able to process limited information about the state.(6)

However, living with the condition means that patients cannot express *ex ante* preferences from behind a veil of ignorance.(47) Consequently their preferences are not expected utilities that conform to vN-M utility theory due to the absence of uncertainty.

Despite this limitation, patient-elicited utilities have, to date, been used widely in the CUA of treatments for eye disease.(48, 49) It can be argued that this has been in response to the perceived lack of suitability of questionnaire-derived utilities.

1.4. Vision and AMD

1.4.1. Disease

Age-related macular degeneration (AMD) is the leading cause of severe visual loss in patients over the age of 50 years in Europe and North America.(50, 51) Late-stage AMD is the third largest cause of blindness.(52) In the UK, there are estimated to be 513,000 cases of AMD and this number is predicted to increase to 679,000 cases by 2020.(53)AMD is the leading cause of visual impairment in industrialised countries.(52)

Neovascular AMD (nAMD) is characterised by choroidal neovascularisation (CNV), which is the growth of abnormal, choroidal blood vessels beneath the macula, which causes severe loss of vision and is responsible for the majority of visual loss due to AMD.(54)

Patients may find it harder to read, recognise faces, or make out fine detail, which can have a severe impact on their quality of life.(55) It predominantly affects central vision, having a severe impact on tasks such as reading.

There are two forms of AMD with distinct causes. nAMD (wet AMD) is caused by the development of new blood vessels in the macular. Geographic atrophy, or dry AMD, is caused by damage to the macula and a build-up of drusens. It is the most common and least serious type of AMD accounting for around 9 out of 10 cases.

The loss of vision is gradual, occurring over many years. An estimated 1 in 10 people with dry AMD will then go on to develop wet AMD.(56)

1.4.2. Impact on HRQoL

Vision loss has a wide-ranging and often severe impact on patients' quality of life and functioning.(52) As a disease that rarely causes mortality, economic evaluations are sensitive to the quality component of the QALY.(57)

However, it has been suggested that both measurement of changes in HRQoL in vision and the valuation of low vision health states fail to fully capture the changes in quality of life for economic evaluation.

Chronic diseases that limit activities of daily living such as AMD present a challenge for eliciting health states as patients often adapt to limitations that would initially seem disabling to the general population.

In AMD, no single visual function outcome captures HRQoL and interventions may have a differential impact on each outcome. Visual acuity (VA) and contrast sensitivity (CS) both have an impact on quality of life in AMD patients.(58)

VA measures the eye's ability to resolve fine detail and is widely used as a proxy for health-related quality of life. A number of studies have associated utilities with VA. Most notably *Brown et al.* asked the time trade off question in a sample of AMD patients in the US.(48) This has enabled the calculation of QALYs from VA outcomes and subsequently this has been used in the majority of economic models for treatments of macular degeneration.(49)

CS measures ability to see low contrast patterns and has also been shown to impact on quality of life. Indeed, it may be more appropriate to base economic models on CS or some combination of CS and VA rather than on VA alone.(58) CS has been associated with utilities via the time trade off, SF-6D, HUI-3 and EQ-5D.(59) It has been used in one economic model for treatment of macular degeneration.(60)

1.4.3. Treatments

One of the key mediators implicated in the pathogenesis of nAMD is vascular endothelial growth factor-A (VEGF). Treatments for CNV target VEGF are administered by injection into the vitreous cavity with high binding specificity

to VEGF (anti-VEGF agents). These agents are administered by intraocular (intravitreal) injections with repeat injections as necessary depending on the agent.

Spending on the anti-VEGF ranibizumab (Lucentis®, Novartis AG, Switzerland) accounted for £129mn of the NHS prescribing budget in 2010, making it the third most costly drug.(61)

Economic evaluations of treatments for AMD have concluded that the two anti-VEGF therapies used within the NHS, approved ranibizumab and off-label bevacizumab (Avastin®, Roche Holdings AG, Switzerland), are cost-effective at commonly applied thresholds.(2, 62) A recent head-to-head comparison found no significant difference between the two drugs in terms of effectiveness.(63)

There is currently no approved treatment for dry AMD. Patients are provided with vision aids such as magnifiers and encouraged to develop strategies to adapt to their reduced vision and to maximise the use of their remaining vision.(64)

1.5. Concluding remarks

In conclusion, there is a need to measure changes in HRQoL in order to perform CUA of treatments for AMD. From a methodological point of view, patients should report their own health states while the public should value these health states in order to reflect society's preferences.(3) While there remain a variety of methods employed, there is an increasing trend for generic HRQoL

questionnaires with associated value sets representative of the general public to

be employed.(65)

Research aims

Four related research questions have been identified with the objective of

developing an improved method for measuring and valuing health benefits in

vision disorders:

1. How do widely used methods for deriving health state utility values in AMD perform and how can these methods be improved?

2. Are non-health attributes important in AMD and how can they be incorporated into the cost-utility economic evaluation framework?

3. How is visual function associated with utility in AMD and how can the association be applied to economic evaluation?

4. What is the economic impact of treating AMD patients with good

starting vision?

2. Literature review

This chapter is a systematic review of the methods to estimate health state utility values to calculate QALYs in AMD. The review identifies where limitations exist and is used to define the research aims of the subsequent chapters of this thesis.

2.1. Introduction

A literature review was conducted to identify the methods that have been used to value health benefits in order to assess the cost effectiveness of treatments for AMD following the methodological guidance published by York Centre for Review and Dissemination (CRD).(66) It was decided that, due to the focus of this thesis on health benefits and the relevance of the QALY within the UK healthcare system, the search would be limited to studies that are suitable for estimating QALYs.

A preliminary screen of systematic reviews using the Cochrane Library (which includes Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effectiveness (DARE) and the HTA Database) identified no directly relevant reviews. The closest match was a review titled "Measuring quality of life for patients with age-related macular degeneration".(67) However, this did not directly consider measures of economic benefit such as QALYs and was conducted a number of years ago (September 2006).

2.2. Search question

The search question was: "How have **utility values** been estimated for health states associated with **AMD** in order to calculate **QALYs**?"

Table 2.2 describes the search question using the system of Population, Intervention, Comparison, Outcome (PICO) components.

PICO	Terms
Population	Macular degeneration and similar retinal diseases
Intervention	Any/all
Comparison	Any/all
Outcome	Health state utilities/QALYs

Table 2.2. PICO components for search question.

It was determined that health state utilities from other retinal diseases with a similar impact on quality of life may be applied to AMD health states, so terms to capture these were included in the search strategy. These were conditions that also cause central vision loss (retinal vein occlusion, diabetic retinopathy and macular oedema).

2.3. Search strategy

Term	Synonyms
Macular degeneration and similar retinal disease	"Macular degeneration" "Macular disease" "Retinal disease" "Macular $edema" "Retinal vein occlusion" "Diabetic retinopathy"
Health state utilities/QALYs	"Quality$adjusted life year*" "QALY*" "EQ$5D" "Euroqol" "SF$6D" "HUI" "Health utilities index"

Table 2.3. Search terms

It was decided that to increase the search results, all searches would be done with text searches rather than MESH terms in MEDLINE (macular degeneration and quality-adjusted life year are MESH terms). All terms were searched as multipurpose terms in OVID (.mp: Title, Original Title, Abstract, Subject Heading, Name of Substance, and Registry Word fields). The search terms are detailed in **Table 2.3**.

Key words EQ-5D, SF-6D and HUI-3 were added to the QALY search in order to be sure to capture any papers that used these widely used preference-based quality of life questionnaires that are suitable for calculating QALYs. Wildcards were employed to account for UK/US spelling (e.g. oedema and edema), spaces/hyphens (e.g. EQ-5D and EQ5D) and truncations.

The search was limited to articles between 1st January 1990 and 31st December 2012 and to English language abstracts only. The 1990 limit can be justified by the fact that the majority of CUA has been conducted in the past 25 years, with methodological standards improving over time.(68)

MEDLINE, EMBASE and PsycINFO databases were searched via the OVID portal. HTA and NHS EED databases were searched via the York CRD portal.

2.4. Data extraction

A data extraction form was piloted then employed as shown in **Table 2.4**.

	Data item
1.	Endnote ID
2.	Authors
3.	Title
4.	Year
5.	Full reference
6.	Disease
7.	Type of paper: Prospective or retrospective trial, economic model, utility study, review, other
8.	Intervention
9.	Comparator
10.	Sample size
11.	Sample country
12.	Questionnaires
13.	Preference elicitation technique
14.	Preference-elicitation algorithm country
15.	Other comments

Table 2.4. Data extraction form.

2.5. Results

	Term	OVID	CRD
1.	"Macular degeneration".mp	30417	111
2.	"Macular disease".mp	1108	1
3.	"Retinal disease".mp	2974	3
4.	"Macular $edema".mp	14094	23
5.	"Retinal vein occlusion".mp	7225	9
6.	"Diabetic retinopathy".mp	53073	77
7.	1 or 2 or 3 or 4 or 5 or 6	96423	196
8.	"Quality-adjusted life year*".mp	24696	4067
9.	"QALY"".mp	11968	3015
10.	"EQ-5D".mp	9020	587
11.	"Euroqol".mp	6382	234
12.	"SF-6D".mp	1215	45
13.	"HUI".mp	2943	55
14.	"Health utilities index".mp	1518	92
15.	8 or 9 or 10 or 11 or 12 or 13 or 14	40743	8095
16.	7 and 15	383	82
17.	Limit 16 to English lang.	383	N/A*
18.	Limit 17 to 1990 - 2012	299	N/A*

Table 2.5. Number of search results by search term.

limits set to each term in CRD

Search details:

- Databases searched: MEDLINE, EMBASE and PsycINFO via Ovid and HTA and NHS EED via York CRD

- Search dates: 01/01/1990 to 31/12/2012

The results returned from the searches are detailed in **Table 2.5**. Titles and abstracts of the search results were screened. **Figure 2.3** shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scheme employed for screening search results.(69)

Studies were included if they applied utility values for retinal conditions i.e. cost-utility studies for treatments, or if they reported utility values for retinal conditions or if they described methods to elicit them.

Identification

- Records identified through OVID. n = 299
- Records identified through CRD. n = 82

Screening (Level 1)

- Records screened. n = 381
- Records excluded at level 1. n = 199
  - Record type (e.g conference abstract, letter, editorial). n = 47
  - Therapy area (e.g. diabetes). n = 90
  - Duplicate. n = 62

Eligability (Level 2)

- Abstracts screened. n = 182
- Records excluded at level 2. n = 88
  - Record type (e.g. comment). n = 14
  - Non-QALY-based. n = 23
  - Duplicates. n = 51

Included

- Number of papers included. n = 94

Figure 2.3. PRISMA scheme depicting record identification and screening.

The 94 included studies were categorised as follows:

- Economic model employing utility values, n = 53

- Prospective trial collecting utility values, n = 10

- Other study collecting utility values, n = 18

- Review or discussion of utility values, n = 13

The search showed that a wide range of techniques have been used to elicit utility values in AMD. These are described below and summarised in **Table 2.6**.

Techniques that have been applied to estimate utility values in AMD for the calculation of QALYs have included direct elicitation from patients via the TTO, SG and contingent valuation, elicitation from members of the public using the TTO, generic preference-based questionnaires (EQ-5D, HUI-3, SF-6D), mapping from a condition specific questionnaire to a generic preference-based questionnaire (NEI VFQ-25 to EQ-5D), and a condition-specific preference-based questionnaire (VisQoL).

Among the studies that used direct preference elicitation from patients, a study by *Brown et al.*, elicited utilities from a sample of 80 patients with AMD using the TTO and SG valuation techniques and associated these with different levels of VA.(48) The TTO values in this study were most frequently used to provide utility values for health states in economic models (see **Appendix B** for details of AMD CUA models).

However, another study highlighted that different utility values were obtained depending on who they were elicited from. *Stein et al.* compared TTO valuations of AMD health states in patients, medical doctors and the general public. It

found that the general public and doctors rated the condition less severely than patients and argued that this suggested an underestimation of the severity of the condition on the part of members of the public and doctors.(70)

A number of studies have derived utility values from preference-based questionnaires. *Espallargues et al.* compared several methods for eliciting utilities in a sample of AMD patients. The study administered the EQ-5D, SF-6D, HUI-3 and TTO.(58) The utility values from this study were applied to an economic evaluation of PDT for AMD based on CS health states by *Bansback et al.*(60)

One mapping algorithm was identified which allows utility values to be derived from a non-preference based vision-specific questionnaire. *Payakachat et al.* developed a mapping algorithm to convert NEI VFQ-25 scores to EQ-5D utilities in AMD patients.(71) They recommended a CLAD short model over OLS or Tobit models. However, overlap was weak and, as of the date of the search, this algorithm had not been applied to an economic evaluation.

Tosh et al. reviewed the performance of generic preference-based HRQoL questionnaires in measuring changes in vision. They found that the HUI-3 seemed to perform better in some vision disorders, but the evidence on it and SF-6D is limited. The EQ-5D performed poorly in AMD and diabetic retinopathy.(14)

Further evidence of the insensitivity of the EQ-5D in vision disorders was identified in *Loftus et al.* The paper compared visual function and HRQoL in pegaptanib-treated patients with DMO. (30) They found statistically significant

improvements in visual function as measured by VA and in vision-specific quality of life as measured by the NEI VFQ-25 overall score, but no significant change in the mean change in utility from the EQ-5D.

There remain unclear associations between visual function and HRQoL. VA has been noted to be weakly associated with utility and another measure of visual function, CS, has been shown to have an independent impact on utility.(59)

In an attempt to solve the limitations with both direct patient elicitation and public tariff-based utilities, *Czoski-Murray et al*. developed utilities derived from members of the public who were asked to conduct a TTO while wearing contact lenses to simulate AMD.(72) These were used in the economic evaluation that was part of NICE's HTA of ranibizumab and pegaptanib for AMD.(73)

In terms of investigating the economic impact of treating different severities of disease: *Javitt et al.* developed an economic model to compare the cost-effectiveness of treatment of nAMD with pegaptanib in cohorts of early, moderate and late disease.(74) They found that patients treated early incurred lower lifetime total direct costs than those treated later and that the ICER for early nAMD patients was around a third of that for late nAMD patients. However, NICE did not recommend pegaptanib for use in the NHS and recommended ranibizumab (another anti-VEGF) for treatment in only patients with vision worse than 6/12 (i.e. not in early patients).(73)

Instrument	Category
EQ-5D	Generic preference-based
SF-6D	Generic preference-based
HUI-3	Generic preference-based
NEI-VFQ 25	Condition specific non-preference based (mapped)
VisQoL	Condition specific preference-based
Time trade-off (TTO)	Preference elicitation technique
Visual analogue scale (VAS)	Preference elicitation technique
Contingent valuation	Preference elicitation technique
VF-14	Condition specific non-preference based (mapped)
Visual acuity (VA)	Visual function (mapped)
Contrast sensitivity (CS)	Visual function (mapped)

Table 2.6. Summary of instruments used in utility measurement in AMD.

2.6. Discussion

Few clinical trials have incorporated measures suitable for calculating QALYs. All CUA models have been based on QALY weights derived from visual function measures of which most used a study that applied the TTO in AMD patients based on VA states.(48)

Generic questionnaires, and particularly the EQ-5D, have been found to be insensitive. Elicitation of utility values for common vision disorders have used both perfect health and perfect vision as the anchor with several studies reporting CUA in vision years.(46) Valuations of AMD health states between patients, public and clinicians appear to vary.(70)

2.7. Interpretation and refined aims

Four related research aims have been identified and refined to address the need to develop an improved method for measuring and valuing health benefits in vision disorders:

2.7.1. How do widely used methods for deriving health state utility values in AMD perform and how can these methods be improved?

The literature review highlights that methods for eliciting utilities for health states associated with vision problems have limitations in terms of the descriptive system employed.

Generic preference-based questionnaires are used to measure health states in patients, the TTO is used to elicit utilities in patients. (**Chapter 3**). Following the identification of a paper describing the use of simulation contact lenses to elicit utilities via the TTO in members of the public, it was decided to also investigate this method as part of this research question. (**Chapter 3**).

A method for augmenting the descriptive system for informed valuation of health states is developed applying the TTO with additional disease information (**Chapter 4**).

2.7.2. Are non-health attributes important in AMD and how can they be incorporated into the cost-utility economic evaluation framework?

QALYs are the most widely used framework for the economic evaluation of health technology. Yet, there may be non-health benefits associated with treatments from which patients derive welfare and vision may have an impact on aspects beyond health. For example, a treatment that has a more convenient delivery method may be valued by patients despite leading to an unchanged health gain. A method for incorporating these benefits into CUA is developed using a DCE (**Chapter 5**). A theoretical framework for assessing the benefits of improved patient decision making using decision support tools is also presented (**Chapter 8**).

2.7.3. How is visual function associated with utility in AMD and how can the association be applied to economic evaluation?

Many economic evaluations require the use of visual function variables as a surrogate for health state utility: generally because health state utility values have not been collected in a trial or because of the need to extrapolate the outcomes of a trial to a longer time horizon.

There remain unclear associations between visual function and HRQoL. VA has been noted to be weakly associated with utility and another measure of visual function, CS, has been shown to have an independent impact on utility.(59) The impact on cost-effectiveness is investigated using a CUA model and a more comprehensive measure of visual function to extrapolate health state utilities in economic models is developed using mapping (**Chapter** Error! Reference source not found.).

2.7.4. What is the economic impact of treating AMD patients with good starting vision?

The level of vision for which treatment is initiated may impact on the QALY gain generated by the intervention.(74) A CUA model comparing the initiation of treatment early or delaying treatment is developed to estimate the cost-effectiveness of immediate treatment compared with current NICE guidance of delayed treatment (**Chapter 7**).

3. Measurement of health state utility values in vision

This chapter investigates the performance of HRQoL questionnaires and valuation techniques currently used to elicit health state utility values for AMD in order to address the first part of research aim 1: *How do widely used methods for deriving health state utility values in AMD perform and how can these methods be improved?*

3.1. Patient-reported outcome measures

3.1.1. Introduction

A systematic review of preference-based questionnaires in vision by *Tosh et al.* identified in the literature review (**Chapter 2**) describes concerns surrounding the performance of generic preference-based HRQoL questionnaires for measuring and valuing health states associated with AMD.(14) The authors found that the performance of the EQ-5D in visual disorders was inconsistent and there was limited evidence on either the HUI-3 or the SF-6D.

It may be hypothesised that these questionnaires suffer from limitations in their descriptive systems and fail to contain sufficient information to reflect a patient's health state, especially for diseases like AMD, which are neither painful nor life-threatening.(75) This would both make it hard for the patient to accurately express their health state and for the valuer to value that state.

 Alternatively it could be that when patients classifying their health state, they misclassify the severity. Patients with chronic diseases are generally thought to report their health state less severely than those without the condition would expect due to the phenomenon of adaptation.(76) In AMD patients there is

evidence that this trend is reversed and that patients rate their health state more severely than the public.(70)

This section compares four frequently used measures used to derive utilities for the estimation of QALYs:

- The EQ-5D is a widely used HRQoL questionnaire with preferences derived from the general public.(18) With just 5 questions defining HRQoL and no mention of vision, there are concerns that it fails to provide a sufficient description of an AMD health state for accurate valuation by the public.(14)

- The SF-36 is an alternative HRQoL questionnaire with a different descriptive system and associated valuation tariff (the SF-6D) that has shown greater sensitivity to changes in health with fewer ceiling effects in some conditions.(16)

- The TTO is a preference-based technique allowing the patient to express preferences for their own health state on a utility scale bounded by 0 (dead) and 1 (perfect health).(36)

- The VAS is a non-preference-based technique allowing the patient to express their health state on a 0 to 100 scale between best and worst imaginable health.(77)

Espallargues et al. previously reported health state utilities for AMD using a range of questionnaires including the three-level EuroQol EQ-5D and SF-6D.(58) The new five-level EQ-5D provides a more comprehensive descriptive system and may be more sensitive to differences in patients'

level of visual disability.(78) Meanwhile, direct patient valuations of their health states have been produced by *Brown et al.* using the TTO.(48)

3.1.2. Methods

Sixty patients diagnosed with exudative (wet) or atrophic (dry) AMD with VA of 0.3 logMAR (6/12) or worse in the better seeing eye were recruited from clinics at Moorfields Eye Hospital, London, UK. Patients were excluded if they had ocular comorbidities. An accurate sample size calculation could not be done prior to the start of the study given the lack of data comparing utilities from two different questionnaires. Post hoc sample size calculations are of limited value, but using the observed standard deviation of the difference between the EQ-5D and SF-6D equal to 0.22, a sample size of 60 gave a power in excess of 0.9 to detect a difference in utilities as small as 0.1. The power calculations was performed with the XSAMPSI routine in STATA (V12.1; Stata Corp LP, College Station, Texas, USA) with alpha = 0.05.

The study was approved by the West London Research Ethics Committee (see **Ethical approval**) and followed the tenets of the Declaration of Helsinki. Patients gave informed written consent before taking part in the study.

A trained interviewer administered the four instruments listed in **Table 3.7** in a random order.

Instrument	Preferences	Valuation technique
EQ-5D	UK public (EQ-5D-5L interim value set)	Time trade-off (preference-based)
SF-6D	UK public (UK valuation of SF-36 US v1)	Standard Gamble (preference-based)
Time trade-off	Patients' Own	Time trade-off (preference-based)
Visual analogue scale	Patients' Own	Visual analogue scale (non-preference-based)

Table 3.7. Health status questionnaires.

The EQ-5D has five dimensions, each defined by a single question with five response levels. The five dimensions constitute a health state profile and the profiles were assigned a utility based on modelling from a large-scale survey of the UK general population using the TTO valuation technique.[20]

The SF-6D is derived from items of the SF-36 questionnaire. It has six dimensions: physical functioning, role limitation, social functioning, bodily pain, mental health and vitality. It was valued using the SG valuation technique in the UK general population.[79]

The TTO was a variant of the TTO used to value the EQ-5D developed by the University of York, UK.[80] Respondents were asked to value their own health state using a 10-year ping-pong technique (analogous to an adaptive staircase procedure) against perfect health and the result was converted to a utility.

The EQ-5D VAS requires the respondent to rate their overall health on a scale between 100, the best imaginable health state, and 0, the worst imaginable health state. (EQ-5D, SF-6D, TTO and EQ-5D VAS questionnaires are presented in **Appendix B**)

Sociodemographic information was also obtained from the participants. VA was taken from chart notes. While this is likely to be less accurate than if we had measured VA with a standardized protocol using ETDRS charts, the VA in the chart notes was the information available to the clinician at the time a decision was made regarding treatment.

Repeated measures analysis of variance (ANOVA) was used to compare utilities among techniques. The contribution of VA to utility was assessed using regression.

3.1.3. Results

Of 60 patients recruited to the study, two withdrew before completing all of the questionnaires. Analysis was conducted on 58 patients with complete data.

The sample was typical of AMD patients in a hospital setting. Mean age was 83.8 (SD = 6.5) years and 67% (39) were female. Seventy nine percent of patients (46) had a diagnosis of wet AMD. The mean time since diagnosis was 7.0 (SD = 6.2) years. Mean best-corrected VA in the better seeing eye was 0.65 (SD = 0.30) logMAR.

Mean and median health state utility values are reported in **Table 3.8** and the distributions for the four methods are shown in **Figure 3.4**. Mean EQ-5D utility

scores were 0.61 and skewed towards 1, perfect health (left skew). Two

patients reported EQ-5D health states that resulted in utilities of states worse

than death. SF-6D scores were centred around 0.63. The TTO had a mean of 0.48

and a large standard deviation (0.41). VAS scores had a mean of 57 and

displayed a right skew.
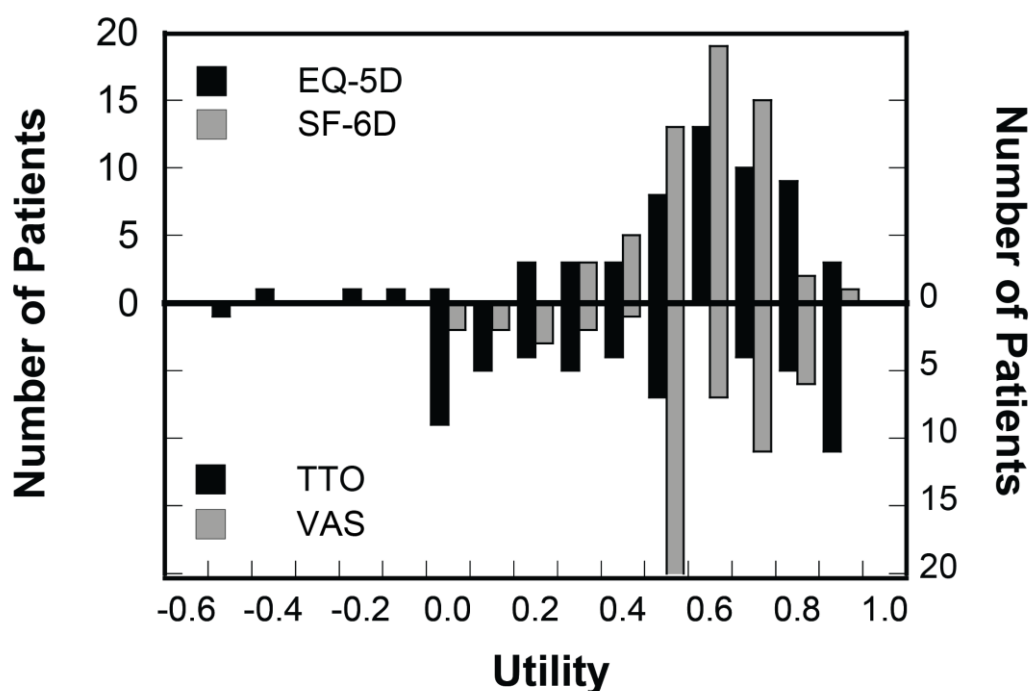
Figure 3.4. Histogram of utility scores by instrument.

Repeated measures ANOVA showed that there were significant differences in

utilities derived with the four methods $F_{(3, 33.6)} = 5.21$, $p<0.01$). Mauchly's test

indicated that the assumption of sphericity was violated ($p < 0.05$) therefore the

degrees of freedom were corrected using Huynh-Feldt correction. Although

ANOVA is quite robust to skew in the distributions of dependent variables, we

repeated the analysis using the non-parametric Friedman test. The differences

were still significant ($p < 0.001$)

Instrument	Mean (SD)	Median	Interquartile range
EQ-5D	0.613 (0.275)	0.657	-0.352 to 1.000
SF-6D	0.628 (0.114)	0.640	0.340 to 0.920
TTO	0.481 (0.411)	0.488	-1.000 to 1.000
VAS	56.7 (21.8)	50.0	5.000 to 100.000

Table 3.8. Frequencies of reported utility scores.

The mean utility scores of the four instruments were compared using a set of orthogonal contrasts. The two patient-based instruments TTO and VAS gave significantly lower utilities than the two instruments based on public tariffs, TTO and VAS [$F_{(1, 57)}$ = 12.8, $p < 0.001$]. The EQ-5D was not significantly different from the SF-6D [$F_{(1,57)}$ = 0.3, $p > 0.6$].

Figure 3.5 illustrates the similarity between the EQ-5D and SF-6D (left panel) and between the EQ-5D and TTO (right panel).
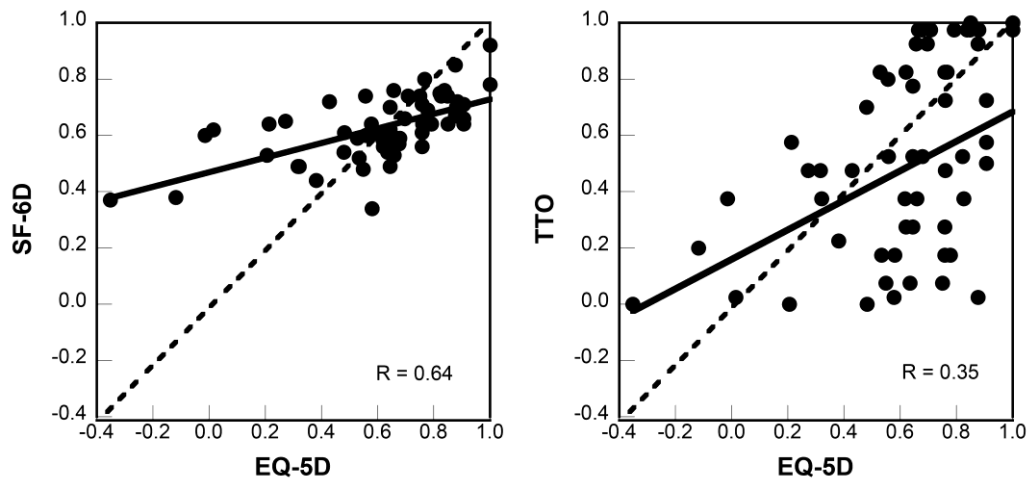
Figure 3.5. Comparison of methods for deriving public and patient preferences.

3.1.4. Discussion

These results showed no difference between utilities generated from the two generic HRQoL instruments tested, so public preferences for AMD health states appear to be independent of the two different descriptive systems used by the EQ-5D and SF-6D. Furthermore, there was no difference between patient preferences for their own health states when elicited by TTO or VAS, so patient preferences appear to be independent of the two techniques used.

However, there was a significant difference between public and patient utilities, with patients classifying their own health state as more serious than the public reading a description of their state. Within the valuation task there appears to be an inherent difference when asked to value one's own health compared to a hypothetical health state described by a HRQoL instrument.

This study finds a much more marked difference between public EQ-5D and patient TTO utilities than *Espallargues et al.* Such a finding may be explained by

the fact that we used the new 5-level EQ-5D with its more comprehensive descriptive system compared to the 3-level EQ-5D used previously.

The sample of patients may differ from the general public in sociodemographic characteristics. AMD patients are likely to be an older sample with more females than the general public sample used to establish the tariff. Patients with other diseases will differ from the general public in other ways. Consequently, the gap between public and patient preferences may differ not only due to the descriptive system, but also due to the different characteristics of the sample populations.

The difference between patient TTOs and EQ-5D scores may also be due to the TTO not measuring HRQoL in this population. Non-health time-related concerns such for living alongside a partner have anecdotally been mentioned as important when AMD patients undertake a TTO exercise.[81] Furthermore, the age of the patient sample and prevalence of comorbidities may make it hard to imagine living 10 years in perfect health. The VAS is not a choice-based method and therefore not recommended for use CUA. Furthermore, its scale between perfect and worst imaginable health is not directly comparable with the other measures that anchor zero at death.

The two forms of AMD (dry and wet) have similar impact on activities of daily living so we would expect no difference between the two groups. There was an insufficient number of patients with dry AMD recruited to assess this. However, a previous study by *Bansback et al.* identified no significant differences in utilities derived from the TTO or Health Utilities Index Mark-3 (HUI-3) between patients with wet or dry AMD.[59]

3.1.5. Conclusion

This study demonstrates that public and patient preferences are different, making it important to have a clear rationale for the choice of perspective. This study is not designed to recommend whose preferences to use. This remains a choice for health care decision makers, taking account of whose preferences they wish to rely on when allocating resources. However, the utilities derived by *Brown et al.*,(48) which are widely used in economic evaluation, are patient utilities and cannot be directly compared with utilities derived from public surveys.

The size of the difference in health state utilities can be illustrated in QALYs by including the length of life component. If an AMD patient were to live in the mean health state for ten years, they would accumulate 6.1 QALYs according to the EQ-5D (public preferences), but only 4.8 QALYs according to the TTO (patient preferences).

The implications for CUA of vision treatments are difficult to predict. It is the incremental change in QALYs before and after treatment compared to current standard care that is important when assessing cost effectiveness. Put another way, the methodology is distribution neutral and an improvement in health state utility for a moderately ill patient is equivalent to the same improvement in a severely ill patient.(82) However, given the different starting position on the scales, we would hypothesize that changes would be different. Furthermore, there is an emerging body of evidence that preferences for resource allocation are driven by the starting position on the scale, with some surveys suggesting

preferences for treating groups of patients with more severe disease ahead of those with less severe disease.(83)

Future work is needed to isolate the impact of the descriptive HRQoL system on preferences in order to determine if the differences in preferences identified in this chapter are due to a lack of information for public valuations or an inherent difference in perspective of patients and general public in their preferences for health states. From this work, given the two descriptive systems tested gave similar scores, the latter appears more likely.

3.2. Simulating health states

3.2.1. Introduction

An alternative approach to the use of PROMs to measure health states for valuation has been to create a simulation of AMD in members of the general public and ask them to value the health state that they experience.

Treatments for AMD and diabetic macular oedema (DMO) have been appraised by NICE in recent years. Appraisals of treatments for AMD and DMO were based on utilities from *Czoski-Murray et al*. which conducted a contact lens simulation of AMD.(72) In the study, members of the general public wore a contact lens with a central opacity that was meant to simulate the patient's view of the world through a central scotoma. Participants then completed a series of HRQoL questionnaires and the TTO to produce utility values associated with different levels of AMD severity. These health state utility values were applied to health economic models based on levels of VA (which represents a person's ability to resolve fine detail).

NICE Multiple Technology Appraisal 155 recommended ranibizumab for the treatment of AMD.(2) Following appeal and rapid review of Single Technology Appraisal 237, ranibizumab was recommended as an option for treating visual impairment due to diabetic macular oedema if the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and the manufacturer provides ranibizumab with the discount agreed in the revised patient access scheme (PAS).(84)

The performance of the contact lenses was assessed in order to assess the validity of this simulation. Both of these conditions can, in advanced cases, lead to the development of an absolute scotoma (a complete absence of retinal function) in the central retina. Broadly speaking, scotomas caused by AMD, DMO and similar diseases are a consequence of abnormalities at a retinal level. In advanced cases, these retinal abnormalities lead to dysfunction of the rod and cone photoreceptors in a confined area of the retina (the macula) which results in a blind spot at or near fixation. This blind spot greatly interferes with reading and recognizing faces and object. In contrast, a contact lens sits on the cornea, in front of the nodal point of the eye. Opacities on a contact lens would be expected to cause an overall reduction in the amount of light that reaches the retina, but not to cause a blind spot (see **Figure 3.6** and **Figure 3.7**). While this reduction in retinal illumination may affect vision, the impairment is far less debilitating than that caused by a blind spot on the visual axis.

 The effect of the opaque contact lenses was measured on five healthy volunteers who underwent a standard battery of vision tests, comparing their performance to the performance of actual AMD patients with real central scotomas.

A

Without Occlusion

OBJECT   EYE LENS   RETINAL IMAGE

B

With Occlusion
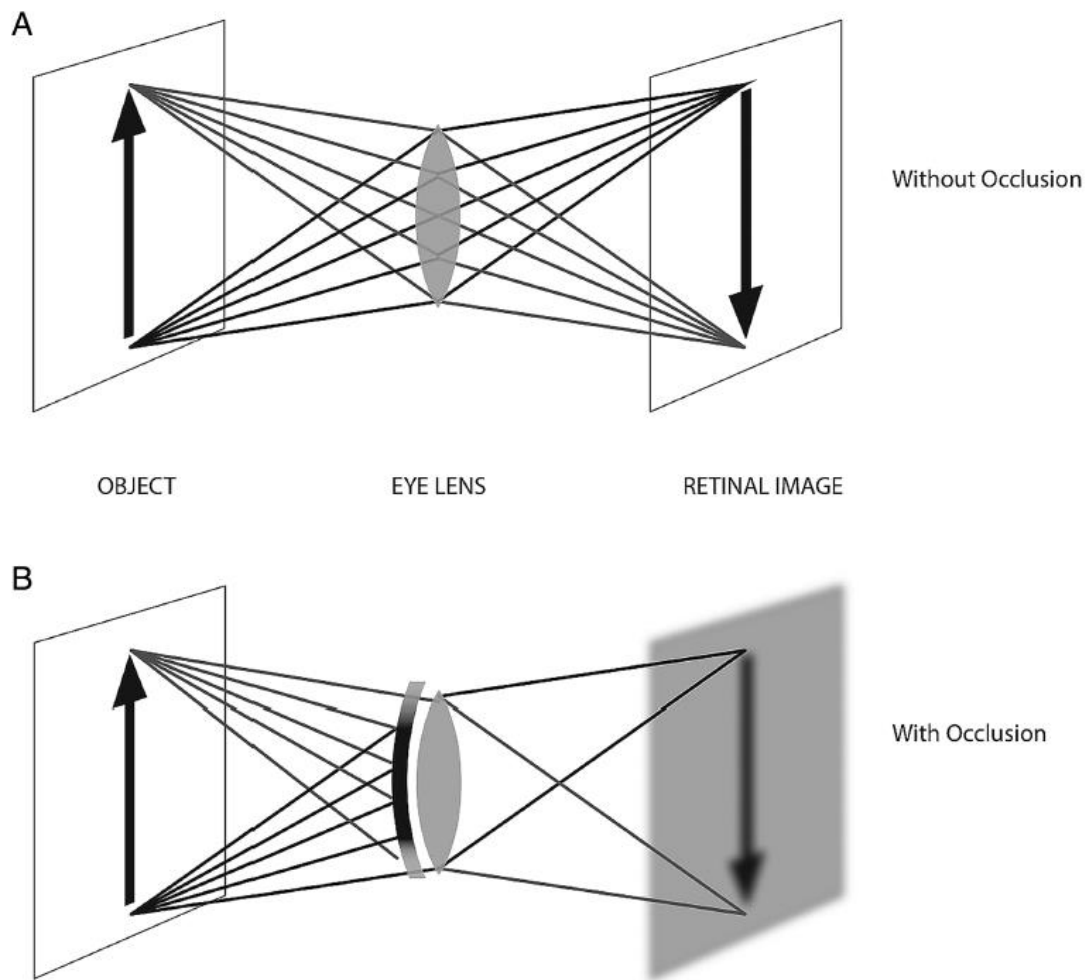
Figure 3.6. Ray diagram illustrating the optical effect of a contact lens with an opaque centre. In figure 3.6A the object (an arrow, left) is focused on the retina (right) with a plus lens (the crystalline lens and cornea, centre). Rays from all points in the object will be imaged onto the retina. In figure 3.6B, a contact lens is placed in front of the cornea. The contact lens has an opaque central zone which blocks some rays emanating from the object reaching the image. But some rays from all parts of the object still reach the retina. The retinal image is darker with the occluder and the image is blurred somewhat, because the optics at the edge of the crystalline lens have worse aberrations than the central optics, but the retinal image is complete and there is no scotoma.
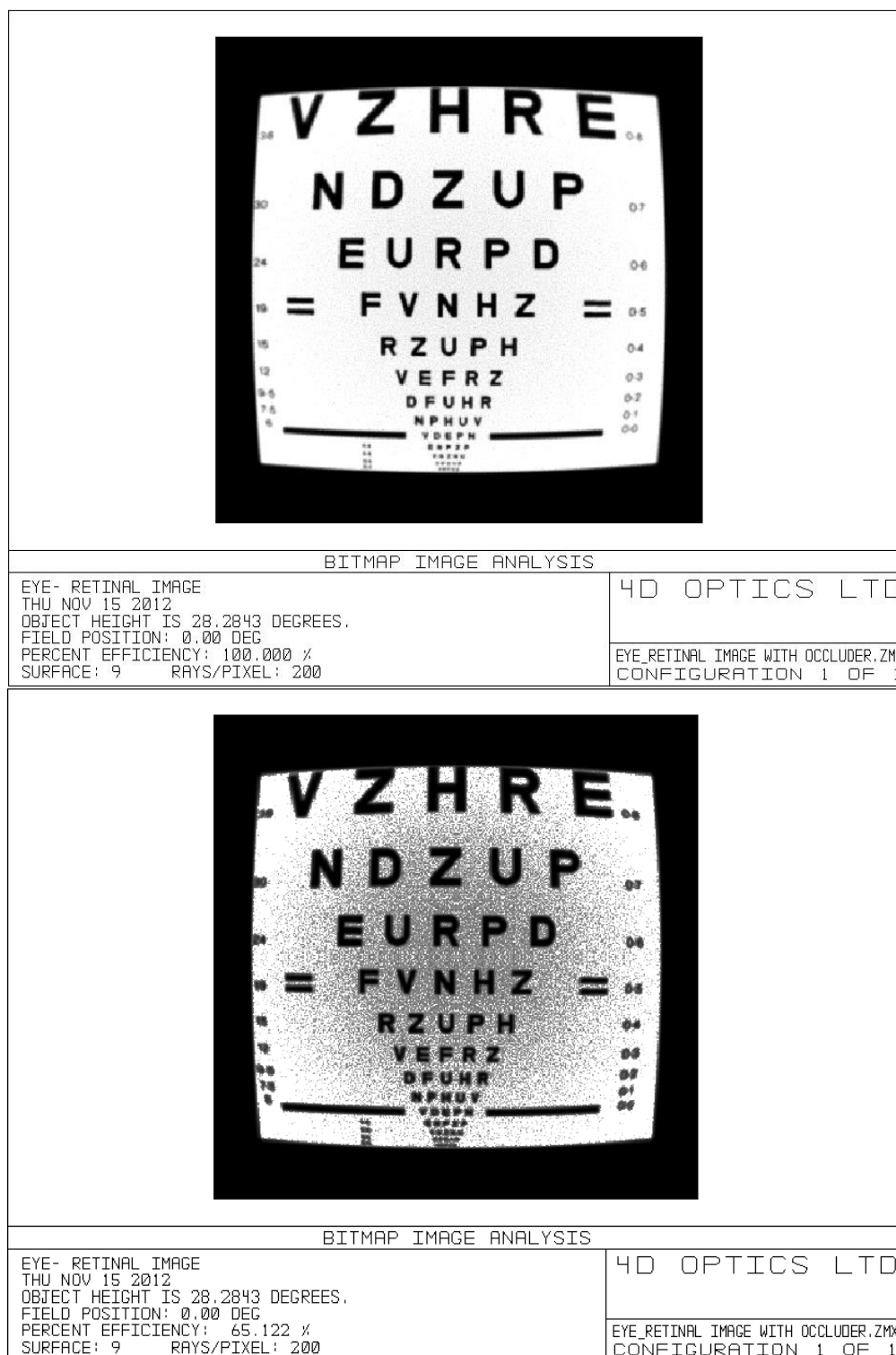
Figure 3.7. A simulated image of a logMAR visual acuity test is shown without (A) and with (B) an occlude showing a reduction in luminance of the test chart, but no central opacity..

3.2.2. Methods

Five control subjects with good VA and no history of eye disease were recruited from colleagues and staff of the Institute of Ophthalmology.

The study was approved by the University College London ethics committee (see **Ethical approval**), informed consent was obtained from all participants prior to data collection, and the study conformed to the Declaration of Helsinki.

A soft contact lens with an opaque pupil was selected for all participants based on keratometry readings. The lens design was similar to that used in the *Czoski-Murray et al.* study. In all cases the lens was a 67% water content afocal soft contact lens of diameter 14.5mm, with a 6mm black central pupil (Ultravision CLPL, Leighton Buzzard, UK).

All vision tests were performed monocularly with and without the contact lens in place. The test eye was selected by each participant.

The vision tests included distance VA (measured at 4 m using a standard ETDRS acuity chart (Lighthouse Low Vision products, New York, USA)) and CS (measured using either the MARS chart at 40cm or the Pelli-Robson chart at 1m).

Microperimetry was performed using the MAIA microperimeter (CenterVue, Padova, Italy). This is a scanning laser ophthalmoscope based perimetry system which performs visual field testing whilst simultaneously imaging the retina, enabling the retinal location of each visual field position to be controlled.(85) 68 points were tested over the central 10 degrees of retina, spaced at 2° intervals. Retinal sensitivity was measured using white Goldmann III targets,

presented for 200 ms, and thresholds were calculated using an adaptive

staircase algorithm. Fixation stability was measured as the area of a bivariate

contour ellipse encompassing 95% of fixation points.

3.2.3. Results

The contact lens reduced VA by an average of 17 letters (median logMAR = -

0.34 ; p< 0.01) and reduced CS by an average of 7 letters (median logCS = 0.36 ;

p < 0.01) (**Table 3.9**). Fixation stability was not affected by the contact lens

(p>0.2).

Subject		1	2	3	4	5	Median	IQR
VA (logMAR)	With CL	0.50	0.22	0.18	0.24	0.20		
	No CL	-0.20	-0.12	-0.08	-0.08	-0.18		
	Diff	0.70	0.34	0.26	0.32	0.38	0.34	0.32 to 0.38
CS (log units)	With CL	1.04	1.28	1.52	1.35	1.16		
	No CL	1.72	1.64	1.72	1.65	1.82		
	Diff	0.68	0.36	0.20	0.30	0.66	0.36	0.30 to 0.66
Retinal sensitivity	With CL	18.1	18.2	20.4	18.0	17.3		
	No CL	27.5	26.5	28.3	27.0	24.9		
	Diff	-9.4	-8.3	-7.9	-9.0	-7.6	-8.3	-9.0 to -7.9
Fixation stability (degrees²)	With CL	0.2	2.9	0.1	0.0	0.1		
	No CL	0.1	3.4	0.1	0.0	0.1		
	Diff	0.1	-0.5	0.0	0.0	0.0	0.0	0.0 to 0.0

Table 3.9. Results of visual tests for each participant, with and without simulation contact lens.

CL: contact lens. IQR: interquartile range.

Figure 3.8 shows microperimetry plots of retinal sensitivity for each

participant. The figures on the left ("a" panels) show data without the contact

lens and the figures on the right ("b" panels) are with the contact lens. "Hotter"

colours (yellow, orange, red) indicate poorer retinal function and "cooler"

colours (green, blues) show areas with better retinal sensitivity. It can be seen

that the contact lens reduces retinal function over the central retina but does

not produce any central region of absolute scotoma (with sensitivity less than 0

dB). Median retinal sensitivity without the contact lens was 27.0 dB, and 18.1

dB with the contact lens. The median difference was -8.3 dB.

 For comparison, a microperimetry plot for a subject with AMD is shown in

Figure 3.9. It can be seen that this individual has a large area with no retinal

function (sensitivity less than 0 dB, black circles on **Figure 3.9**).
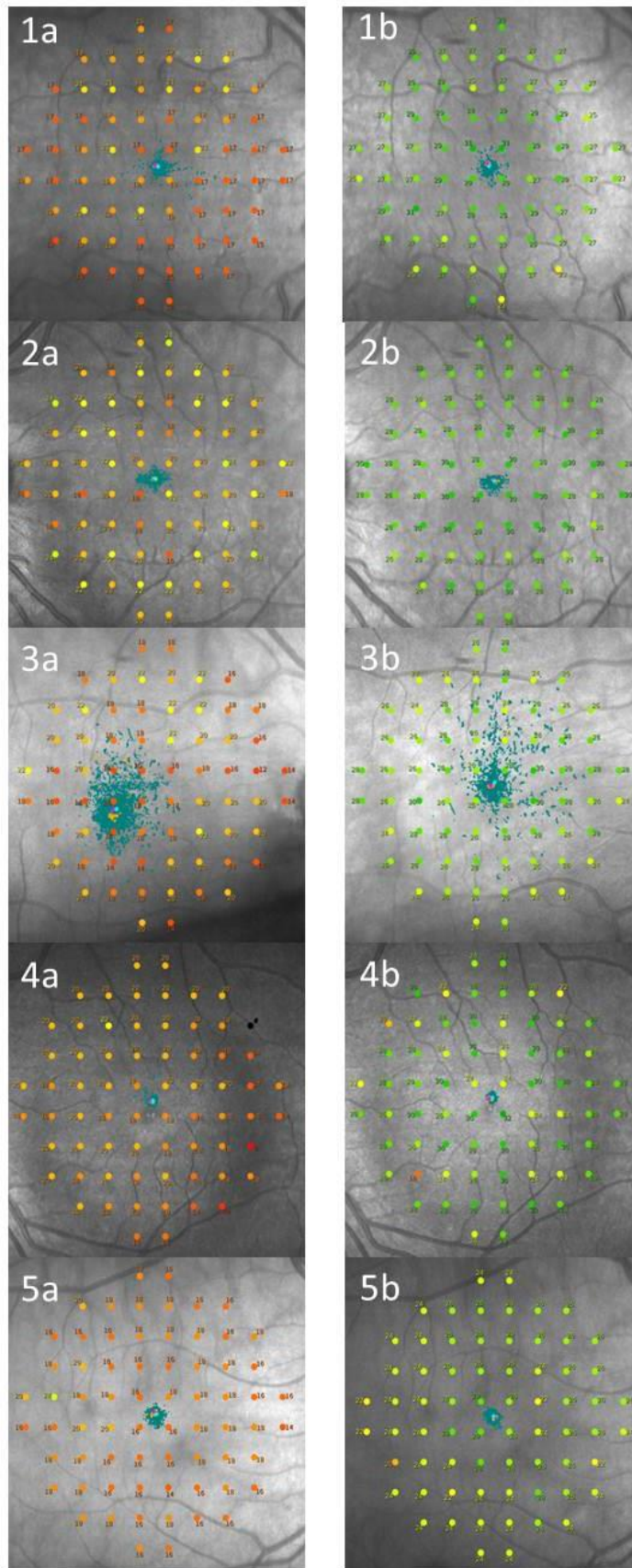
Figure 3.8. Microperimetry images for each participant with and without simulation contact lens.
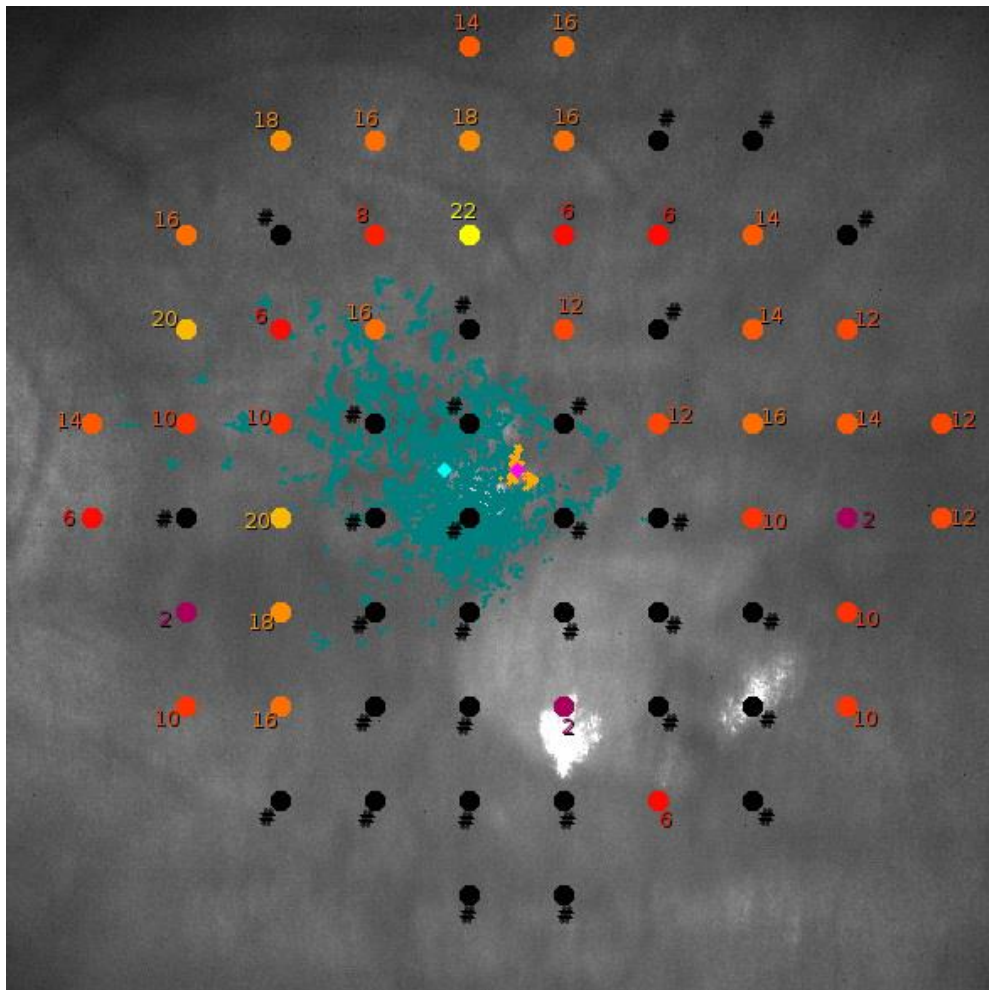
Figure 3.9. Microperimetry image for a subject with age-related macular degeneration.

3.2.4. Conclusion

A contact lens with central opacity reduces retinal illumination across the macula which reduces VA and CS. It causes a general reduction in retinal sensitivity but importantly does not create any area of absolute scotoma. Therefore, a contact lens with a central opacity does not accurately simulate the effects of advanced AMD.

Whether this will impact on the accuracy of the derived utility values is dependent on the strength of the association between VA and utility across eye conditions.

Most studies of vision and utility have shown that utility values worsen as visual impairment increases, although different conditions may affect vision differently, for example some conditions impact on visual field whereas others affect visual acuity.

It has been shown that VA is weakly associated with utility and that other aspects of visual function such as CS and visual field have a large impact on utility.(59, 86) A drop in VA due to a central scotoma in AMD has a different impact of quality of life and consequently utility than the same drop in VA due to cataract.

Brown et al. reported utility values using the TTO in AMD, cataract and diabetic retinopathy by levels of VA. For the same level of vision (20/70-20/100) patients with AMD reported a mean utility of 0.62, patients with cataract reported a mean utility of 0.71 and patients with diabetic retinopathy reported a mean utility of 0.78.(87)

Given the more severe impact of reduced acuity on utility in patients with AMD compared with cataract, it can be expected that a true simulation of AMD would lead the public to rate AMD more severely than predicted by contact lens.

An error of the magnitude of 0.09 on the utility scale is a major shift in a disease that impacts on QALYs through long term decrease in utility, although the impact on the incremental cost-effectiveness ratio (ICER) of this difference is difficult to quantify.

Evidence from the DMO ERG report suggests the ICER is sensitive to the utility values used. ICERs ranged from £16,585 to £39,712 in sensitivity analysis based around the *Czoski-Murray et al.* utility values, compared with £21,504 to £50,879 for the same sensitivity analysis based around *Brown et al.* utility values. The cost-effectiveness threshold is generally considered to be between £20,000 and £30,000 per QALY. Both analyses included the Novartis PAS discount, so represented the actual cost to the NHS.(88)

It could be argued that the generalised reduction in sensitivity induced by the contact lens is akin to a relative scotoma in early AMD. However, this was not the aim of the original research papers, which was designed to simulate a central scotoma.(72) Further, at the stage of AMD associated with reduced VA, some absolute central scotoma is to be expected.

A well reported functional consequence of AMD is reduced fixation stability.(89) Poor fixation stability is known to be associated with poorer visual function, particularly for reading.(90) Reduced fixation stability was not identified by the contact lens simulation, further limiting its applicability to true macular disease.

This study was conducted in a sample of five participants. Although the sample size was small, the results were consistent, with all observers showing a drop in acuity and contrast sensitivity, but no scotoma. The use of "forced-choice" testing procedures increases the reliability of the tests and reduces the opportunity for subjects to consciously influence the results.

How should central vision loss be simulated? Spectacles with opacities on are not a valid option as eye movements will alter the retinal position of the opacity. Although contact lenses seem like an attractive option to simulate vision loss, we have shown that this does not create a central scotoma. The most appropriate way of simulating a scotoma in people with good vision is to use feedback from an eye tracking system. These devices display an image on a computer screen whilst simultaneously measuring the position of the eye. Software can produce a scotoma at the region of the image corresponding to the centre of gaze. These systems have been used in research settings (91, 92) but have not, to date, been used to elicit utility values for AMD states in a public sample. A simulation is likely to be the most accurate way for people with good vision to imagine the health state of a scotoma caused by AMD. However, the simulation will still have limitations since participants are unlikely to be able to experience the simulation for long enough to imagine the long term impact of the condition on daily activities in a real world setting. Further, the simulation of a single state would not allow the participant to imagine the progressive nature of the condition.

Alternatively, one could return to the reason for the use of the simulation. The deviation from generic HRQoL questionnaires to derive health state utilities was

due to concern that standard questionnaires were not sensitive to changes in visual function due to limitations with the descriptive system. Future work to enhance the sensitivity of generic questionnaires may again place vision disorders on a common health state utility scale required for economic evaluation.

A contact lens with a central opacity does not simulate a retinal scotoma that is characteristic of diseases of the central vision like AMD. Opaque contact lenses reduce retinal illumination which leads to a reduction in VA and CS, but the overall dimming effect bears little resemblance to a central scotoma that is the hallmark of AMD

The association with a lower level of VA is not AMD-specific and contact lens utilities could represent many causes of visual impairment. The VA association has been shown to be different across disorders, therefore public valuations using this method may misinform the public.

The use of these utility values in economic evaluations may lead to an incorrect estimation of the cost effectiveness of treatments for AMD and other eye diseases that cause central scotomas.

4. Valuation of health state utility values in vision

This chapter investigates the impact of information on the valuation of health states by the general public. The descriptive system of the EQ-5D is augmented with disease information to derive health state utility values for AMD in order to address the second part of research aim 1: *How do widely used methods for deriving health state utility values in AMD perform and how can these methods be improved?*

4.1. Introduction

It is widely accepted in the health economics literature that the general public should value health states.(3) As payers in a tax-funded health system, it is considered right that the public's preferences are taken into account when allocating health care resources. Furthermore, the public offers an unbiased view of health states, unaffected by the condition they are valuing.

Having said this, there are serious information problems within health, which may mean the public lack information about health conditions. Indeed, the Washington Panel on Cost Effectiveness argued that *'…the best articulation of society's preferences for a particular state would be gathered from a representative sample of fully informed members of the community'*.(8)

In the UK, NICE currently recommends generic preference-based health-related quality of life questionnaires, namely, the EQ-5D, for use in CEA.(2) The EQ-5D UK value set was obtained from a population of 'uninformed' general public by conducting TTO valuation tasks on EQ-5D health states.(80)

Concerns have been raised about the performance of the EQ-5D in some health conditions, including vision-loss, as demonstrated in the previous chapter of this thesis.(14, 93) Information provided by the questionnaire may give the uninformed valuer limited information on what it is like to live with a disease and how one may adapt to achieve high quality of life despite what may initially appear to be disabling limitations of a chronic condition.(76) This information problem may be accentuated by the relatively short nature of generic preference-based HRQoL questionnaires used to value health states: the EQ-5D-5L questionnaire consists of 5 questions each with 5 levels.

Vision-loss is one such example where lack of information about the condition and the process of adapting to it may not be fully captured in the EQ-5D health state.(14, 58) A study in AMD patients found that patients value their health more severely than the general public using the TTO.(70)

Recognising these limitations, contact lenses simulating AMD have been tried as a method of informing the public about AMD prior to valuing the health state.(72) Indeed, health state utilities derived from this approach were used in NICE's technology appraisal of treatments for AMD.(73) However, contact lenses do not simulate the loss of central vision that typically occurs with AMD as demonstrated in **Chapter 3** of this thesis. Furthermore, wearing lenses for a short time may not accurately simulate the long-term effects of living with a chronic disease.(94)

Perhaps most importantly, if decision-makers wish to maintain cross-program comparability for CUA, the method of informing for health state valuation should be as standardised as possible across conditions. Simulating an eye

condition may be technically feasible, but simulating a disease in the general public would be challenging and ethically undesirable in many other conditions. For this reason, it can be argued that the provision of information prior to a valuation task using a generic HRQoL instrument is the most promising way to close the information gap if bias can be avoided.

A study by *Rowen et al.* investigated the impact of providing different disease labels on valuations. (75) The study investigated the effect of labelling on health state valuations in cancer and irritable bowel syndrome (IBS). It found no significant differences between health state values when the description contained no label or an IBS label. However, a cancer label affected health state values and the impact depended on the severity of the state: values were significantly lower when labelled for worse states, but there was no significant difference for mild states.(75) They suggested that people may bring their preconceptions about a condition to the valuation task.

The aim of this study was to investigate the effect of different types of information on valuations of AMD heath states by the UK general public. This study takes a single condition where there are thought to be information problems and seeks to determine if the framing of information influences valuations of EQ-5D health states by the general public.

The study assessed how different types of information affect valuation by comparing no information, a label and patient descriptions. It also tested how the way this information was presented affects valuation by including two different patient descriptions.

4.1.1. Pilot

The survey was piloted in a convenience sample. 40 members of the general public each completed TTO tasks on 4 health states (**Table 4.12**) accompanied by varying levels of information about AMD generating 150 health state utility values after missing data. The four information levels were:

- Group 1: Unlabelled AMD patient EQ-5D profiles. (No Information).

- Group 2: Short objective label of AMD from the NHS Choices website followed by the same 4 AMD patient EQ-5D profiles. (Label).

- Group 3: Short objective label of AMD and a patient description of their quality of life with the condition followed by the same 4 AMD patient EQ-5D profiles. (Patient Description)

- Group 4: Short objective label of AMD and a patient description of their quality of life with the condition and information on how a patient might adapt to life with AMD followed by the same 4 AMD patient EQ-5D profiles. (Adaptation)

Participants were randomly drawn into one of four information groups prior to beginning the task resulting in 13, 7, 7 and 13 participants entering groups 1, 2, 3 and 4 respectively. There were more females than males in the sample and the mean age was slightly lower than the UK average (**Table 4.10**).

Group (n=40)	1 (n=13) no information		2 (n=7) label		3 (n=7) patient description		4 (n=13) adaptation	
Mean age (SD)	36.8 (11.1)		38.1 (12.4)		29.1 (6.7)		35.7 (9.8)	
Gender	F: 9	M: 5	F: 6	M: 1	F: 5	M: 2	F: 6	M: 7

Table 4.10. Pilot demographic information

The public TTO valuations for each health state by group are summarised in

Table 4.11. Utilities were generally skewed towards 1.0 (left skew). While due

to the small sample, statistical significance cannot be inferred from the pilot

results, respondents generally valued the health state similarly to the EQ-5D

tariff as would be expected since the TTO valuation of an EQ-5D profile by a

sample of the general population used in the study follows the methods used to

obtain the tariff (with the exception of the elicitation method for this study

being online). A trend for respondents to value health states accompanied by a

label or a patient description more severely may be observed across health

states. While adaptation information caused respondents to value the health

state less severely than the social tariff. These trends agreed with the

hypothesis that additional information caused respondents to change their

valuation and that the type of information is important to determine the

direction and magnitude of effect.

Group	1 (uninformed)	2 (label)	3 (information)	4 (adaptation)	All
Health state 1 (0.76*) Mean (SD)	0.73 (0.24)	0.64 (0.22)	0.49 (0.56)	0.81 (0.16)	0.70 (0.30)
Median	0.81	0.73	0.68	0.83	0.78
Health state 2 (0.82*) Mean (SD)	0.85 (0.16)	0.70 (0.23)	0.72 (0.30)	0.87 (0.12)	0.80 (0.20)
Median	0.90	0.78	0.88	0.90	0.88
Health state 3 (0.88*) Mean (SD)	0.87 (0.20)	0.90 (0.09)	0.88 (0.14)	0.88 (0.16)	0.87 (0.17)
Median	0.94	0.93	0.95	0.96	0.93
Health state 4 (0.43*) Mean (SD)	0.49 (0.39)	0.45 (0.46)	0.58 (0.53)	0.69 (0.21)	0.56 (0.37)
Median	0.51	0.63	0.71	0.73	0.63

Table 4.11. Pilot utility values by information group and health state. SD = standard deviation.

*EQ-5D-5L UK interim value set.

Information from pilot for design of main study

Based on feedback obtain through discussion of a paper describing the results of the pilot at the Health Economists' Study Group meeting in Oxford (June 2011), it was determined that providing information on adaptation to AMD was challenging due to the difficulty separating out a treatment from the psychological process. For example, a personal decision to use a white cane may make movement easier and so improve the mobility domain of HRQoL. However, the cane itself is a treatment. Consequently, it was decided that for the full study, the adaptation information would be replaced by a second patient description in order to test the stability of preferences to different wording of the same type of information.

Feedback from the pilot also led to the addition of a question to test that respondents had understood the information that they had read. In the full study a multiple choice question was included at the end of the survey to test what respondents understood about AMD.

In the full survey, the four AMD health states, the label and the patient description were retained, and an additional patient description was substituted in place of adaptation

4.2. Methods

550 members of the general public were recruited via an online survey panel. Recruitment quotas were set for age, gender, location and socio-economic group

in order to obtain a sample that was representative of the English general public for these characteristics.

Participants were randomised to 4 groups to receive different levels of information about AMD before completing TTO valuations on AMD patient health states elicited in a prior patient study described in **Chapter 3** (**Table 4.12**).

- *Group 1* was asked to perform a series of 4 TTOs on 4 unlabelled AMD patient EQ-5D profiles. (*No Information*).

- *Group 2* read a short objective label of AMD from the NHS Choices website before being asked to perform a series of 4 TTOs on the same 4 AMD patient EQ-5D profiles. (*Label*) (56).

- *Group 3* read a short objective label of AMD and a patient description of their quality of life with the condition before being asked to perform a series of 4 TTOs on the 4 AMD patient EQ-5D profiles. (*Patient Description A*) (95)

- *Group 4* read a short objective label of AMD and a patient description of their quality of life with the condition before being asked to perform a series of 4 TTOs on the 4 AMD patient EQ-5D profiles. (*Patient Description B*) (56)

The two descriptions were selected to contain the common features of AMD, while presenting the information in slightly different ways. Both describe how the disease affects central vision and does not cause complete blindness, how it affects reading, driving, recognizing faces and aspects of depression or coping with the disease. In terms of differences, the first profile describes the condition

as 'age-related macular degeneration' whereas the second describes the condition as 'macular degeneration'. The first profile uses a third person description with quotes from the patient, whereas the second profile is a first person description. (**Box 4.1**)

Health State 1 (11112), 0.88*	Health State 2 (31211), 0.82*	Health State 3 (31312), 0.76*	Health State 4 (21513), 0.43*
I have no problems in walking about	I have moderate problems in walking about	I have moderate problems in walking about	I have slight problems in walking about
I have no problems washing or dressing myself	I have no problems washing or dressing myself	I have no problems washing or dressing myself	I have no problems washing or dressing myself
I have no problems doing my usual activities	I have slight problems doing my usual activities	I have moderate problems doing my usual activities	I am unable to do my usual activities
I have no pain or discomfort	I have no pain or discomfort	I have no pain or discomfort	I have no pain or discomfort
I am slightly anxious or depressed	I am not anxious or depressed	I am slightly anxious or depressed	I am moderately anxious or depressed

Table 4.12. Patient EQ-5D profiles selected for valuation by the public.

Utility scores derived using the EQ-5D-5L UK interim value- set.

An online TTO programme was developed to collect public utility values on patient health states. A screenshot of this tool is provided in **Appendix B**). The TTO was consistent with the York Measurement and valuation of Health (MVH) study (including 10-year timescale, ping-pong technique, certainty of health over time period, slider props).(80)

The programme consisted of the following:

- An introduction screen

- Socio-demographic questions

- An introduction to the TTO technique

- Information about AMD (*Groups 2, 3, 4* only)

- 4 TTOs on 4 patient EQ-5D health states (the state was labelled as 'macular degeneration' in *Groups 2, 3, 4*, and unlabelled in *Group 1*).

A question at the end was included for *Groups 2, 3, 4* to test participants' understanding of AMD to confirm if they had read the information carefully. The time that participants took to complete the survey was recorded and a minimum completion time of 8 minutes was set to exclude participants who did not read the information.

Each participant completed TTOs on the same four EQ-5D profiles. The order in which health states were presented was randomised. The EQ-5D profiles were selected from AMD patients who had reported no significant comorbidities in a previous study so as to present to the public health states that could plausibly be due to AMD in an otherwise healthy individual. The health states are described in **Table 4.12**.

Utility data was non-parametric, therefore Kruskal–Wallis one-way analysis of variance tests were used to estimate the impact of levels of information and health states on utility values. Analysis was conducted using Stata 12.1 (StataCorp).

Box 4.1. Health state information provided to respondents prior to valuation tasks.

Group 2 (label)

The health states that you are about to be presented with describe a person with macular degeneration (although please note that this condition may not be the only cause of their health status). Please read this description of macular degeneration carefully.

Macular degeneration is a painless eye condition that leads to the gradual loss of central vision (the ability to see what is directly in front of you). Central vision is used while:

- reading

- writing

- driving

Macular degeneration does not affect the peripheral vision, which means that the condition will not cause complete blindness. The peripheral vision is sometimes known as "side vision".

Group 3 (patient description A)

The health states that you are about to be presented with describe a person with macular degeneration (although please note that this condition may not be the only cause of their health status). Please read this description of macular degeneration carefully.

Macular degeneration is a painless eye condition that leads to the gradual loss of central vision (the ability to see what is directly in front of you). Central vision is used while:

- reading

- writing

- driving

Macular degeneration does not affect the peripheral vision, which means that the condition will not cause complete blindness. The peripheral vision is sometimes known as "side vision".

Here is a description by a patient of what it may be like to live with macular degeneration

Shirley's granddaughter Caroline is four years old, and for most of her life, her grandmother has had age-related macular degeneration (AMD), a condition that causes a loss of central vision.

"She always wanted to know what was wrong with Nana," says Shirley.

For the longest time, Caroline couldn't understand why her grandmother had trouble getting around. "I was always bumping into things," says Shirley. "And I didn't dare hold her when she was a baby – I was afraid of dropping her."

AMD also made it difficult for Shirley to see Caroline's face. "I would look at someone and see eyes on each side, but I couldn't see anything in the middle. There was no nose or mouth or anything."

Shirley first began to notice her vision was changing 10 years ago. "A road would look like it was hilly when in fact it was straight, and things like the edge of the stove or a painting would look like they were wavy. It was the strangest thing."

Her vision loss progressed rapidly, and soon she had to give up driving and reading, two activities that had been very important to her. Losing the ability to drive forced Shirley into retirement, because she no longer had a way to get to her job. And her long-time, three book-a-week habit fell by the wayside.

"I got very depressed." she recalls.

Group 4 (patient description B)

The health states that you are about to be presented with describe a person with macular degeneration (although please note that this condition may not be the only cause of their health status). Please read this description of macular degeneration carefully.

Macular degeneration is a painless eye condition that leads to the gradual loss of central vision (the ability to see what is directly in front of you). Central vision is used while:

- reading

- writing

- driving

Macular degeneration does not affect the peripheral vision, which means that the condition will not cause complete blindness. The peripheral vision is sometimes known as "side vision".

Here is a description by a patient of what it may be like to live with macular degeneration

"I found out I had macular degeneration when I went to the optician for some new glasses. The optician examined my eyes and told me: "You've got macular degeneration, but don't worry, you won't go completely blind."

"It was a surprise. My mother had suffered from macular degeneration, but it hadn't occurred to me that I might have it one day. The signs had probably been there, but I hadn't noticed them. I'd been doing a lot of numerical work and was having problems reading the numbers 6, 8 and 3. I had to concentrate very hard in order not to get them muddled up.

"At first it wasn't too much of a problem. My right eye was affected, and it stayed that way for three years. But when I began to get macular degeneration in my left eye, I had to give up driving. That was hard – a part of my independence had gone. Luckily, my husband drives, so I can still get around, but it was a difficult time.

"In the last few years, the macular degeneration has progressed more rapidly. I've had to give up a number of things I really liked doing, such as calligraphy and tapestry. Reading has become

difficult, so I now listen to talking books. I've also been in some embarrassing situations when I've passed friends in the street and not recognised them.

Adaptation information (used in pilot study only)

There are adjustments that can be made to adapt to life with macular degeneration:

* Getting around

You will be able to rely on peripheral or remaining vision, hearing, or the white cane to provide guidance. Devices such as telescopes can be used to identify street signs and addresses.

* Recognising faces

Arrange for a friend or peer to accompany you. It may be easier for them to explain to people that their smiles and waves can't be seen and to encourage them to identify themselves when they want to talk to you.

* Usual activities (reading and driving)

Driving is one activity that people with severe vision loss find extremely hard to give up. However, activities such as reading can continue with a little patience and adjustment. For instance, large-print books or a magnifier may help with reading. Talking books are an excellent substitute when reading becomes too difficult.

4.3. Results

550 members of the general public completed 2,200 TTO tasks. The sample had a mean age of 45.7 (all >18) and was representative of the general population for gender and socio-economic group. Participants lived in England in order to

represent the preferences of the group that should inform decision-making in the English NHS. Groups were similar with respect to these characteristics (**Table 4.13**).

		No information (n=136)	Label (n=139)	Patient description A (n=137)	Patient description B (n=138)	All (n=550)	ANOVA P value by group
Mean age, years (SD)		45.1 (13.5)	46.3 (13.8)	45.3 (14.2)	45.9 (14.4)	45.7 (14.0)	0.88
Age, %	18-40	39%	40%	42%	40%	40%	
	41-65	57%	48%	49%	47%	50%	
	Over 65	4%	12%	9%	13%	9%	
Gender: Female, %		52%	50%	56%	58%	54%	0.56
Activity, %	Employed/self-employed	83%	76%	72%	83%	79%	
	Full-time education	3%	2%	4%	0%	2%	
	Retired	3%	6%	3%	6%	4%	
	Looking after the home	1%	1%	1%	1%	1%	0.03
	Long-term illness/disabled	4%	7%	8%	1%	5%	
	Unemployed	6%	8%	12%	9%	9%	
Education: Degree level or above, %		37%	39%	40%	41%	39%	0.83
Mean own health state utility* (SD)		0.83 (0.19)	0.79 (0.22)	0.79 (0.24)	0.81 (0.20)	0.81 (0.21)	0.31
Correct understanding, %		-	59%	64%	51%	58% (n=414)	
Mean time to complete, min.s (SD)		13.38 (8.32)	12.43 (6.06)	13.18 (6.03)	13.26 (9.32)	13.16 (7.35)	0.78

Table 4.13. Respondent characteristics.

*EQ-5D 5L UK value set

103

The public TTO valuations for each health state by group are summarised in

Table 4.14. Mean health state utilities were lower in the groups receiving

patient profiles than in the groups receiving no information or the AMD label

(0.65 and 0.66 vs. 0.70 and 0.71 respectively). Median values followed the same

trend (0.88 and 0.88 vs. 0.83 and 0.83 respectively). TTO valuations were

similar for Groups 3 and 4 (two versions of patient profiles) so these two groups

were combined for further analysis.
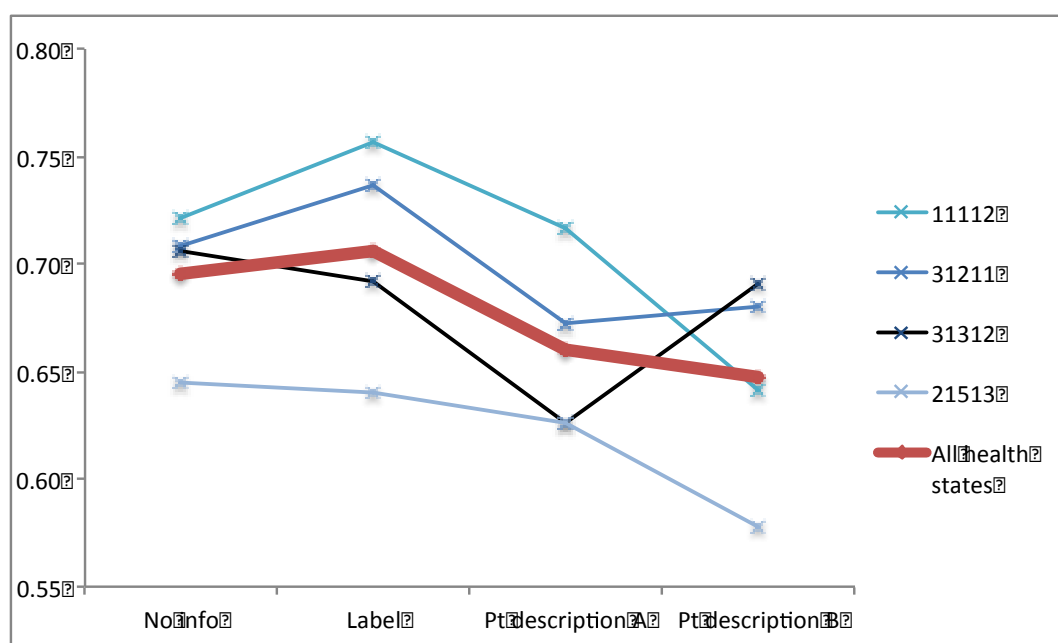
Figure 4.10. Health state values by group.

Kruskal–Wallis one-way analysis of variance tests were used to estimate the

impact of levels of information and health states on utility values since utilities

were non-parametric. (**Table 4.14**). Pooled across all four health states, information led to different utility values (p<0.1).

Median health state utility values for the information *Groups 2, 3, 4* (label and patient description) were compared to *Group 1* (no information). Neither of the information groups were significant when compared with *Group 1*.

a. By group
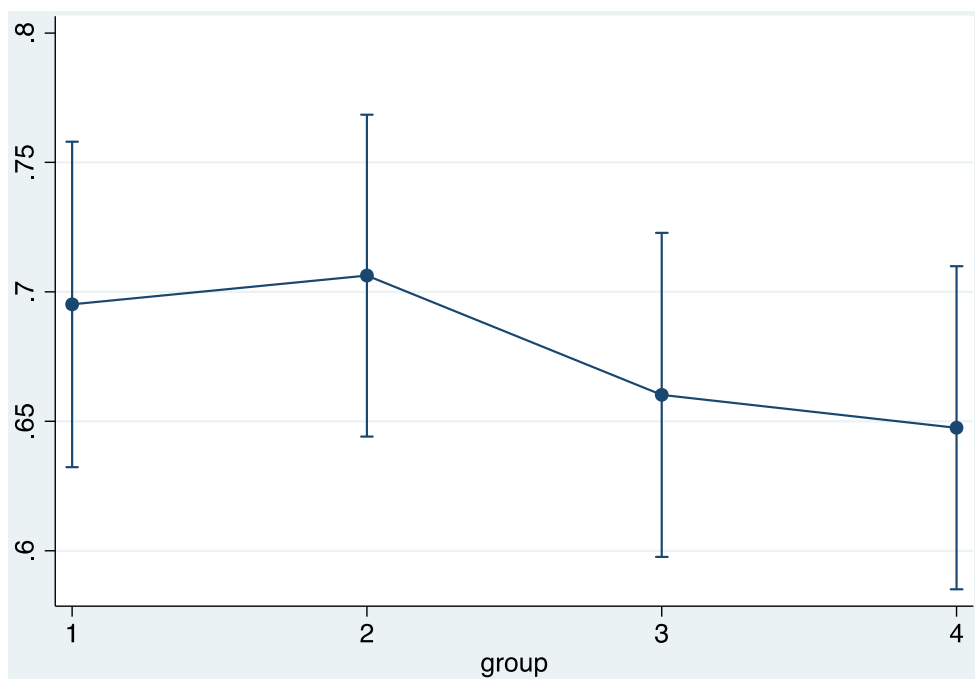
b. Groups 3 and 4 combined into 3
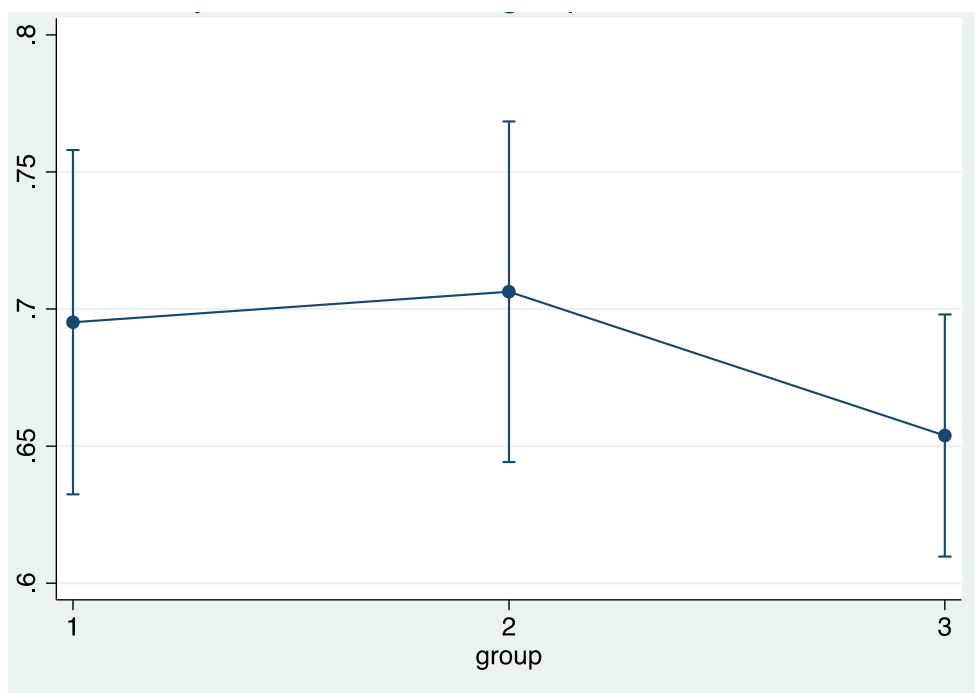
Figure 4.11. Means and CIs for health state utilities averaged across four health states.

Health state	No info (n=136)			Label (n=139)			Pt description A (n=137)			Pt description B (n=138)			All (n=550)		
	Mean (SD)	Median	IQR	Mean (SD)	Median	IQR	Mean (SD)	Median	IQR	Mean (SD)	Median	IQR	Mean (SD)	Median	IQR
31312, 0.76*	0.71 (0.43)	0.90	0.63 to 0.98	0.69 (0.42)	0.88	0.55 to 0.98	0.63 (0.45)	0.78	0.50 to 0.93	0.69 (0.42)	0.88	0.56 to 0.98	0.68 (0.43)	0.88	0.53 to 0.98
31211, 0.82*	0.71 (0.43)	0.93	0.63 to 0.98	0.74 (0.39)	0.88	0.70 to 0.98	0.67 (0.42)	0.83	0.58 to 0.98	0.68 (0.44)	0.88	0.53 to 0.98	0.70 (0.42)	0.88	0.58 to 0.98
11112, 0.88*	0.72 (0.39)	0.88	0.64 to 0.98	0.76 (0.42)	0.93	0.78 to 0.98	0.72 (0.41)	0.93	0.60 to 0.98	0.64 (0.50)	0.88	0.58 to 0.98	0.71 (0.43)	0.93	0.63 to 0.98
21513, 0.43*	0.65 (0.45)	0.83	0.49 to 0.95	0.64 (0.44)	0.83	0.48 to 0.98	0.63 (0.40)	0.78	0.50 to 0.93	0.58 (0.51)	0.78	0.48 to 0.98	0.62 (0.45)	0.80	0.48 to 0.93
All Health states	0.70 (0.43)	0.88	-	0.71 (0.42)	0.88	-	0.66 (0.42)	0.83	-	0.65 (0.47)	0.83	-	-	-	-

Table 4.14. Health state utility values by group. SD = standard deviation, IQR = interquartile range.

107

4.4. Conclusion

No differences were found in health state values with and without an AMD label. Mean health state utility in the label group was 0.71 compared with 0.70 in the no information group. AMD does not have a direct mechanism of action to increased mortality and this lack of a 'dread' risk factor may explain how a label does not change preferences for health states associated with AMD. Furthermore, we suspect that AMD is not well known as a condition among the general public, so the condition itself will not elicit strong emotions.

These results are consistent with the findings by *Rowen et al.* relating to labelling milder health states, which found that there was no significant difference for milder health states associated with cancer or for health states associated with IBS.(75)

There was a trend (not significant) towards lower utility in the patient description groups when compared with no information (0.70 vs 0.66 and 0.65 respectively). This trend was consistent across all health states and patient profiles except one (31312 and patient description B). The two patient descriptions led to similar health state utilities across health states (0.66 and 0.65 respectively) suggesting that the wording of the profile had little impact on the valuation.

The number of participants in *Groups 2, 3 and 4* who correctly answered the knowledge test was low (58%). Such a situation may have contributed to the finding of no significant difference between groups. Adjusting for this by excluding participants who answered the question incorrectly resulted in no

significant difference, although this adjustment also reduced the statistical power.

Knowledge of AMD may be influenced by having friends or family with the condition. This information was not gathered in the demographic details, although it could be expected that the random selection of the sample as representative of age and gender should not have led to one group having more knowledge than others.

The range of utilities associated with vision run across a small range. The difference between normal vision and severe sight impairment (blindness) is a little over 0.1 on the utility scale derived from the EQ-5D, with wide standard errors.(58) In this context, additional information can be expected to lead to a small change in utility, which this study may not have had the power to detect. The difference between the mean utilities of *Groups 1 and 4* averaged across the four health states was 0.047. Even small differences in health state utility may lead to a different outcome for the cost effectiveness of an AMD intervention as the health gains are relatively small, but run for several years. 0.05 shift downwards from no information (0.70) to patient descriptions (0.65), represents almost half of the range of vision on the EQ-5D utility scale. Therefore while differences of the magnitude detected in this study did not reach statistical significance, they could have major economic implications for resource allocation decisions if central utility values were applied to cost effectiveness models.

Group 1 (no information) provided mean health state utility values that were different from the EQ-5D UK value set. The survey was completed online in

order to generate a large sample size rapidly, whereas the EQ-5D values are based on the MVH project, which used face-to-face interviews. There are questions of comparability between TTO elicitation exercises completed face-to-face and online.(96) In this study as we seek to compare between subjects all using the online program, this should not impact on the internal validity of the results.

The framing of information influences health state valuations in AMD. The choice of preferences is a normative decision, but the choice of informed or uninformed preferences has the potential to impact on cost-effectiveness decisions in vision.

The use of an AMD label in the valuation task does not lead the public to different preferences for health states. Taken with the results of other studies, labelling does not seem to influence valuations in mild health states.

There may be a trend that reading AMD patient descriptions leads the public to value health states more severely. While the differences detected were not statistically significant, the magnitude would be sufficient to influence economic evaluations.

This study raises the prospect that not only does additional information influence valuation, the content of the additional information can have an equally strong impact. Further investigation around the content validity of vignettes would be recommended. In the meantime, care should be taken to provide objective information and vignettes should go through validity testing.

As described, adaptation information was removed from the study on the basis of the results of the pilot. Other work has shown similar results to the pilot study: that information about adaptation increased the utility values reported.(97) A future area of research could be how to incorporate adaptation into health state valuations. If an adjustment factor for adaptation were available, this could be incorporated into economic modelling (using patient level simulation) with, for example, a utility adjustment for length of time with the condition or length of time in a particular health state.

The age of people completing the TTO may affect results. *Dolan* found that utility values elicited using the TTO for EQ-5D health states from those aged 60 and over were lower than values from those aged 18-59.(98) AMD is a condition of older people, however, based on the recommendation to elicit preferences from a representative sample of the community (8)

5. Valuation of non-health benefits in vision

This chapter investigate preferences for health and non-health attributes of AMD and its treatment and develops a weighting for health state utility values according to these preferences in order to address research aim 2: *Are non-health attributes important in AMD and how can they be incorporated into the cost-utility economic evaluation framework?*

5.1. Introduction

To date, economic evaluations of treatments for AMD have focused on QALY maximisation for CUA. Previous chapters have investigated methods for measuring and valuing health state utilities for the calculation of QALYs for use in CUA. However, there are several aspects of AMD and its treatment that impact outside of health states that may contribute to public preferences on whether a new technology should be adopted.

At the same time, decision makers have been looking at ways to account for a wider range of benefits than the QALY when assessing health technology. In the UK, the cancer drugs fund has operated since 2011, allowing a higher cost effectiveness threshold for drugs that meet certain end-of-life criteria.(99)

In 2010 the UK Department of Health consulted on Value-based Pricing with the view that other attributes beyond the QALY.(100) It proposed that system should function as follows:

- there would be a basic threshold, reflecting the benefits displaced elsewhere in the NHS when funds are allocated to new medicines;

- there would be higher thresholds for medicines that tackle diseases where there is greater "burden of illness": the more the medicine is focused on diseases with unmet need or which are particularly severe, the higher the threshold;

- there would be higher thresholds for medicines that can demonstrate greater therapeutic innovation and improvements compared with other products;

- there would be higher thresholds for medicines that can demonstrate wider societal benefits.

However, the budget constraint remains fixed, therefore introducing additional items on the benefit side requires a method to weight benefits currently considered by CUA (i.e. QALYs) to account for the opportunities forgone.

DCEs are an increasingly popular method for eliciting preferences for health and health care.(43, 44) Respondents express preferences for hypothetical scenarios consisting of varying attributes drawn from all possible choice sets.

Recently a DCE has been employed to derive distributional weights for QALYs.(101) *Lancsar et al*. demonstrated that a DCE could be used to elicit preferences for weighting QALYs due to other characteristics (age at onset, age at death if untreated and QoL if untreated). The study demonstrated that in certain circumstances, respondents chose to trade off some QALY gain for other characteristics.

Meanwhile *Linley and Hughes* conducted a choice-based survey to investigate preferences for prioritising treatments by nine criteria including those in the

VBP consultation.(102) They found that respondents supported the criteria proposed by the VBP consultation (disease severity, unmet need, innovation and have wider societal benefits) but did not support a premium for end-of-life treatments, the prioritisation of treatments for children or disadvantaged populations, the special funding status for treatments of rare diseases, nor the Cancer Drugs Fund.

Green and Gerrard investigated the social value of health technologies by presenting respondents with social value judgements (SVJs) in a DCE.(103) They included attributes for health improvement, value for money, severity of health, and availability of other treatments.

Similar methods may be applied to investigate preferences for applying weights to health state utility values by aspects of the disease and its treatment in respect to AMD. The aim of this chapter was to investigate preferences for health and non-health attributes of AMD and its treatment and to develop a quantitative system by which these preferences could be applied to conduct an economic evaluation for a new treatment for AMD.

5.2. Methods

Attribute selection was guided by aspects of ranibiumab treatment, the current standard of care for AMD, which may be important to a health care decision maker. A number of other attributes were considered. Attributes that were excluded from the choice task were included in a final Likert scale survey

question to ascertain the importance of each attribute to inform future survey design.

A common method for generating preference weights in DCEs is to include a cost attribute and calculate the marginal rate of substitution (MRS). In this experiment, it was decided that the attribute that would be used for weighting would be health gain and cost was not included as an attribute.

5.2.1. Attributes and levels

Four attributes were selected for the choice task. Three attributes had four levels and one attribute had two levels (**Table 5.15**).

Health gain

Health gain is the attribute that is currently maximised in CUA. Its inclusion allows health gain to be traded against other characteristics and distributional weights to be calculated using the Hicksian compensating variation.

Four levels were identified: 5%, 10%, 15% and 20%. Levels offered a health gain as a percentage of health between 0% (dead) and 100% (perfect health) over 10 years. The scale was analogous to a health state utility scale where 0 is dead and 1 is perfect health.

Severity

Disease severity is an attribute that is often supported

Four levels were identified: 20%, 40%, 60% and 80%. Levels described a starting level of health between 0% (dead) and 100% (perfect health). The scale

was analogous to a health state utility scale where 0 is dead and 1 is perfect health.

Unmet need

Ranibizumab treatment is considered relatively effective for wet AMD and is recommended for use in this population. However, there is currently no treatment available for patients with dry AMD. Preferences for a new product may differ between one that generates a health gain for patients with dry AMD compared with one that generates an equivalent health gain for patients with wet AMD.

Two levels were identified: current treatment available and no current treatment available.

Process

The process of ranibizumab treatment may be considered relatively inconvenient for patients. Generally patients are required to attend the hospital for monthly injections. With the NHS pursuing policies that encourage improved process such as 'care closer to home',(104) it is important to test whether the public are willing to forgo some health gain by diverting resources to improved process. In terms of AMD, this could mean a treatment that may be administered at home, or one that is longer-acting, requiring a single hospital visit.

Four levels were identified: monthly hospital injection, monthly home-based nurse-administered hospital injection, monthly home-based self-administered injection, one-off hospital injection

Attribute	Levels
Health gain over 10 years	+5% +10% +15% +20%
Severity	20% 40% 60% 80%
Unmet need	- Patients currently receive an existing adequate treatment, new treatment is an improvement - Patients currently receive basic NHS comfort care, but no adequate treatment currently exists
Process	- Monthly hospital appointment for injection - Monthly visit by nurse for injection - Monthly home-based self-administered injection - One-off hospital appointment for injection

Table 5.15. Attributes and levels.

5.2.2. DCE design

The number of attributes and levels was guided by the following criteria:

Amount of information

Guidance from the literature is that a maximum of seven attributes can be considered by respondents at any time due to cognitive limits. It was

determined that the number of attributes should be lower than this due to the relative unfamiliarity of the task of prioritising health treatments.

Length of survey

A higher number of attributes and levels requires a greater number of choice tasks. A full factoral design would require 4^4 = 256 possible combinations. It was not necessary to constrain the design as the choice of attributes and levels meant there were no implausible scenarios. A main effects design was selected from an experimental plan catalogue and a foldover design selected to systematically vary the levels of the second choice.

Based on information from piloting the survey in a convenience sample, the survey took approximately 15-20 minutes, which was considered a suitable length for online administration.

A binary forced choice design was chosen which required the participant to choose option A or option B for each choice task. A 'neither' option was not included as it was considered realistic that a health care decision maker would fund one of the two options and not leave the budget unspent. **Figure 5.12** is a screen shot of the survey showing one such choice.

The choice of attributes and levels meant that there were no implausible combinations, so no combinations needed to be excluded from the design.

The survey consisted of the following sections:

- Introduction
- Sociodemographic questions

- Introduction to choice tasks and practice task

- Choice tasks (randomised) – 16 plus one choice with one set of attributes

  set to 'best' and one set to 'worst' to test understanding.

- Likert scale to rate importance of other attributes

Now please consider the choice to treat these two groups of patients with two new treatments

	Group A	Group B
What do patients currently receive?	Patients currently receive an existing adequate treatment, but new treatment is an improvement	Patients currently receive basic NHS comfort care, but no adequate treatment currently exists

Group A: Current health, 20%; Health gain from new treatment, 5%

Group B: Current health, 40%; Health gain from new treatment, 10%

How does the new treatment work?	Monthly home-based self-administered injection	Monthly home visit by nurse for injection

*12. Which group of patients do you think the NHS should treat?

◯ Group A   ◯ Group B

Figure 5.12. Screenshot of choice task.

*The full list of choice tasks is provided in **Appendix B**.*

Sample

800 respondents were recruited via an online survey panel. Criteria were set that the respondents must be from the UK and be at least 18 years of age in order to represent UK general public preferences. As described in the next section, respondents were stratified into four groups, receiving the same choice tasks, with different perspectives.

5.2.3. Impact of perspective and framing

	Ex ante	*Ex post*
Personal	What value do you attach to treatment being available should you need it?	What value do you attach to your own treatment?
Social	What value do you attach to treatment being available to others should they need it?	What value do you attach to the treatment of others?
Socially inclusive personal	What value do you attach to treatment being available to a group of people amongst whom you might find yourself?	What value do you attach to the treatment of yourself and others?

Table 5.16. Six perspectives for eliciting preferences.

Adapted from Dolan et al.(47)

There are a number of perspectives that can be used to elicit preferences (**Table 5.16**).(47) In health state valuation, it is common for preferences to be elicited for oneself from behind a veil of ignorance (personal *ex ante*). For example the TTO asks a respondent to imagine that they are in a given health state and elicits how much time they would trade for perfect health.

The use of DCEs to derive distributional weights is relatively novel. However, approaches to date have asked respondents to prioritise treatments for groups of patients (others), social *ex ante*.

The perspective of the choice may have an impact on preferences for resource allocation. For example, risk aversion or the importance of process relative to health gain may vary when thinking of oneself compared with choosing for others. Three perspectives were chosen to reflect choosing for oneself, choosing for others and an intermediate perspective of choosing for others like oneself. These perspectives also reflected those being investigated in the re-valuation of the EQ-5D value-set. Additionally a labelled version of the survey was designed to investigate whether additional information impacted on preferences.

Four surveys were designed with identical choice tasks, but taking the following different perspectives. Each survey was completed by 200 adult members of the UK general public recruited via an online survey panel.

Others

Respondents were asked to choose to fund one of two new treatments offered for two different groups of patients imagining that they are the health care decision maker.

Someone like you

Respondents were asked to choose to fund one of two new treatments offered for two different groups of patients imagining that someone like themselves is in each of the groups.

You

Respondents were asked to choose to fund one of two new treatments offered for two different groups of patients imagining that they have an equal chance of being in either of the two groups.

Labelled others

A labelled version of the survey was identical to the 'others' perspective, but respondents were informed the treatment choices were for AMD and read a short description of the condition before beginning the choice tasks. The AMD label was taken from the NHS Choices website, which is designed to help patients understand diseases and treatments.(56) In the choice tasks, the no adequate treatment option was labelled as 'dry AMD' and the adequate treatment option was labelled as 'wet AMD' to reflect the current situation in clinical practice where wet AMD has a treatment (ranibizumab injections) and dry AMD has no treatment, only rehabilitation to help patients to adapt to the condition.

Box 5.1. AMD label.

Age-related macular degeneration is a painless eye condition that leads to the gradual loss of central vision. Central vision is used to see what is directly in front of you, during activities such as reading or watching television for example. The central vision becomes increasingly blurred leading to symptoms including

---

- Difficulty reading printed or written text (because it appears blurry)
- Colours appear less vibrant
- Difficulty recognising people's faces

There are two main types of AMD:

Dry AMD develops when the cells of the macula become damaged due to lack of nutrients and a build-up of waste products called drusens.

Wet AMD develops when abnormal blood vessels from underneath the macula and damage its cells (doctors sometimes refer to wet AMD as neovascular AMD).

There is currently an effective injection for wet AMD. For dry AMD, there is currently no treatment and patients receive basic NHS care such as training to use low vision aids like magnifiers. AMD usually affects both eyes but the seed in which it progresses can vary from eye to eye.

5.2.4. Statistical methodology

Model

Discrete choice responses are modelled within a random utility framework. For QALY maximisation to hold, utility would be a function of health gain alone. If other characteristics are important, utility will be a function of health gain and other characteristics (**Equation 5.1**).

$$V = f(HG, S, UN, P_{homenurse}, P_{homeself}, P_{onehospital})$$

Equation 5.1. Utility function.

where Health gain (HG), Severity (S), Unmet need (UN), Process (P)

Process attributes were coded as dummy variables. The reference was chosen as monthly hospital injections.

The limitations of an additive function is that it assumes that other attributes have an effect on utility where health gain is zero. Assuming a multiplicative model instead, a log-linear model is generated (**Equation 5.2**).

$$\log(V) = b_1 \log(HG) + b_2 \log(S) + b_3 \log(UN) + b_4 \log(P_{\text{hom}enurse}) + b_5 \log(P_{\text{hom}eself}) + b_6 \log(P_{onehospital})$$

Equation 5.2. Log-linear model of utility function.

A conditional logit model can be estimated (**Equation 5.3**).

$$D\log(V) = b_1(D\log(HG)) + b_2(D\log(S)) + b_3(D\log(UN)) + b_4(D\log(P_{\text{hom}enurse})) + b_5(D\log(P_{\text{hom}eself})) + b_6(D\log(P_{onehospital}))$$

Equation 5.3. Conditional logit model.

The model allows for the fact that each individual responds to several choice questions. The *clogit* command was used in STATA in order to calculate coefficients for individual attributes.

Utility weights for these attributes were derived using the compensating variation method. As per *Lancsar et al.*,(101) the marginal utility of a QALY was used to value the change in expected utility arising from a move from the reference to alternative case in order to derive CV.(**Equation 5.4**) Given the marginal utility of a QALY represents the slope of the utility function with respect to QALYs and, due to the non-linear functional form of the choice model

the slope of the utility function will be smaller for larger QALY gains. It was decided that a gain of one QALY would be used to calculate the marginal utility of a QALY used in the CV equation in common with the range of QALY gains often seen in HTA.(4)

Utility weights

$$CV = \frac{1}{\gamma} \left[\ln \sum_{j=1}^{J} e^{V_j^0} - \ln \sum_{j=1}^{J} e^{V_j^1} \right]$$

Equation 5.4. Compensating variation.

$$Weight = \frac{1 - CV}{Utility_{base}}$$

Equation 5.5. Utility weights.

Weights for individual attributes

In order to calculate utility weights for each attribute, a reference case was chosen against which the alternative scenarios would be compared:

- Health gain = 10% over 10 years
- Severity = 60%
- Unmet need = adequate treatment available
- Process = monthly hospital

5.3. Results

A total of 813 responses were received.

Characteristic		Value
Age	18 to 24	3%
	25 to 34	12%
	35 to 44	16%
	45 to 54	25%
	55 to 64	26%
	65 to 74	15%
	75 or older	3%
Gender	Female	53%
	Male	47%
Employment status	Unemployed, retired, student	43%
	Manual worker (with no qualifications)	6%
	Manual worker (with industry qualifications)	8%
	Supervisor, clerical; junior managerial, administrative or professional	23%
	Intermediate managerial, administrative or professional	14%
	Senior manager or professional	6%
Health status (where 0 = dead and 100 = perfect), Mean (SD)		71 (24)
Disability	Yes	26%
	No	73%
	Prefer not to say	1%

Table 5.17. Respondent characteristics.
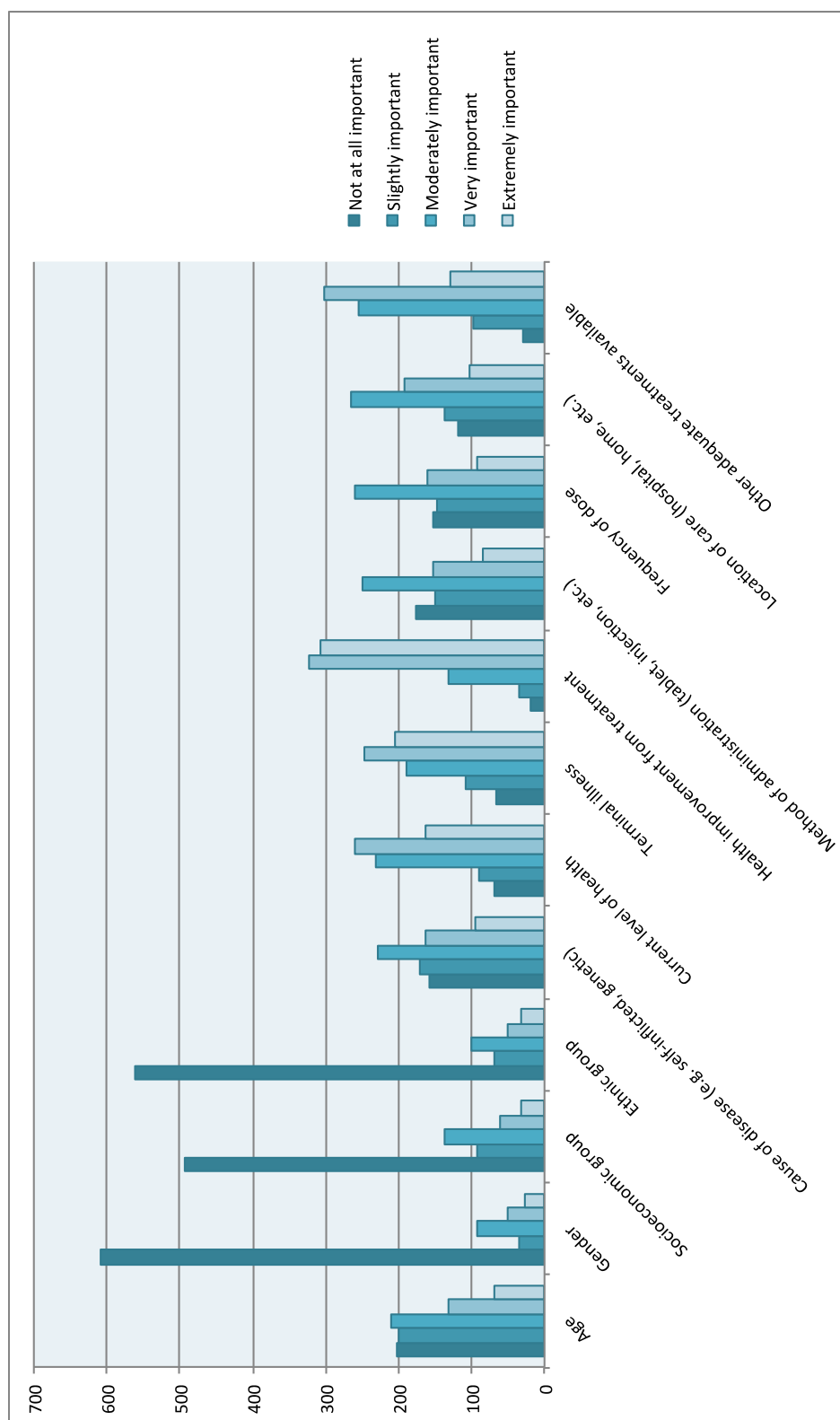
Figure 5.13. Bar chart of responses to 'long list' of possible attributes.

132

In order to validate the choice of attributes, a longer list was presented to respondents who were asked to rate the importance of each. The most important attributes (measured by the number of ratings of very important and extremely important) were current level of health, terminal illness, health improvement from treatment, location of care and other adequate treatment being available. Unimportant attributes were gender, socioeconomic group and ethnic group. (**Figure 5.13**)

The results confirmed the selection of attributes for the choice task. Only terminal illness was not included from those ranked most important. Since the study focused on a disease and treatment that affects quality of life and not length of life, this attribute could not be practically included.

		Health gain	Severity	Unmet need (adequate=1)	Process (Monthly home nurse)	Process (Monthly home self)	Process (One-off hospital)
You	Coef.	0.291**	-7.225**	-0.140**	0.520**	0.197**	0.395**
	SE	0.113	0.458	0.038	0.065	0.064	0.075
Someone like you	Coef.	1.133**	-6.305**	0.007	0.150**	0.056	0.072
	SE	0.111	0.449	0.037	0.062	0.065	0.074
Someone else	Coef.	0.878**	-6.334**	0.048	0.151**	0.147**	0.158**
	SE	0.108	0.444	0.037	0.062	0.064	0.073
Label someone else	Coef.	1.296**	-5.945**	0.046	0.266**	0.226**	0.205**
	SE	0.111	0.441	0.037	0.062	0.065	0.074

Table 5.18. Coefficients derived from conditional logit models.

* significant at p<0.1 **significant at p<0.05

The coefficients derived from conditional logit models of the four surveys are described in **Table 5.18**. Across all scenarios, the coefficients for health gain were positive and were significant at p<0.05, meaning that respondents preferred treatments that provided a greater health gain.

Across all scenarios the coefficients for severity were negative and were significant at p<0.05, meaning that respondents preferred treatments that were for patients with a lower starting level of health.

Unmet need was only significant for respondents answering the choices about themselves, with a negative coefficient meaning that respondents preferred treatments that addressed a disease without an adequate treatment currently available. This attribute was not significant for respondents answering the choices about others.

Process of care was significant across all scenarios except someone like you (where only a monthly home nurse visit was significant). All scenarios had positive coefficients, indicating that respondents preferred home treatments or less frequent hospital-based treatments over monthly hospital treatments.

In the '*you*' scenario, respondents answering about themselves appeared to have a less strong preference for health gain, instead severity and unmet need had larger coefficients compared with the three other scenarios where respondents were answering about others. When prioritising treatments for oneself, attributes other than health gain become relatively more important.

	Process				Unmet need		Severity					
	One off hospital	Monthly home self	Monthly home nurse	Monthly hospital	No adequate treatment	Adequate treatment	0.2	0.4	0.6	0.8		
You	-1.54	-0.39	-0.54	0.00	0.00	0.23	-5.70	-2.04	0.00	0.73	CV	
	2.54	1.39	1.54	1.00	1.00	0.77	6.70	3.04	1.00	0.27	Weight	
Someone like you	-0.05	-0.03	-0.04	0.00	0.00	0.00	-1.19	-0.43	0.00	0.17	CV	
	1.05	1.03	1.04	1.00	1.00	1.00	2.19	1.43	1.00	0.83	Weight	
Someone else	-0.16	-0.09	-0.05	0.00	0.00	-0.03	-1.55	-0.56	0.00	0.23	CV	
	1.16	1.09	1.05	1.00	1.00	1.03	2.55	1.56	1.00	0.77	Weight	
Label someone else	-0.15	-0.10	-0.06	0.00	0.00	-0.02	-0.95	-0.35	0.00	0.15	CV	
	1.15	1.10	1.06	1.00	1.00	1.02	1.95	1.35	1.00	0.85	Weight	

Table 5.19. Weights for individual attributes.

Reference case: HG=10% (1 QALY over 10 years), S=60%, UN=no adequate treatment available,

P=monthly hospital. CV=compensating variation to move from reference case.

In the 'dominant' choice task included to test for the rationality of responses
(**Table 5.20**), 73.0% of respondents chose the dominant option. This ranged
from 70.1% in the 'you' sample to 77.3% in the 'label' sample.

Attribute	Choice A	Choice B
Health gain	+20%	+5%
Severity	20%	80%
Unmet need	No adequate treatment currently available	Adequate treatment currently available
Process	One-off hospital	Monthly hospital

Table 5.20. 'Dominant choice'.

5.4. Conclusion

This study derived distributional weights for QALYs, allowing the external
weighting of health gain by other characteristics. This allows the preferences for
other characteristics to be incorporated into the cost-per-QALY economic
evaluation framework.

Respondents were willing to forego health gain for other attributes. This
indicates that the UK public may wish that QALYs gains be modulated by

severity of disease, process of care (and to a lesser extent) unmet need when a new treatment is evaluated for use in the health care system.

Preference elicitation is influenced by the perspective of the DCE task. It appears that preferences are affected by a change in perspective, but remain stable to framing. There is evidence that preferences for treating self are different to treating others.

This study does not itself provide evidence on the most appropriate perspective. The choice of perspective is a normative decision. When weighting QALYs, is it most appropriate for public preferences to reflect those of the decision-maker (someone else), or to be consistent with utilities (you)?

This study was limited in the attributes under consideration. Future work is needed to investigate additional attributes. The rating task undertaken by respondents on a longer list of attributes gives some guidance on what may be included in future choice tasks.

6. Definition of health states in vision

This chapter investigates the association between measures of visual function and utility in AMD health states. A CUA model is developed to test the impact on cost effectiveness of using different individual measures of visual function and a mapping algorithm is developed from visual function to utility in order to address research aim 3: *How is visual function associated with utility in AMD and how can the association be applied to economic evaluation?*

6.1. Association between VA and utility

There is evidence that VA alone may not fully account for changes in health status in visual disorders. Indeed, CS has been shown to impact on quality of life in AMD, not only VA. In an observational study to determine this relationship, CS remained a statistically significant predictor of all outcome measures even when VA was included.(59)

VA measures the eye's ability to resolve fine detail, whereas, CS measures ability to see low contrast patterns and VF allows peripheral vision. Although good VA is necessary for activities such as reading, it is only weakly associated with ability to discriminate between visual targets or performance of tasks requiring distance judgment.

Therefore, both VA and CS can be expected to impact on a patient's quality of life and consequently that utility values based on VA alone may underestimate quality of life.

Further evidence of the weak association between VA and utility is derived from analysis of the dataset used to test the performance of EQ-5D, SF-6D, TTO and VAS (**Chapter 3**).

The relationship between VA in the better-seeing eye and the four utility measures are shown in **Figure 6.14**. There was no association between VA and any utility measure (Pearson correlation; all $R < 0.04$; $p > 0.2$).

This raises concerns that treatment decisions based on this outcome measure may reflect neither public nor patient preferences on how health care resources should be allocated. This is believed to be the first comparison of VA from hospital records and preferences. The finding is especially concerning given that most CUA of AMD interventions have used Markov models based on the association between VA and health state utility.(62) However, it is also unsurprising given that most AMD patients are likely to have multiple comorbidities unrelated to vision, which may also have an impact on the utility. The low explanatory power of VA has been identified in other studies and other measures of vision such as CS may be better associated with health state utility.(59) Given that this data did not measure VA, but recorded it from hospital notes, another explanation for the weak agreement could be that the hospital notes may not represent accurate or up-to-date measures of the patient's vision.
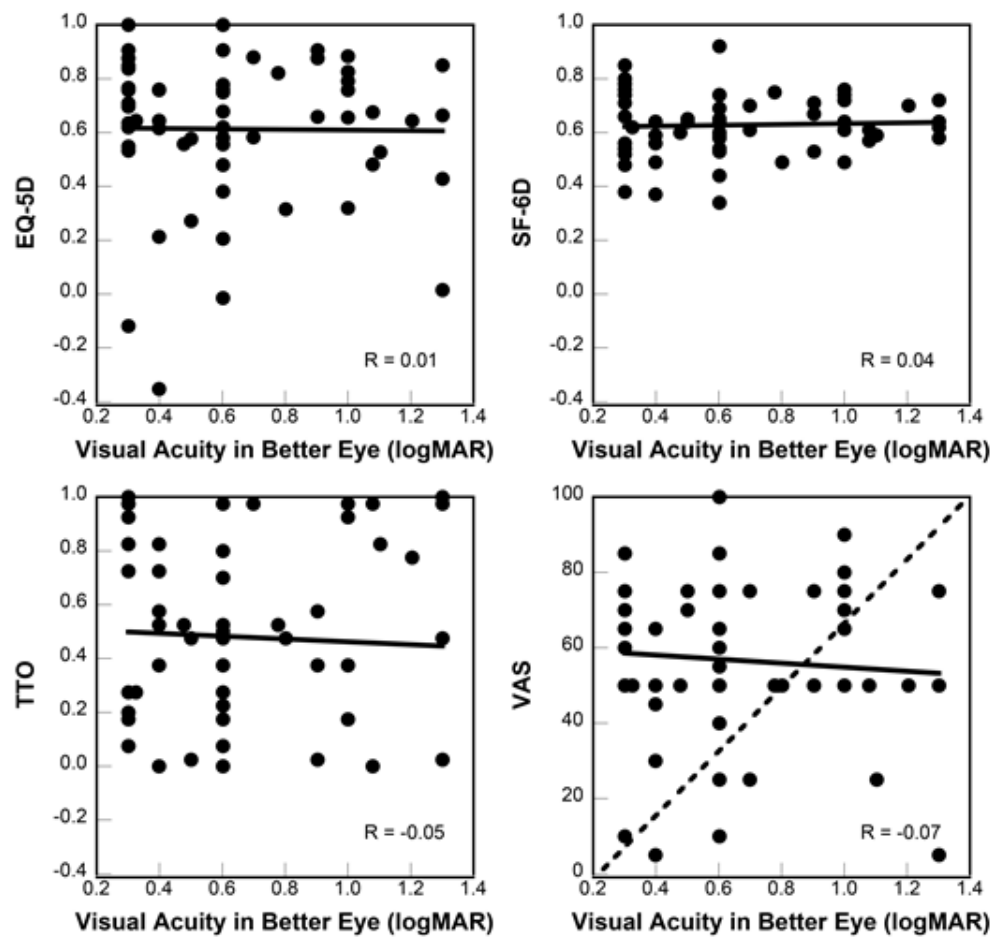
Figure 6.14. Association between VA and utility. Data from 58 patients described in Chapter 3.

6.2. VA vs. CS in health economic models

Previous health economic models in treatments for AMD, including those used to develop the UK NICE's guidelines on ranibizumab and pegaptanib for AMD, have relied on the association between VA and health state utility to construct Markov models.(2) Yet there is evidence that anti-VEGF therapy is effective in reducing the deterioration in CS, another measure of visual function.

A cost-effectiveness model based on CS outcomes may offer advantages over previous modelling techniques. Firstly, no single visual function outcome captures HRQoL in AMD and interventions may have a differential impact on each outcome. CS has an independent impact on health state utility and has been shown to be more closely associated with HRQoL than VA.(59) CS was found to remain a statistically significant predictor of utility even when VA was included in a regression model. VA measures the eye's ability to resolve fine detail at high contrast, while CS measures the ability to perceive differences between light and dark.(105)

Secondly, utility values for CS have been reported for binocular vision, so a model based on this outcome takes account of visual function in both eyes. Models based on VA outcomes alone have considered only visual function in the better seeing eye, while the impact of the worse seeing eye on health state utility values is uncertain.(106) In clinical practice, the eye with the disease will be treated, whether this is the better or worse seeing eye, therefore, taking account of vision in both eyes more closely reflects clinical practice.

Only one previous model has investigated cost-effectiveness using CS. *Bansback et al*. investigated the cost-effectiveness of photodynamic therapy (PDT) with

verteporfin for AMD and estimated an incremental cost-effectiveness of approximately GBP20,996 over 10 years compared to best supportive care.(60)

From the previous model, it was not possible to compare the implications of using CS or VA on the cost-effectiveness of treatments for AMD since there was no directly comparable VA model. Furthermore, in recent years, PDT has been replaced by anti-VEGF therapy as standard clinical practice to treat AMD, so there is no estimate of the cost-effectiveness of current clinical practice using CS.

Economic evaluations of treatments for AMD have concluded that the two anti-VEGF therapies used within the NHS, approved ranibizumab and off-label bevacizumab (Avastin®, Roche Holdings AG, Switzerland), are cost-effective at commonly applied thresholds when compared with photodynamic therapy (PDT) with verteporfin.(2, 62) A recent head-to-head comparison found no significant difference between the two drugs in terms of effectiveness.(63)

This model assesses the cost-effectiveness of anti-VEGF therapy using CS for the first time and investigates the impact on cost-effectiveness of basing a model on CS compared with VA.

The choice of using VA or CS in the model is a case of structural uncertainty, the impact of which can only be tested by redesign of the model.(107)In this chapter two Markov models are developed based on the Avastin (bevacizumab) for choroidal neovascular age-related macular degeneration (ABC) trial, which assessed VA and CS outcomes in AMD patients. Bevacizumab was compared with standard NHS treatment at the time of the trial, which was a mixture of

PDT with verteporfin (Visudyne®, Novartis AG, Switzerland), pegaptanib (Macugen®, Pfizer, USA), an alternative anti-VEGF and no treatment (sham injection) depending on the clinical diagnosis. The trial demonstrated that bevacizumab was an effective treatment in terms of both outcomes.(108, 109)

6.2.1. Methods

State transition Markov models were constructed to simulate the progression of the disease in terms of VA and CS. The VA model had 4 states of VA in the better-seeing eye and a death state. The CS model had 4 states of binocular CS and a death state. (**Figure 6.15**) States were chosen that represented clinically relevant levels of visual function and had associated utility values.

A
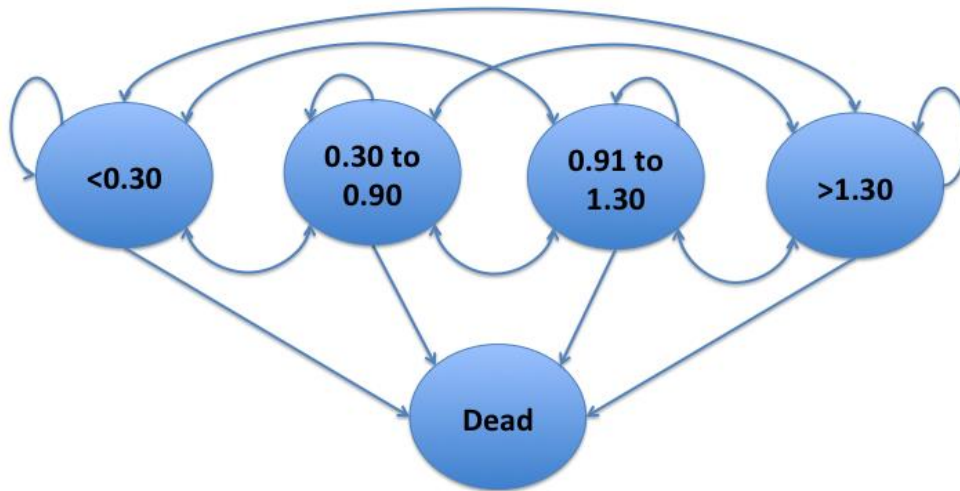
B
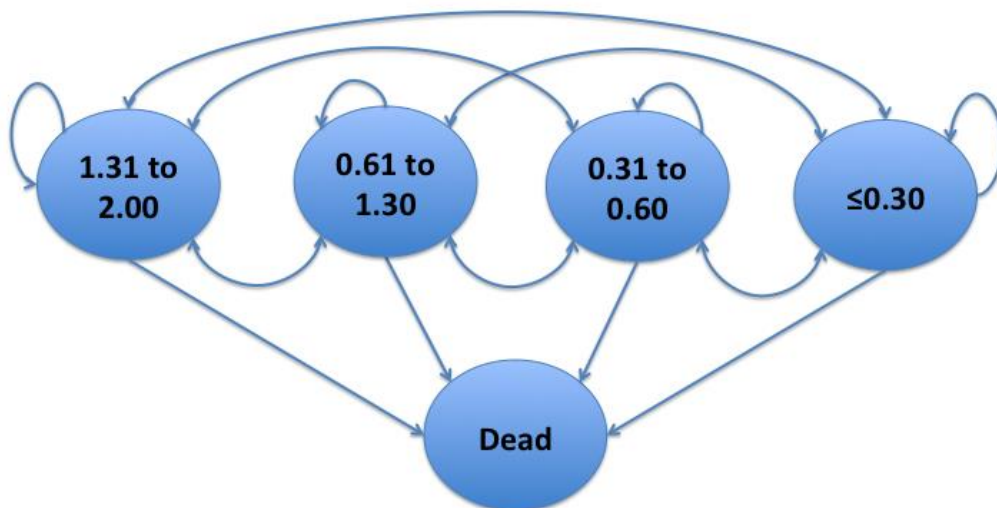
Figure 6.15. Markov models. A. Visual acuity states (better seeing eye logMAR). B Contrast sensitivity states (binocular log units)

In the models, patients were allowed to move forwards to a better health state, move backwards to a worse health state, remain in their current health state or die at each model cycle. Death was an absorbing state, meaning that patients could not leave the state.

	Bevacizumab (n=65)	Comparator (n=66)
Gender		
- Male	26	25
- Female	39	41
Mean age (years)	79	81
Mean ETDRS VA in study eye (logMAR)	0.68	0.64
Mean binocular CS (log units)	1.26	1.22

Table 6.21. Baseline summary of patient demographics in the ABC trial.

Transition probabilities were calculated from patient level data on VA and CS from the ABC trial (n=131, **Table 6.21**). Better-seeing eye VA transition rates were approximated from the study eye. As CS measurement was monocular, binocular CS transition rates were estimated using a published algorithm, which found that binocular CS could be calculated as the square root of the sum of the square of each eye.(110) Age-specific mortality rates were taken from the Office for National Statistics rates for England and Wales for 2009.(111) The rates were adjusted to take account of the sex of the cohort using the ratio of participants in the ABC trial. (**B.**

Table 6.22)

A.

VA (better seeing eye logMAR)	1.31 - 2.00	0.61 - 1.30	0.31 - 0.60	≤0.30
To bevacizumab				
1.31 - 2.00	0.62	0.03	0.00	0.01
0.61 - 1.30	0.33	0.80	0.10	0.00
0.31 - 0.60	0.00	0.16	0.72	0.24
≤0.30	0.05	0.01	0.17	0.76
To comparator				
1.31 - 2.00	0.85	0.06	0.03	0.00
0.61 - 1.30	0.11	0.84	0.22	0.05
0.31 - 0.60	0.04	0.10	0.69	0.63
≤0.30	0.00	0.00	0.07	0.32

B.

CS (binocular log units)	<0.30	0.30 - 0.90	0.91 - 1.30	>1.30
To bevacizumab				
<0.30	1.00	0.06	0.00	0.00
0.30 - 0.90	0.00	0.44	0.04	0.00
0.91 - 1.30	0.00	0.50	0.77	0.11
>1.30	0.00	0.00	0.19	0.89
To comparator				
<0.30	0.00	0.03	0.00	0.00
0.30 - 0.90	0.00	0.67	0.10	0.01
0.91 - 1.30	1.00	0.31	0.69	0.29
>1.30	0.00	0.00	0.20	0.70

Table 6.22. Transition probabilities between Markov states for bevacizumab and comparator. A. Visual acuity (VA). B. Contrast sensitivity (CS).

The trial measured VA every six weeks and CS every 12 weeks for 54 weeks. The cycle length was 6 weeks for the VA model and 12 weeks for the CS model, reflecting the ABC trial protocol.

SF-6D utility values reported by *Espallargues et al.* were applied to the health states in the model. 209 patients with unilateral or bilateral AMD at a hospital in Sheffield, UK were asked a series of preference-based questionnaires and the derived utility values were associated with their visual function. The SF-6D showed greater sensitivity than the EQ-5D, but less sensitivity than the HUI-3 to changes in vision. The SF-6D derived utilities were chosen over the HUI-3 since

the HUI-3 showed little agreement with other measures and gave extremely low utility scores compared to other measures. The HUI-3 reported a utility of just 0.10 for the worst VA state, compared with 0.63, 0.63 and 0.47 for the EQ-5D, SF-6D and TTO respectively. TTO utilities were applied as sensitivity analysis. The utilities values grouped by levels of VA and CS were applied to the model health states.(58) (**Table 6.23**)

A.

VA (better seeing eye, logMAR)	Utility, mean (95% CI)
1.31 to 2.00	0.65 (0.11)
0.61 to 1.30	0.66 (0.14)
0.31 to 0.60	0.67 (0.14)
≤0.30	0.70 (0.18)

B.

CS (binocular, log units)	Utility, mean (95% CI)
<0.30	0.65 (0.11)
0.30 to 0.90	0.64 (0.14)
0.91 to 1.30	0.68 (0.14)
>1.30	0.73 (0.16)

Table 6.23. Utility values assigned to health states. A. Visual acuity (VA). B. Contrast sensitivity (CS).

Utilities calculated from SF-6D by Espallargues et al. (58)

Item	Unit cost	Source
Avastin	£242.66	BNF
Macugen	£514.00	BNF
First PDT with verporfin	£1,181.00	*Bansback et al.*
Subsequent PDT with verporfin	£1,113.00	*Bansback et al.*
Ophthalmic antibiotic	£2.17	BNF
Anaesthetic	£0.45	BNF
Dilating drops	£0.45	BNF
Initial consultation	£179.63	*Patel et al.*
Subsequent consultation	£49.98	*Patel et al.*
Eye examination	£51.00	*Patel et al.*
Optical coherence tomography	£44.00	*Patel et al.*

Table 6.24. Unit costs.

*BNF= British National Formulary.(60, 112)

Resource use was estimated from the ABC trial protocol and presented in British Pounds. (**Table 6.24**) Treatment rates were calculated from the trial to reflect that patients were not treated at every time point. If treated, costs were incurred from the drug, the examination and the consultation. Otherwise, only costs associated with the examination and consultation were incurred. A higher cost was applied to the first consultation to reflect a more extensive first visit. (**Table 6.25**)

A.

VA (6-week cycle)	First cycle	Subsequent cycle
Bevacizumab		
Drug	£208	£208
Examination	£95	£95
Consultation	£180	£50
Total	£483	£353
Comparator		
Drug	£374	£367
Examination	£95	£95
Consultation	£180	£50
Total	£649	£512

B.

CS (12-week cycle)	First cycle	Subsequent cycle
Bevacizumab		
Drug	£416	£416
Examination	£191	£191
Consultation	£230	£100
Total	£836	£707
Comparator		
Drug	£747	£733
Examination	£191	£191
Consultation	£230	£100
Total	£1,168	£1,024

Table 6.25. Costs per cycle. A. Visual acuity (VA). B. Contrast sensitivity (CS).

Unit costs for drugs were obtained from the British National Formulary (BNF) and adjusted for the volumes used in the ABC trial. Consultation and examination costs were obtained from other published AMD models.(60, 112)

The perspective of the model was the UK NHS and personal social services as recommended in the NICE Guide to the Methods of Technology Appraisal reference case.(2) Each model was run for 5 years, which represented an extension of the 54-week trial follow-up and captures the long-term costs and effects of the treatments. Since there is no evidence on the long-term outcomes of anti-VEGF therapy on either VA or CS, it was assumed that transition rates

estimated from the 54-week trial were maintained to 5 years. A discount rate of 3.5% for costs and QALYs was applied as recommended by UK HM Treasury.(9)

The model compared bevacizumab (1.25mg in 0.05ml per injection) with a comparator of mixed standard care in the UK in 2009 (16 patients received PDT, 38 patients received pegaptanib, 12 patients received sham injection) as used in the ABC trial.

Appropriate probability functions were fitted to model parameters to incorporate uncertainty. Probabalistic sensitivity analysis was performed using Monte Carlo simulation to randomly sample each parameter.(113) Utilities were characterised by a beta distribution, costs by a gamma distribution and transition probabilities by a dirichlet distribution. A cost-effectiveness acceptability curve (CEAC) was constructed to represent the probability of the treatment proving cost-effective at a given value of health effect.(114) One-way sensitivity analysis was employed to test structural uncertainty within the model.

6.2.2. Results

The models indicate that bevacizumab is less costly and more effective than the comparator treatment over 5 years using either VA or CS outcomes (bevacizumab dominates the comparator).

A higher incremental QALY gain is obtained from the CS model compared with the VA model. The central estimates of the probabilistic sensitivity analysis are 0.076 in the CS model and 0.061 in the VA model, which indicates that

bevacizumab is 25% more effective using CS outcomes than the VA outcomes.

(**Table 6.26**) This difference was statistically significant (P<0.05) when 10,000

Monte Carlo simulations of the model were assessed using an unpaired t-test.

VA	Comparator	Bevacizumab	Incremental
Cost	£21,258	£14,714	-£6,545
QALYs	3.028	3.089	0.061
ICER	Bevacizumab dominates		

CS	Comparator	Bevacizumab	Incremental
Cost	£20,931	£14,490	-£6,441
QALYs	3.114	3.190	0.076
ICER	Bevacizumab dominates		

Table 6.26. Central cost-effectiveness results: average of Monte Carlo analysis

5-year time horizon, 3.5% discount rate for costs and QALYs.

The results remain robust when parameters were varied in sensitivity analysis.

Bevacizumab dominates the comparator in all model assumptions varied in

one-way sensitivity analysis (**Table 6.27**). The CS model generates a higher

incremental QALY gain than the VA model in all scenarios. The model is most

sensitive to the choice of utility set.

A. VA

Parameter	Base case	Sensitivity	Costs			QALYs			Change in ICER (%)
			Comparator	Bevacizumab	Difference	Comparator	Bevacizumab	Difference	
Base case	-	-	£21,005	£14,529	-£6,477	2.995	3.053	0.058	-
Utilities	SF-6D	TTO	£21,005	£14,529	-£6,477	2.905	3.055	0.150	-61%
Discount rate	3.5%	0%	£22,947	£15,868	-£7,078	3.273	3.338	0.064	-1%
		5%	£20,243	£14,003	-£6,240	2.886	2.942	0.056	0%
Time frame		5 yrs	£8,911	£6,184	-£2,727	1.260	1.281	0.021	+17%
		10 yrs	£39,345	£27,183	-£12,162	5.625	5.740	0.115	-5%
Starting age	65	80	£29,342	£20,281	-£9,061	4.191	4.275	0.084	-3%

B. CS

Parameter	Base case	Sensitivity	Costs			QALYs			Change in ICER (%)	Difference in QALYs VA vs. CS
			Comparator	Bevacizumab	Difference	Comparator	Bevacizumab	Difference		
Base case	-	-	£20,972	£14,500	-£6,471	3.125	3.199	0.075	-	+29%
Utilities	SF-6D	TTO	£20,972	£14,500	-£6,471	3.273	3.484	0.211	-65%	+41%
Discount rate	3.5%	0%	£22,950	£15,866	-£7,084	3.421	3.503	0.082	-1%	+28%
		5%	£20,197	£13,966	-£6,231	3.009	3.081	0.072	0%	+28%
Time frame	5 yrs	2 yrs	£8,900	£6,171	-£2,729	1.316	1.344	0.027	+15%	+30%
		10 yrs	£39,288	£27,139	-£12,149	5.869	6.009	0.140	0%	+22%
Starting age	65	80	£29,312	£20,255	-£9,057	4.374	4.478	0.104	+1%	+23%

Table 6.27. One-way sensitivity analysis. A. Visual acuity (VA). B. Contrast sensitivity (CS).

Bevacizumab remains cost-effective when probabilistic sensitivity analysis is applied to utilities, costs and transition probabilities. **Figure 6.16** shows the probabilistic sensitivity analysis on a cost-effectiveness plane.

A. Visual acuity

B. Contrast sensitivity
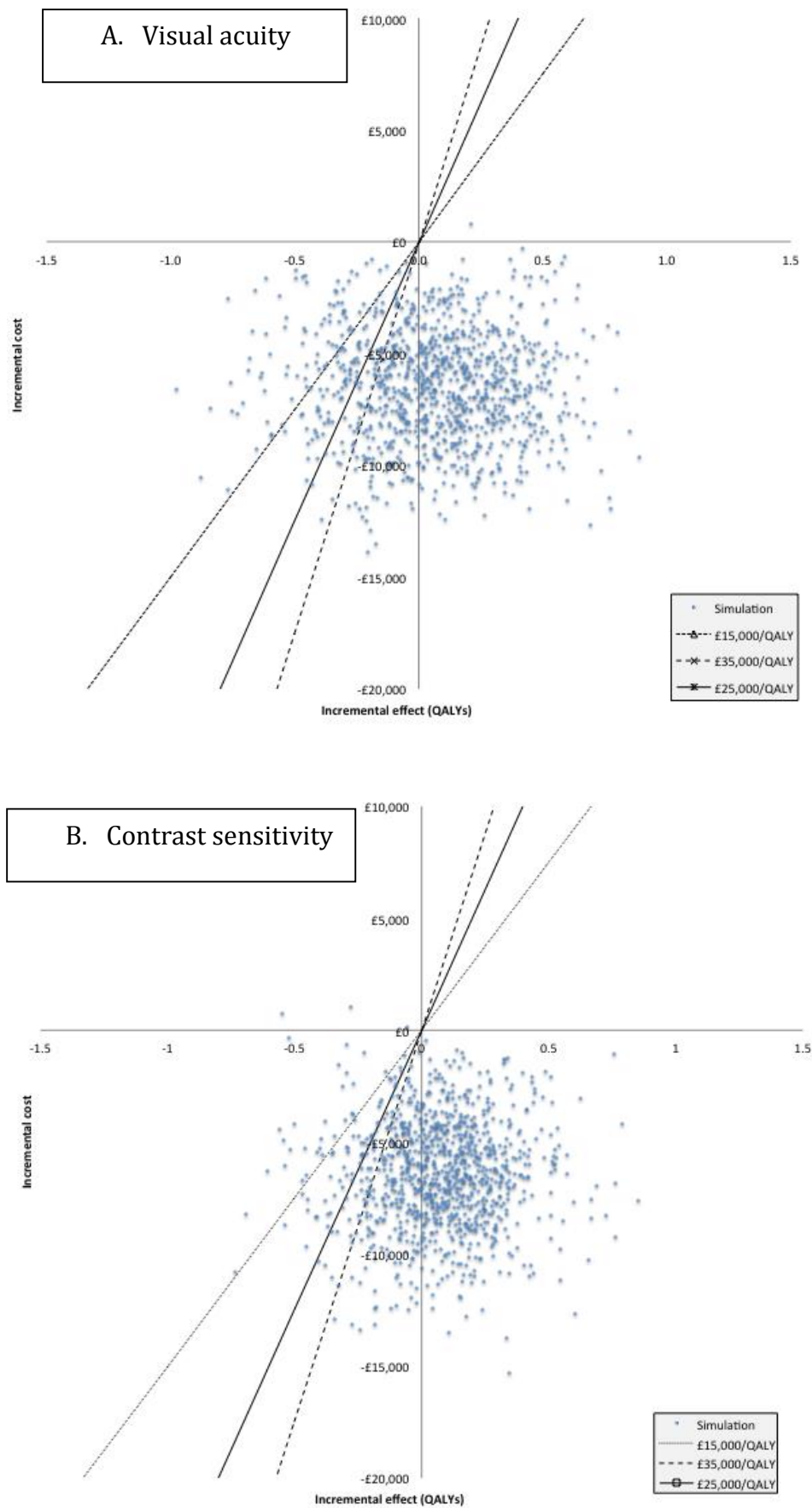
Figure 6.16. Cost-effectiveness plane of incremental costs + QALYs for bevacizumab vs. comparator.

The CEAC highlights that for the same cost as the comparator, bevacizumab has a probability of being cost-effective of more than 60% when assessed using VA and 65% when assessed using CS (**Figure 6.17**). At most costs, there is a higher probability of bevacizumab being cost-effective in the CS model than in the VA model.
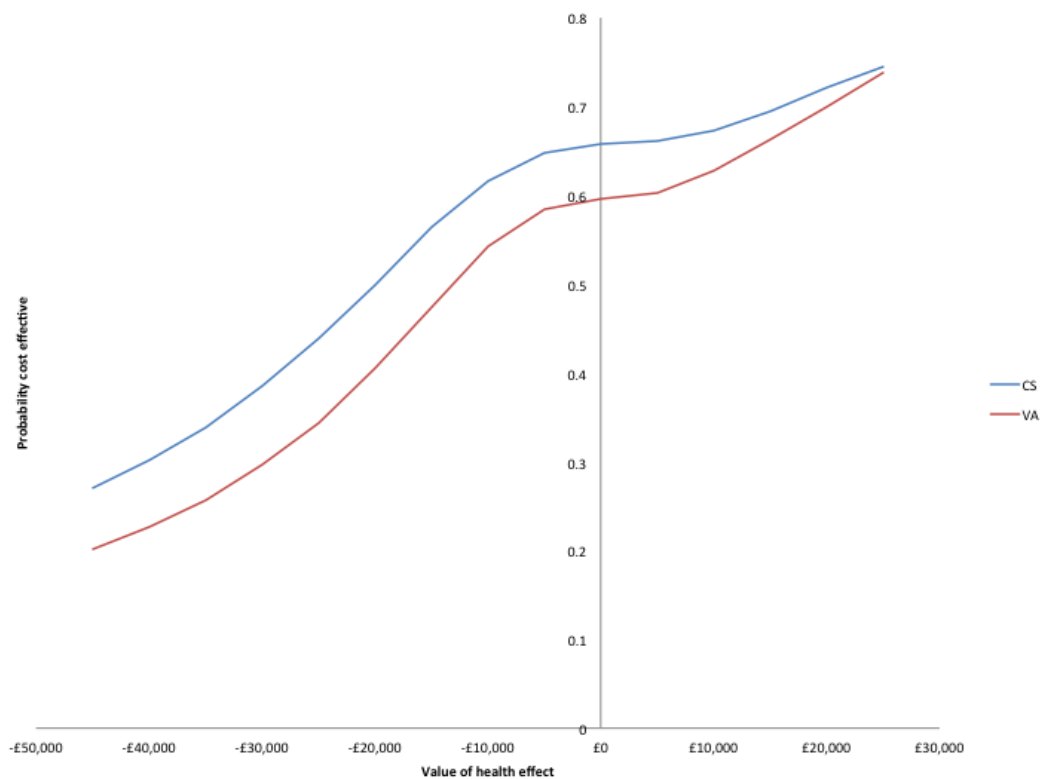
Figure 6.17. Cost-effectiveness acceptability curve. VA = visual acuity, CS = contrast sensitivity.

6.2.3. Conclusion

The choice of outcome represents a major source of structural uncertainty when constructing models to assess the cost-effectiveness of treatments for AMD and has been shown to have a large impact on cost-effectiveness estimates.

Bevacizumab appears more cost-effective when assessed using CS outcomes rather than VA outcomes. In this trial, as bevacizumab dominates the comparator, the decision on the use of bevacizumab in AMD would not be altered by the choice of outcome used in the model.

The difference in incremental QALY gain between the CS and VA models when assessing the cost-effectiveness of anti-VEGF therapy is potentially significant in health care decision-making, particularly in decisions close to the cost-effectiveness threshold. The uncertainty associated with the choice of clinical variable to associate with utility cannot be assigned a distribution and tested using probabilistic sensitivity analysis as is frequently done for costs, utilities and transition rates.

Another anti-VEGF therapy, ranibizumab, is currently recommended for treatment of AMD patients within the NHS.(73) It has been shown to be equally effective to bevacizumab, but is more costly.(63, 115) It can be expected that a higher QALY gain would be accumulated and a lower ICER would be achieved in a model based on CS rather than previously used VA, although this cannot be directly concluded from the current study due to a different intervention and comparator.

Traditionally, a CEAC such as that shown in **Figure 6.17** would only show positive values of health effects. However, the negative value of health effect is shown to allow inferences to be made about how the two outcomes may impact on the cost-effectiveness of a more costly drug. The CEAC demonstrates that for a given value of health effect, the CS model predicts bevacizumab to be more likely to be considered cost-effective.

There are two potential reasons for the different QALY estimates from the two models. Firstly the closer association between CS and HRQoL may mean that the CS model is more accurately representing the utility gain of the treatment than the VA model. Alternatively, the intervention may have a differential effect on VA and CS and anti-VEGF therapy may improve CS more than VA in terms of relative utility.

There are a number of limitations with this study. The comparator treatment (a mixture of pegaptanib, PDT and no treatment) as used in the ABC trial is no longer standard NHS practice since the approval of ranibizumab. This limits interpretation of the absolute ICERs. Indeed, the absolute size of the incremental QALY gain in both models is small because the comparator in this trial was an active intervention. A comparison of bevacizumab with ranibizumab based on CS outcomes would be a valuable area for future research. Furthermore, another anti-VEGF therapy, aflibercept (®Bayer) is approved for the treatment of AMD in the USA and has been shown to be equally effective compared with bevacizumab and ranibizumab.(116) NICE is currently reviewing the use of aflibercept for AMD in the UK.

Both VA and CS have limitations when measuring very poor vision. Both measures rely on patients reading letters on a chart, so when patients cannot read the first letter, patients are assumed to have the most severe health state in the model.

Transition rates were based on trial data and allowed patients' vision to worsen, remain the same or improve at each cycle. Anti-VEGF therapy is generally believed to maintain or reduce deterioration in vision rather than improve it. However, the nature of VA and CS as performance measures means there may be variation in the exact scores achieved by patients on each visit.

These models do not include adverse events. The number of adverse events in the ABC trial was very low. Given the incidence in the two models would be the same, adverse events should not impact on the difference between VA and CS identified.

Generally, these results highlight that the choice of clinical outcome on which a model is based can have a large impact on the cost-effectiveness estimates of the model. Attention should be paid to the association between clinical disease states and HRQoL when developing health economic models. The clinical outcome that is best associated with HRQoL in the condition should be used where practical. If there is uncertainty over the most suitable clinical outcome for defining model states, the alternatives could be presented in one-way sensitivity analysis.

6.3. Visual function algorithm

Given

- the weak association with VA

- the large impact on cost effectiveness estimates of using different aspects of visual function in economic models

It appears desirable to investigate individual and combined mapping algorithms from visual function to utility.

6.3.1. Methods

Multiple OLS and tobit regression models were developed to associate individual and combined measures of visual function (and sociodemographic covariates) with utility.

Dependent variable	Independent variables	Model types	Performance
EQ-5D index (utility)	-VA - CS -Microperimetry	-Linear ordinary least squares -Tobit (outputs censored at 1)	Goodness of fit: -Statistical significance, sign and size of coefficients - R-squared Predictive ability: -Root-mean squared error (RMSE) -Observed vs. predicted scores

Table 6.28. Approach to mapping.

Adapted from Longworth et al.(117)

Sample

It was intended that a mapping algorithm would be developed based on 200 patients with AMD from the baseline data of the Eccentric Fixation From Enhanced Clinical Training (EFFECT) randomised control trial. The sample size was estimated based on *Espallargues et al.* which elicited utility values for levels of VA and CS had a sample size of 207.(58)

EFFECT trial recruitment began in July 2011 with a projected recruitment rate of 3 patients per week. Consequently the full baseline sample was projected to be available in November 2012.

Due to a slower than anticipated rate of recruitment, the full sample was unavailable. Data was extracted in July 2013. Baseline data from 81 patients were available for development of the mapping algorithm. (**Table 6.29**)

Dependent variable

The dependent variable was utility derived from the EQ-5D. The 5-level EQ-5D was administered to patients. Utility values were calculated using the EuroQoL 5L interim value-set for UK public preferences.

The TTO (patient utility) was also planned to be analysed as sensitivity analysis. Due to the number of refusals and non-traders for the TTO, data was only available for 19 subjects. Due to the very small sample, it was decided to proceed only with the EQ-5D.

Independent variables

VA was measured using an ETDRS letter chart and recorded in logMAR. Left eye, right eye and binocular VA was measured. The better eye was identified based on the better VA.

CS was measured using a MARS chart, and recorded in log units. Left eye and right eye CS was measured. Binocular CS was calculated using from the vector sum of the study and fellow eyes.

Retinal microperimetry of the left and right eyes was measured using a Nidek MP-1 microperimeter. Microperimetry was used to approximate the size of the scotoma. A data file of containing each point presented and its location was extracted for each eye of each patient and the proportion of points seen within

the potential visual field was calculated. (see **Appendix B** for details of how microperimetry data was used to approximate the size of the scotoma).

Sociodemographic variables were age, gender, diagnosis (wet or dry AMD), and comorbidities. Comorbidities were included as the sum of conditions mentioned by the patient in an open-ended question phrased as "Please list any other conditions that you have today".

Subjects with one or more missing variables were excluded from the model.

Analysis was conducted using Stata 12 (StataCorp).

Variable	Value
N	81
Mean age, years (SD)	80.8 (11.2)
Female, %	61.7
Mean ETDRS better eye VA, logMAR (SD)	0.64 (0.24)
Mean binocular CS, log units (SD)	1.37 (0.34)
Wet AMD, %	62.5
Mean utility, EQ-5D-5L UK interim value-set (SD)	0.66 (0.21)

Table 6.29. Sample characteristics.

6.3.2. Results

Correlation coefficients were calculated for variables. Pairwise deletion was used for missing data i.e. data points are deleted from the calculation of the correlation if one or both of the data points in that pair was missing.

Correlations were in the expected direction. As logMAR acuity increased, or vision worsened, generally contrast decreased (worsened) and % points seen in microperimetry decreased (worsened). However, only the correlation between better eye and binocular CS and % points seen in microperimetry were significant at $p < 0.05$.

	Better eye VA	Better eye CS	Binocular CS	% points seen microperimetry, better eye	EQ-5D (utility)
Better eye VA	1.00				
Better eye CS	-0.19*	1.00			
Binocular CS	-0.14	0.80**	1.00		
% points seen microperimetry, better eye	-0.19	0.53**	0.48**	1.00	
EQ-5D (utility)	-0.03	0.15	0.15	0.03	1.00

Table 6.30. Correlation coefficients.

*significant at p<0.1 **significant at p<0.05

Models were developed for visual function variables alone (short, **Table 6.31**) and for visual function variables plus sociodemographic variables (long, **Table 6.32**). Comorbidities reduced the explanatory power of the model and were therefore excluded.

Variable	OLS			Tobit		
	Coef.	SE	P>t	Coef.	SE	P>t
Better eye VA	-0.081	0.105	0.447	-0.095	0.105	0.371
Binocular CS	0.069	0.080	0.392	0.070	0.080	0.384
% points seen microperimetry	-0.053	0.148	0.721	-0.068	0.149	0.651
Constant	**0.646****	0.141	0.000	**0.667****	0.142	0.000
Prob > F	0.695			0.643		
R-squared	0.023			-0.080		
Root MSE	0.196			-		
Obs.	67			67[1]		

Table 6.31. Short models of the association between visual function and utility.

*[1] 2 right-censored observations at utility ≥1. *significant at p<0.1.*

Variable	OLS			Tobit		
	Coef.	SE	P>t	Coef.	SE	P>t
Better eye VA	**-0.177***	0.099	0.078	**-0.195****	0.096	0.047
Binocular CS	0.052	0.078	0.502	0.051	0.075	0.495
% points seen microperimetry	0.009	0.140	0.950	-0.004	0.137	0.978
Age	-0.003	0.002	0.117	**-0.003***	0.002	0.095
Gender (female)	-0.059	0.047	0.215	-0.060	0.045	0.190
Diagnosis (wet)	**0.185****	0.047	0.000	**0.191****	0.046	0.000
Constant	**0.855****	0.213	0.000	**0.884****	0.207	0.000
Prob > F	**0.004**			**0.002**		
R-squared	0.274			-1.140		
Root MSE	0.176			-		
Obs.	64			64[1]		

Table 6.32. Full models of the association between visual function and utility.

[1] 2 right-censored observations at utility ≥1. *significant at p<0.1. **significant at p<0.05

An algorithm associating visual function and utility was generated from the Tobit full model using VA in the better eye, age and diagnosis. The variables to be included in the algorithm were selected based on a significance level of p < 0.1. This algorithm may be considered exploratory due to using a smaller sample than anticipated.

Equation:

V = (0.884) – (0.195xVA_better) – (0.003xAge) + (0.191xWet)

The performance of the model was assessed by comparing predicted values from the algorithm with patient's actual EQ-5D utility scores. Algorithm predictions were based on patient's own acuity, age and diagnosis. The algorithm followed the trend of the actual data, but diverged at extreme upper and lower values.
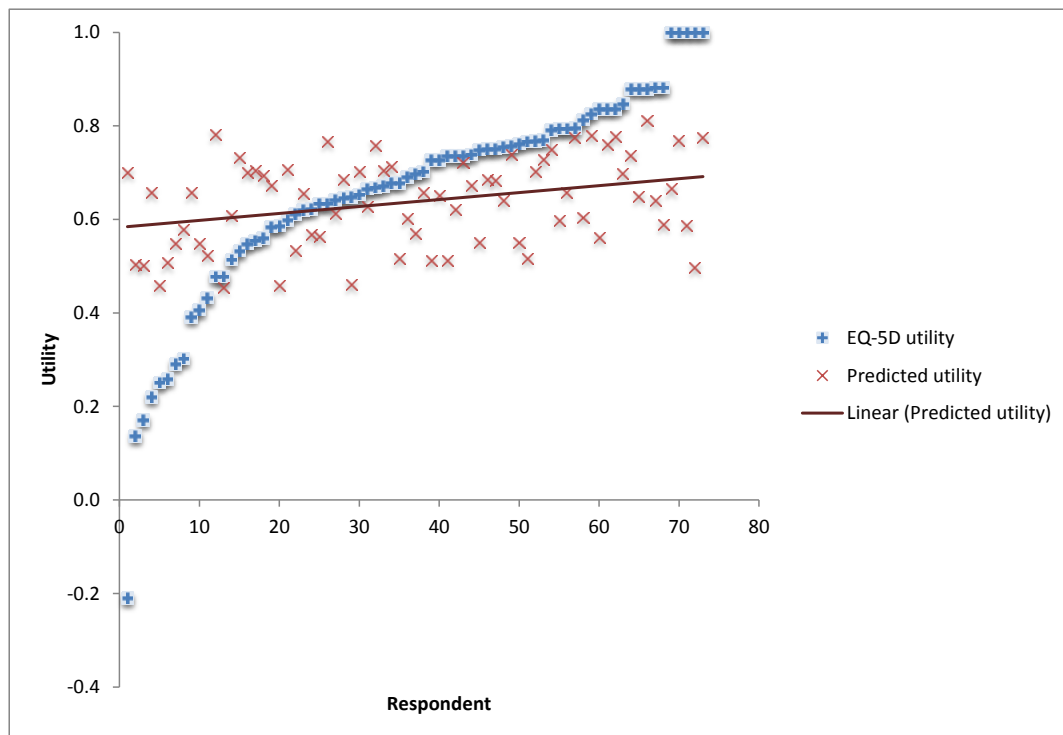
Figure 6.18. Actual vs. predicted utility scores in algorithm sample.

6.3.3. Validation

In order to validate the algorithm, it was applied to an independent sample and reported utility values were compared with those predicted by the algorithm.

The independent dataset chosen was the 58 AMD patients who answered a range of utility instruments as described in **Chapter 3**. The characteristics of these patients are summarised in **Section 3.1.3**. To summarise, mean age was 83.8 (SD = 6.5) years, Seventy nine percent of patients (46) had a diagnosis of wet AMD. Mean best-corrected VA in the better seeing eye was 0.65 (SD = 0.30) logMAR. As described in Chapter 3, the VA was taken from the hospital notes, therefore may have been different than if it had been measured on the day of the assessment. Among the questionnaires completed by these patients was the EQ-5D-5L for which utility scores were calculated using the EQ-5D-5L interim value-set for the UK.

The mean utility predicted by the algorithm was 0.658 compared with the mean utility derived from the EQ-5D of 0.613 (the algorithm predicted an average of +0.045 compared with the actual EQ-5D scores). However, when individual patient scores and predictions are compared (**Figure 6.19**), it can be seen that although the trend line of the algorithm is sloping in the expected direction (higher utility scores correlate with higher predicted utility), the algorithm is considerably over-predicting low utilities and under-predicting high utilities.
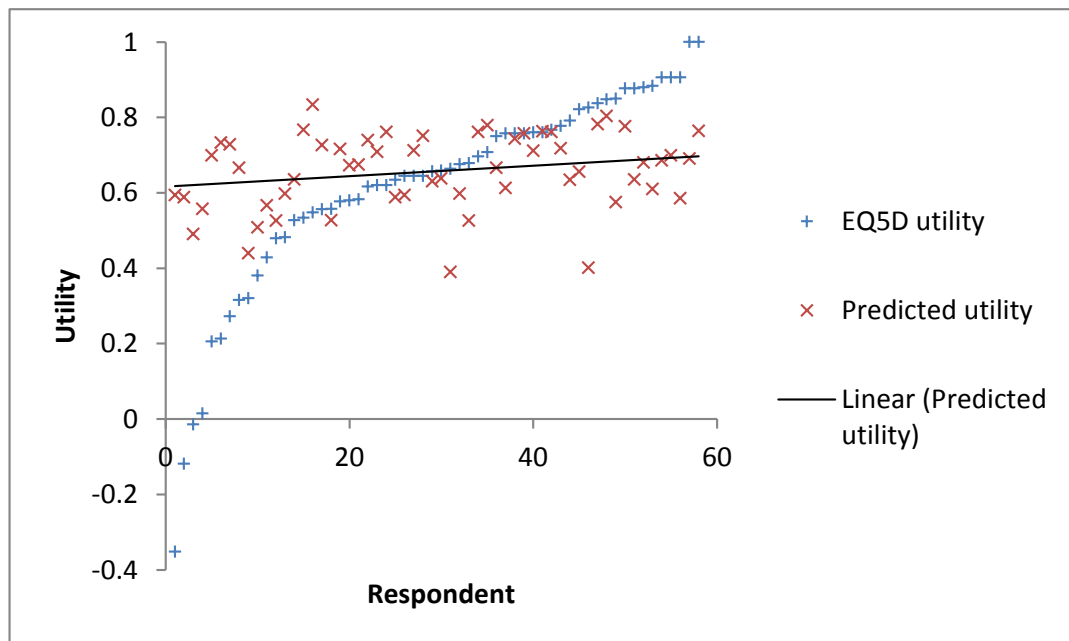
Figure 6.19. Validation (actual vs. predicted utility scores in independent sample)

Utility values from the model were compared with published data. For a 70 year old with wet AMD, the algorithm predicted a utility of 0.48 for a VA of 2.00 and 0.81 for a utility of 0.30.

The range of utilities predicted was greater than for EQ-5D utilities elicited by *Espallargues et al.* (which reported 0.63 and 0.75 respectively). Compared with the contact lens simulation by *Czoski-Murray et al.*, utilities were marginally higher across VA with a similar range. (**Table 6.33**)

VA	Utility (EQ-5D, *Espallargues et al.*)	Utility (contact lens simulation)	Predicted by algorithm*
>2.00	0.63		**0.48**
1.31 to 2.00	0.71	0.314	**0.48 – 0.61**
0.61 to 1.30	0.75	0.511	**0.61 – 0.75**
0.31 to 0.60	0.70	0.681	**0.75 – 0.80**
≤0.30	0.75	0.706	**0.81**

Table 6.33. Comparison with published utility values.

70 year old with wet AMD

6.3.4. Conclusion

These results should be considered exploratory due to the small sample size. Of the three measures of visual function, VA appears to be the best predictor of utility in patients with advanced AMD. Age and diagnosis also contribute to predicting utility.

CS and microperimetry did not predict utility in this dataset. Reasons for the weak association between these measures of visual function and utility may include the impact of comorbidities on health status and the insensitivity of the EQ-5D questionnaire to different levels of visual function. Furthermore, only around a third of the estimated sample size was used in this analysis meaning that the models may be underpowered.

The algorithm performed poorly at extreme upper and lower utility values. Such a result could be expected given that visual function cannot predict comorbidities, which may cause extreme low values of utility.

Improved methods for excluding comorbidities may improve the association in small samples (particularly at extreme values). However, since the recording of comorbidities in clinical trials is not standardised, their exclusion from the model means that it may be used in a wider range of datasets. Indeed, the variables included in the algorithm (VA, age and diagnosis) are routinely available in clinical practice, therefore provide the most useful algorithm for calculating utility values for historic trials where utilities were not originally collected.

Furthermore, most interventions for visual disorders are likely to affect only the components of utility captured by the algorithm, therefore the algorithm can be expected to measure the incremental utility change due to vision whether or not it includes comorbidities.

7. CUA of treating patients with early AMD

This chapter develops a CUA model to investigate the cost effectiveness of treating AMD patients with early disease, and therefore better vision than the published NICE guidance, using a database of real world outcomes in order to address research aim 4: *What is the economic impact of treating AMD patients with good starting vision?*

7.1. Introduction

Intravitreal injection of anti-VEGF drugs such as ranibizumab (Lucentis, Novartis) is an established therapy to treat nAMD and is the most commonly performed retinal procedure in the UK NHS.(118) In the UK NICE recommended the use of ranibizumab for nAMD in August 2008, leading to almost exclusive usage of ranibizumab for nAMD in the UK NHS.(73) In addition to the limitations of evidence on utility investigated in previous chapters, there is an absence of information on the effectiveness and cost effectiveness of treating AMD patients with good starting levels of vision.

Clinical and economic evidence was initially informed by the Anti-vascular endothelial growth factor Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related Macular Degeneration (ANCHOR) and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) Studies, which demonstrated that ranibizumab prevents central vision loss and

improves mean VA at 2 years when given at monthly intervals in eyes with subfoveal nAMD.(119, 120)

Consistent with these pivotal studies, NICE recommended that ranibizumab for nAMD should be funded in eyes presenting with VA's between 6/12 and 6/96, which parallels the entry criteria of the pivotal studies. Due to the trials' exclusion criteria, no direct evidence exists from Phase 3 randomised controlled clinical trials to assess the effectiveness and cost effectiveness of treating patients presenting with early lesions resulting in vision better than 6/12.

However, patients have been presenting with nAMD to treating centres with better visions since NICE initially supported ranibizumab reimbursement on the NHS in 2008. Current guidance is to wait until vision worsens to below 6/12 before treating. It has previously been shown that if ranibizumab therapy is initiated in eyes with good visual acuities the treated eye is more likely to maintain good vision and this is consistent with the indirect evidence from the pivotal trials that eyes are more likely to maintain vision than recover lost vision at initiation of treatment.(119, 120)

The purpose of this chapter is to evaluate whether immediate intervention with ranibizumab in the better seeing eye of patients presenting with nAMD with good vision is cost effective compared with the delayed intervention approach that is currently recommended.

A health economic model with health states based on levels of VA in the better seeing eye was developed. The intervention considered is the initiation of ranibizumab (10mg/ml solution for injection) treatment using 3 loading

injections + a PRN protocol for patients with a confirmed diagnosis of nAMD and vision better than 6/12: immediate treatment. The comparator is the current standard of care for nAMD patients, which is no treatment for patients with a confirmed diagnosis of nAMD with vision better than 6/12 and treatment with ranibizumab using 3 loading injections of ranibizumab at approximately monthly intervals followed by a pro re nata (3 loading injections + PRN) protocol when vision falls below 6/12: delayed treatment (current NHS practice). Effectiveness and resource use was derived from real life outcomes from treated and untreated (fellow) eyes in 14 centres using ranibizumab for AMD in the UK.(121)

This analysis is the first to assess the cost effectiveness of treating VA better than 6/12 in nAMD compared to treating only when vision is worse than 6/12 with ranibizumab. Furthermore, the work demonstrates how real world outcomes and resource use associated with the use of ranibizumab therapy may be used to assess the cost effectiveness of treating nAMD. These results may be more generalizable to routine clinical practice than models based on randomised controlled trial (RCT) data, therefore more appropriate to assess the cost effectiveness of routine use treatment protocol in the NHS.

7.2. Methods

Model structure

A Markov patient level simulation model was developed with an initial 3 month cycle followed by monthly cycles. The model consisted of six health states: five

health states defined by declining VA ranging from 6/15 or better (least severe) to less than 3/60 (most severe), and an additional absorbing state, death, which was accessible from all levels of vision. VA was used for this model as it was the only visual function measure routinely captured in the EMR database. (**Figure 7.20**)

Immediate treatment

Define patient characteristics (age, gender)

6/6 to 6/12 · 6/12 to 6/24 · 6/24 to 6/60 · 6/60 to 3/60 · <3/60 · Dead

Delayed treatment

Clone patient from immediate treatment arm

6/6 to 6/12 · 6/12 to 6/24 · 6/24 to 6/60 · 6/60 to 3/60 · <3/60 · Dead
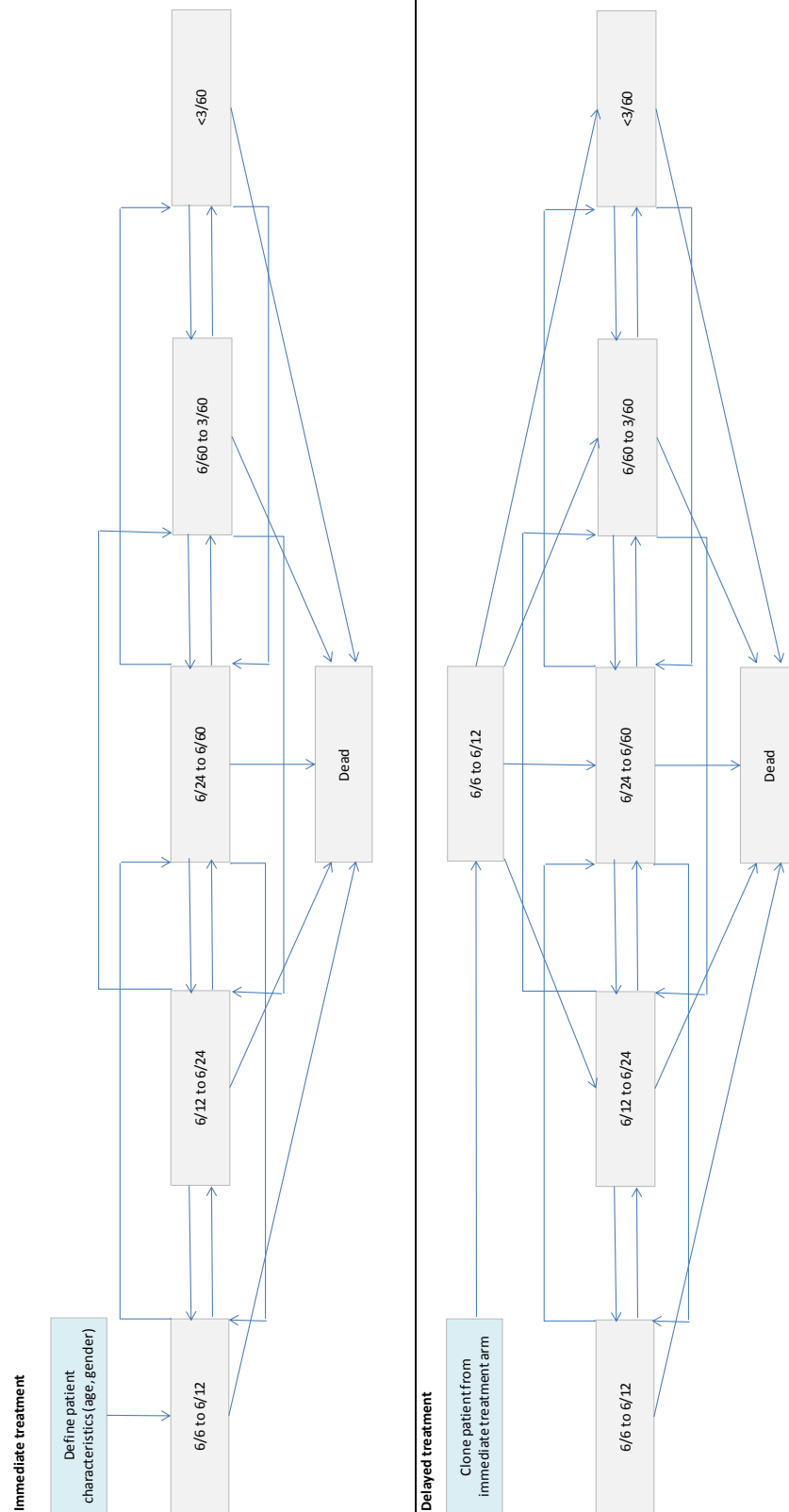
Figure 7.20. Model structure.

On entering the model, a patient was assigned an age and gender based on the distribution of these characteristics among patients with a starting vision of better than 6/12 in the dataset.

For immediate treatment, a patient was simulated to be treated straight away on confirmed diagnosis of nAMD with 3 initial monthly ranibizumab injections followed by PRN for 2 years. For delayed treatment, a patient was assigned a time from diagnosis to vision falling below 6/12. In the initial period (>6/12) a patient received no treatment. After reaching 6/12, treatment began and a patient progressed to a state of vision assigned according to a distribution based on the visions of patients beginning treatment in the dataset (i.e. many eyes with nAMD will initially present with a vision in the NICE guidance allowing immediate treatment but the vision may be any value between 6/12 and 6/96 and not just 6/12). A patient was then treated with 3 initial monthly ranibizumab injections followed by PRN and continued through the model for 2 years including the starting delay. The simulation was run for 10,000 patients.

Perspective

The perspective of the model was the UK NHS and personal social services as recommended in the NICE Guide to the Methods of Technology Appraisal reference case.(2) The model had a two year time horizon, which represented the time horizon used in pivotal trials. Due to the short time horizon, costs and benefits were not discounted.

Transition probabilities

Transition matrices were calculated from the EMR dataset (**Table 7.34**). Data were ordered longitudinally from the first visit for a ranibizumab injection. Since patients returned for injections at a frequency determined by their clinician, there were a large number of time points with missing outcome data. Linear interpolation was conducted in Stata 12 (StataCorp) to estimate VA at time points that were missing between measured VA.

For treatment, transitions were calculated from visual acuities recorded for treated eyes. For no treatment of eyes better than 6/12, transitions were calculated from visual acuities recorded for fellow (untreated) eyes.

In the immediate treatment arm, all patients began in state >6/12 with a three-month loading dose cycle. Patients then received ranibizumab PRN with monthly transitions for the remainder of the two years.

For the delayed treatment arm, patients followed a time-to-event survival curve to define the time in state >6/12 before dropping below 6/12 and beginning treatment. Once their vision dropped below 6/12, they entered the three-month loading dose cycle in the following distribution [state 1: 0, state 2: 0.434484, state 3: 0.3891544, state 4: 0.1456472, state 5: 0.0307501 (based on the distribution of patients beginning treatment in the dataset)]. Patients then received ranibizumab PRN with monthly transitions for the remainder of the two years.

A. Immediate treatment

First 3 months (M 0-2), prob. for 3M cycle	To 6/6 - >6/12	6/12 - 6/24	6/24 - 6/60	6/60 - 3/60	<3/60
From 6/6 to >6/12	.7240	.2222	.0335	.0108	.0096
Remainder of 2 years (M 3-24), prob. for 1M cycle	To 6/6 to >6/12	6/12 to 6/24	6/24 to 6/60	6/60 to 3/60	<3/60
From 6/6 - >6/12	.8778	.1163	.0046	.0006	.0008
6/12 - 6/24	.2937	.6243	.0783	.0032	.0005
6/24 - 6/60	.0359	.2355	.6747	.0479	.0060
6/60 - 3/60	.0219	.0146	.1533	.7007	.1095
<3/60	.0588	.0147	.0147	.2059	.7059

B. Delayed treatment

First 3 months (M after drop to state 2), prob. for 3M cycle	To 6/6 - >6/12	6/12 - 6/24	6/24 - 6/60	6/60 - 3/60	<3/60
From 6/6 - >6/12	.0	.0	.0	.0	.0
6/12 - 6/24	.3300	.4993	.1506	.0139	.0062
6/24 - 6/60	.0699	.3049	.4923	.1057	.0272
6/60 - 3/60	.0157	.0927	.3795	.4123	.0999
<3/60	.0203	.0541	.2432	.4257	.2568
Remainder of 2 years (+ 3 from M after reaching state 2), prob. for 1M cycle	To 6/6 - >6/12	6/12 - 6/24	6/24 - 6/60	6/60 - 3/60	<3/60
From 6/6 - >6/12	.7366	.2408	.0139	.0026	.0062
6/12 - 6/24	.1433	.7161	.1341	.0054	.0011
6/24 - 6/60	.0081	.1414	.7369	.1068	.0068
6/60 - 3/60	.0047	.0093	.2018	.7045	.0797
<3/60	.0380	.0087	.0459	.2985	.6089

Table 7.34. Transition probabilities between health states. A. Immediate treatment. B. Delayed treatment

Utility

Benefits were measured in QALYs. VA was converted to utility for the calculation of QALYs using *Brown et al.*, which elicited utilities in 80 patients AMD using the TTO method and grouped these by the VA health states defined in the model.(48) *Brown et al.* was selected for comparability with the utility values and health states used in the original NICE appraisal of ranibizumab that recommended the treatment for patients with vision better than 6/12.

The health state utility values used in the model are reported in **Table 7.35**.

VA	Utility, mean (SD)
From 6/6 to 6/12	0.89 (0.16)
6/12 to 6/24	0.81 (0.20)
6/24 to 6/60	0.57 (0.17)
6/60 to 3/60	0.52 (0.24)
<3/60	0.40 (0.12)

Table 7.35. Utility values for model health states.

from Brown et al.(48)

Cost

Resource use and costs were applied to reflect UK clinical practice. Resource use consisted of monthly assessment visits and ranibizumab injection. On initiation of treatment, patients received three loading doses of ranibizumab as recommended by clinical guidance followed by PRN injections at a frequency calculated from the dataset.

UK unit costs were assigned for a cost year of 2012. A cost of ranibizumab of £742.17 per injection, an assessment cost of £255.00 and a monitoring cost of £60.00 was used.(122, 123) These costs were consistent with the NICE costing template for Aflibercept (July 2013).(124)

Sensitivity analysis

Appropriate probability functions were fitted to model parameters to incorporate uncertainty. Probabilistic sensitivity analysis was performed using

a Monte Carlo simulation to randomly sample each parameter. Utilities were characterised by a beta distribution, with alpha and beta parameters defined by the means and standard deviations of the utilities. Costs were characterised by a gamma distribution with alpha and beta parameters defined by the means and standard deviations of the costs. Standard deviations were not available for costs, therefore they were assumed to be 10% of the mean in line with recommended practice for health economic models. Transition probabilities were characterised by a Dirichlet distribution. A CEAC was constructed to represent the probability of the treatment proving cost effective at a given value of health effect. One-way sensitivity analysis was employed to test structural uncertainty within the model.

EMR data set

Transition probabilities and resource use were calculated from a large dataset of ranibizumab injections which covered data from the approval of ranibizumab in August 2008 until April 2012.(121) Data were extracted on 12,951 eyes of 11,135 patients receiving a total of 92,976 ranibizumab injections during 317,371 clinic visits at 14 UK hospitals. At two years, 4,420 patients remained in the analysis, at 4 years, 526 patients remained in the analysis. The relatively steep drop-off is due to patients being discharged when ranibizumab is deemed to be no longer effective.

14 NHS hospitals that deliver ranibizumab AMD treatment services in England and Northern Ireland submitted data to this study. Each site is the only NHS provider of nAMD care to their local population and very few patients switch between providers. Following NICE approval for the use of ranibizumab for

nAMD in the NHS in August 2008 all sites used this drug almost exclusively. The lead clinician and Caldicott Guardian (who oversees data protection) at each centre gave written approval for the data extraction. Patient identifiers were completely stripped out and site and clinician data were pseudo-anonymised and on this basis an ethics committee determined that formal ethics approval was not required. This study was conducted in accordance with the declaration of Helsinki and the UK's Data Protection Act

The 14 sites entered their first treatment episodes into the EMR system during the following years: 2006 (n=2 sites), 2007 (n=5), 2008 (n=4), 2009 (n=1), and 2010 (n=2). The first recorded ranibizumab injection was dated November 2006.

Over the period of data collection, anti-VEGF treatment was performed in 13,774 patients, of whom 2,639 received anti-VEGF for reasons other than nAMD or received bevacizumab. Thus this study analyses data on 12,951 eyes of 11,135 patients who received a total of 92,976 ranibizumab injections during 317,371 clinic visits at 14 UK hospitals. 16.3% (n=1,816) of these patients required treatment to both eyes during the follow up period. The demographics of the patients included have been published elsewhere and are summarised in **Table 7.36**.(121)

'Best-measured VA' was the best VA with refraction or habitual correction and/or pinhole as measured on an Early Treatment Diabetic Retinopathy Study (ETDRS) chart and expressed as ETDRS letters and LogMAR vision in this study.

Variable	Male (n = 4,071)	Female (n = 7,062)	Not specified (n = 1)	Total (n = 11,135)
Age (years)				
Mean	78.8	80.1	79	79.7
Median	80	81	79	81
IQR	74-84	76-86	-	75-85
Range	55-103	55-108	-	55-108

Table 7.36. Demographic details of patients used to develop model.

*IQR = interquartile range

Missing data

For patients where data were not available for a particular visit or had been lost to follow-up no missing value substitutions were performed. The only exception to this rule was baseline VA as some treatment centres brought patients back for a 2 stop service—assessment on first visit followed by injection on second visit, and did not repeat VA measurements on the date of the first injection (n=1670), which was always performed within 3 weeks. This was therefore not missing data per se but reflects variation in treatment delivery.

7.3. Results

The central ICER estimate from PSA was £4,251.60 per QALY for immediate intervention compared with delayed intervention.(**Table 7.37**) In the

immediate intervention group, patients accumulated on average 1.59 QALYs and £8,469.79 costs over two years versus 1.35 QALYs and £7,460.21 costs in the delayed intervention group.

Figure 7.23 shows the cost effectiveness plane with 10,000 simulations. The majority of the distributions are located to the lower right of a £20,000 willingness to pay threshold. The results are disaggregated into the incremental cost per QALY of immediate intervention and delayed intervention in **Figure 7.22**.

Figure 7.24 shows the CEAC. Immediate treatment has a 50% chance of being cost effective compared with current treatment practice if the NHS were willing to pay £4,251.60 per QALY. At a willingness to pay threshold of £20,000 per QALY, immediate treatment has a >90% chance of being cost effective.

One-way sensitivity analysis is reported in **Table 7.38**. The model was sensitive to time horizon. Running the model for five years rather than two resulted in a lower ICER of £1,773.21 (58% lower than the base case). Over a longer time horizon, the early intervention arm accumulated more QALYs for a marginally higher cost than the delayed intervention arm. A younger starting age had a marginal impact on the ICER, with a starting age of 60 years generating an ICER of £3,909.36 (8% lower than the base case). Including only drug cost (no visit cost) led to an ICER of £3,697.82 (13% lower than the base case). The ICER was also impacted by the choice of health state utility values. Using values elicited by *Brown et al.* using the standard gamble technique generated an ICER of 5,126.51 (21% higher than the base case using TTO values from the same source).

	Comparator (delayed intervention)	Intervention (immediate intervention)	Incremental
Cost	£7,460.21	£8,469.79	£1,009.58
QALYs	1.35	1.59	0.24
ICER			£4,251.60

Table 7.37. Central cost-effectiveness results: average of Monte Carlo analysis.

Parameter	Base case	Sensitivity	Cost (£)			QALY			ICER	Change in ICER (%)
			Comparator	Intervention	Difference	Comparator	Intervention	Difference		
Base case	-	-	7,460.21	8,469.79	1,009.58	1.35	1.59	0.24	4,251.60	-
Utility	Brown et al. TTO	Brown et al. SG	7,460.21	8,469.79	1,009.58	1.54	1.73	0.19	5,126.51	+21%
Cost	Drug and visit	Drug only	6,232.08	7,110.14	878.06	1.35	1.59	0.24	3,697.82	-13%
Time horizon	2 years	5 years	15,000.16	15,998.43	998.27	3.01	3.57	0.56	1,773.21	-58%
Starting age	78.8*	60+	7,771.01	8,768.44	997.43	1.42	1.67	0.25	3,909.36	-8%

Table 7.38. One-way sensitivity analysis

Brown et al.(48). TTO = time trade-off. SG = standard gamble. *distribution defined by

characteristics of dataset. +fixed starting age for cohort
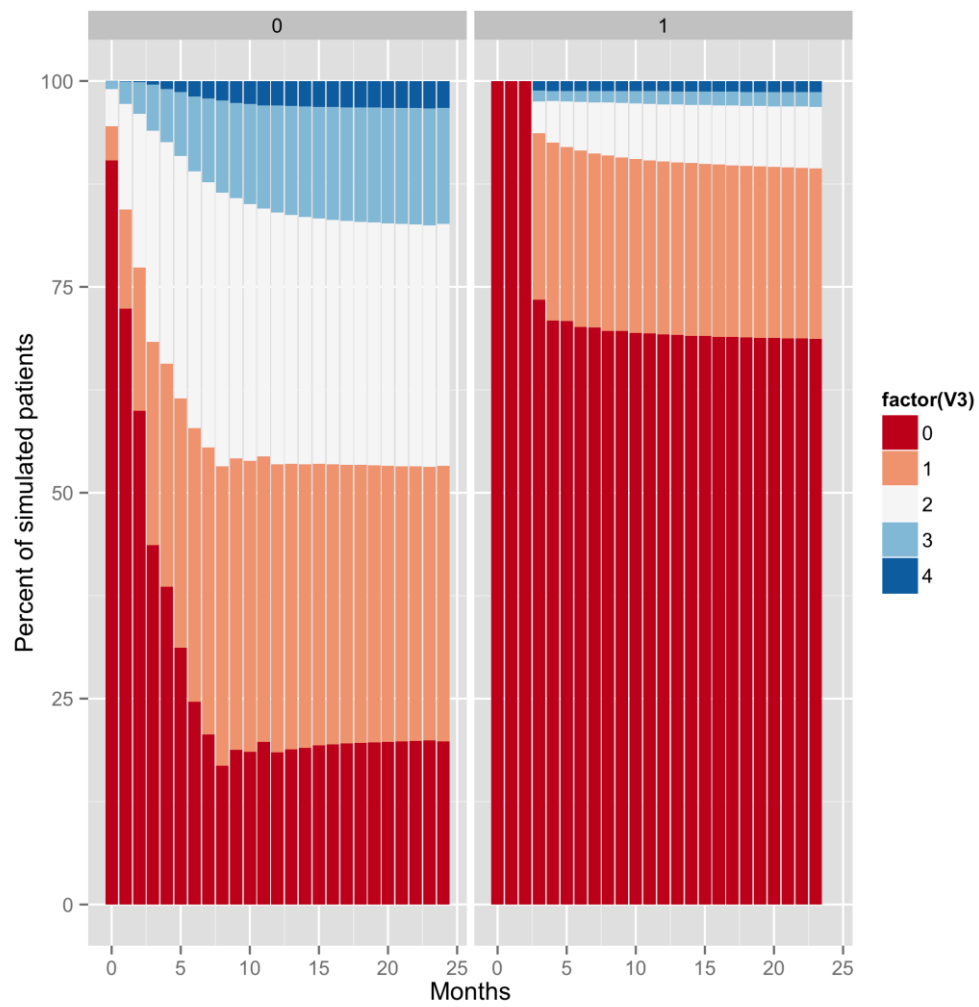
Figure 7.21. Proportion of patients in health states over time.
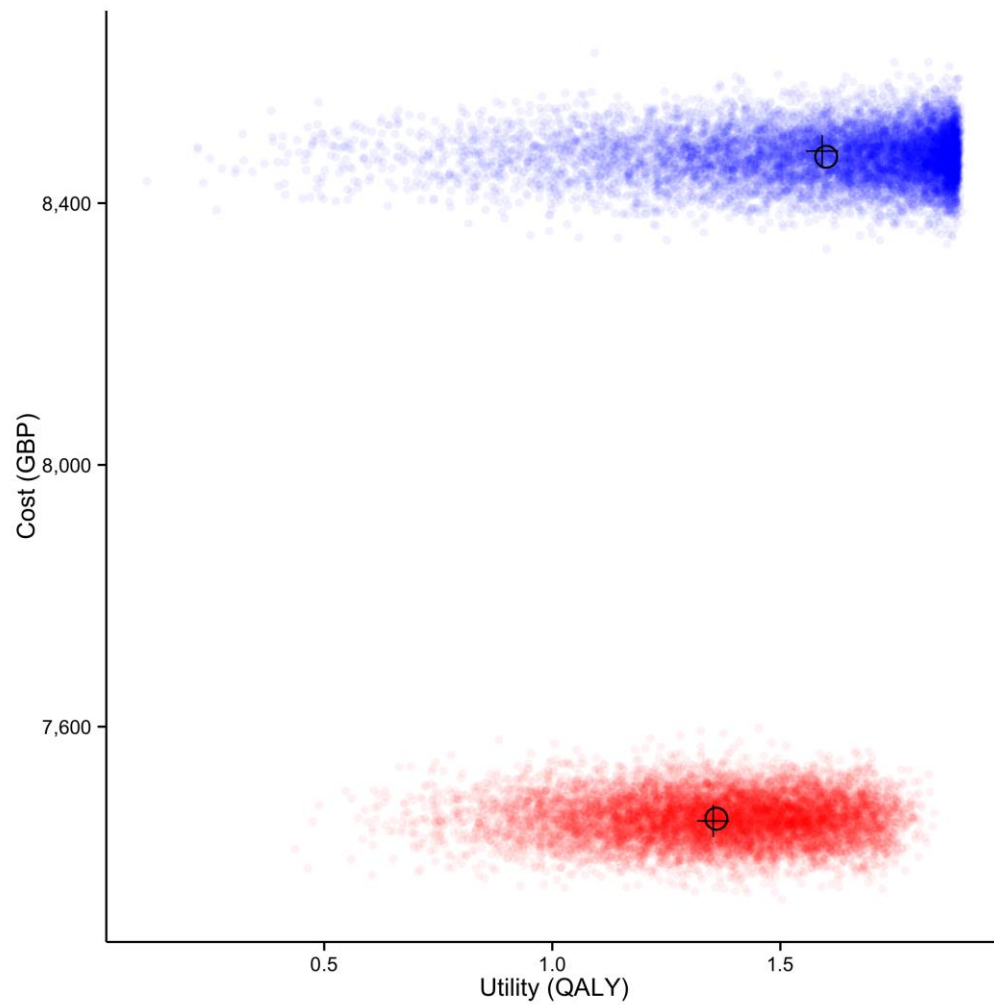
Figure 7.22. Costs and QALYs accumulated over two years by patients treated with ranibizumab according to current NHS practice (red) and with early intervention (blue).
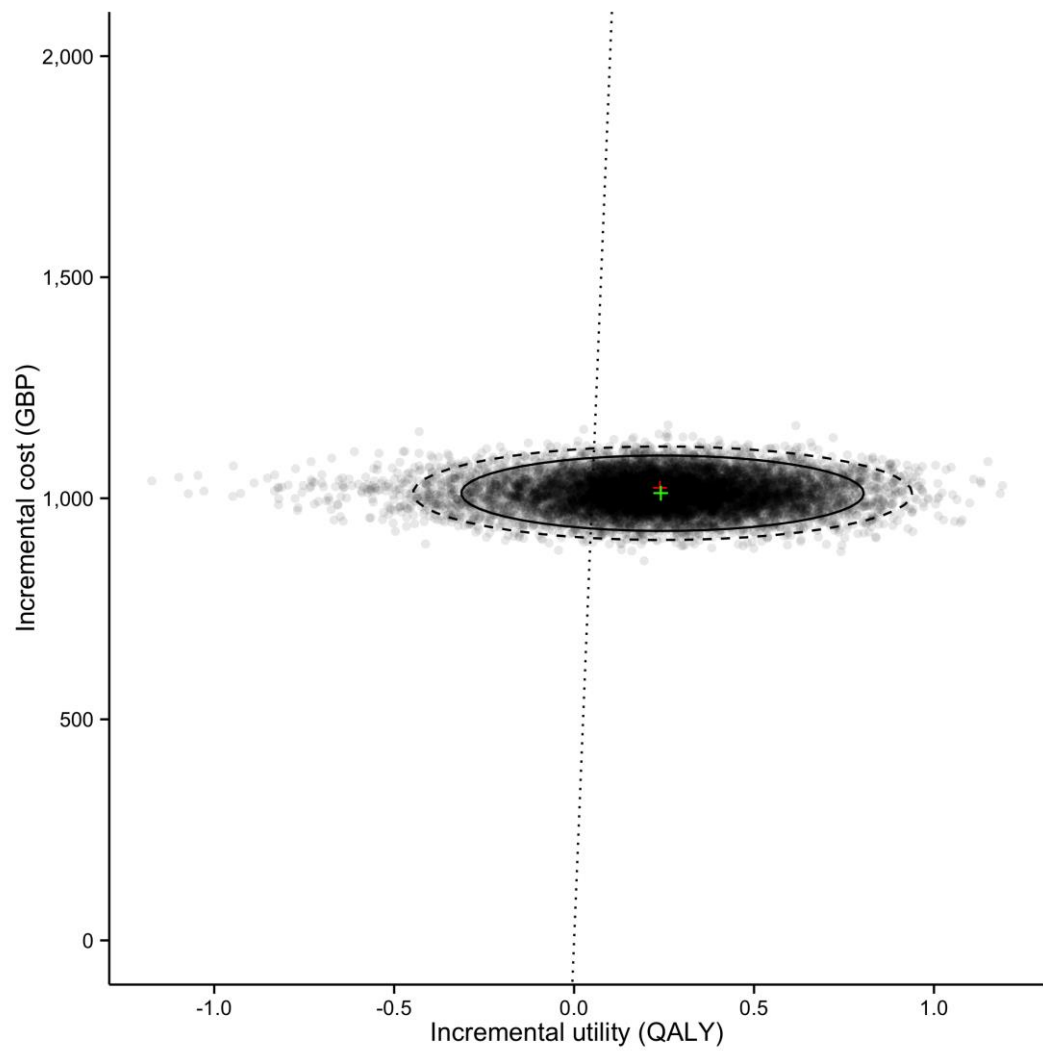
Figure 7.23. Cost-effectiveness plane. GBP = British Pounds.
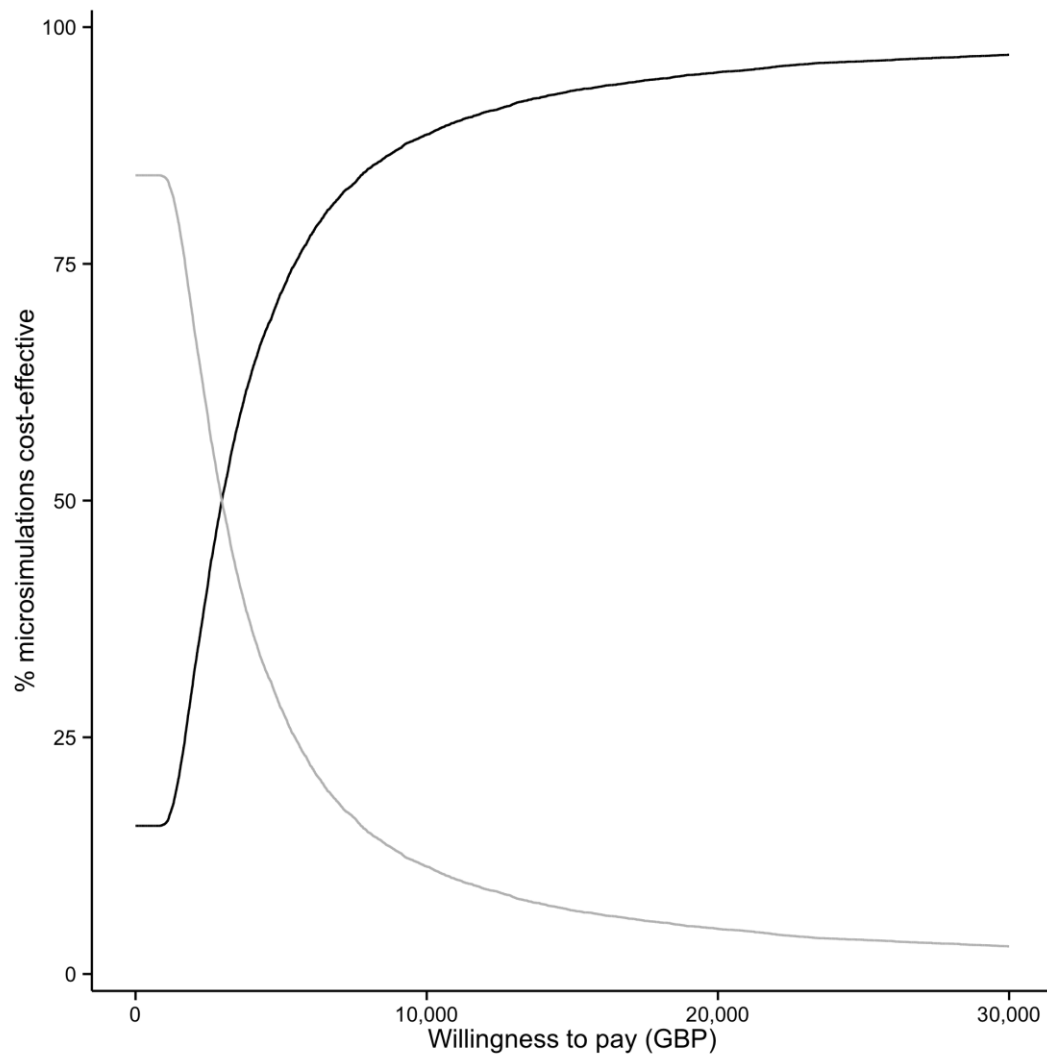
Figure 7.24. Cost-effectiveness acceptability curve of immediate treatment of nAMD with ranibizumab (dark grey) compared with current NHS practice of delayed treatment (light grey).

7.4. Discussion

Immediate intervention in nAMD is likely to be a cost effective strategy. Over two years, patients received an average of 1 more injection and gained 0.24 QALYs compared with current practice of delayed intervention.

The ICER of £4,251.60 of treating early versus current treatment practice is substantially below a threshold of £20,000 per QALY which is often considered the NHS' willingness to pay for health gain.(125)

This is believed to be the first assessment of the cost effectiveness of treating patients with ranibizumab with vision better than 6/12. It appears that the recommendation of treating patients with vision worse than 6/12 was based on the absence of evidence in patients with better vision due to the exclusion criteria in clinical trials of ranibizumab. Therefore, NICE currently do not recommend funding for eyes with good VA, which may result in some patient having to drop below 6/12 to initiate therapy. From a patient perspective, what is more important is maintaining a good functional visual state that allows continuing to be able to read and drive and waiting until the vision falls below 6/12 can be anxiety provoking and delayed treatment can result in worse clinical outcome.(126) This chapter provides evidence that early ranibizumab treatment is associated with a small incremental cost per QALY within the range that the NHS is typically willing to pay for health gain.

As the first assessment of the cost effectiveness of treating a broader range of visual acuities with ranibizumab, the results cannot be directly compared with other models. In NICE's economic evaluation of ranibizumab for AMD, the assessment group used a similar state transition model based on VA.(73) The base case ICERs over a10-year time horizon for predominantly classic lesions were £15,638 per QALY gained compared to PDT with verteporin, and £11,412 per QALY gained compared with best supportive care. For minimally classic lesions and occult lesions, assuming 2 years of treatment, the ICER was £25,098

per QALY gained compared with best supportive care. In terms of clinical effectiveness, VA outcomes from the database previously reported that outcomes do not match the results achieved in most randomized trials, but they were delivered with substantially fewer injections and hospital visits.(121)

This study synthesises outcomes from routine NHS treatment, which is likely to better reflect real world effectiveness and resource use than RCT evidence. Beyond the limited range of visual acuities included in pivotal trials, the use of RCT data for assessing cost effectiveness suffers from limitations of inclusion/exclusion criteria and protocol-driven treatment patterns. Thus, the outcomes and treatment practices derived from RCT data may not reflect today's clinical practice. By contrast, the use of real world data requires robust methods to deal with non-standardised aspects such as missing data.

There are a number of limitations to this study beyond the need to use VA alone as mentioned in the Methods section. First, the study required some assumptions to be made about changes in vision that occur between patients not being treated, which we derived from natural history data, and patients beginning treatment, which we derived from the EMR dataset. Once the delayed treatment group initiates therapy, they immediately fall to the starting VA of any person starting on treatment. Meaning that once they fall below the 6/12 line their VA state changes to match the distribution of starting VA in the dataset of anyone beginning treatment. We believe that this is realistic in clinical practice, since most lesions are likely to have subtle changes that can be seen clinically before the patient notices it or they qualify for treatment. The survival curve on which the model is due to the fellow eye's structural optical

coherence tomography (OCT) data in the EMR dataset. Once the lesion causes the vision to fall below 6/12 patients could realistically end up in any possible vision clinically.

Second, due to the limited number of VA states, a significant number of patients in the treat-early group remain in the best VA state for the lifetime of the model. Such a situation is perhaps not surprising: Ranibizumab treatment is generally associated with a maintenance of vision rather than an improvement (recovery of lost vision due to nAMD). Therefore in the model initiating treatment early, patients maintained a better VA state and accumulated more QALYs.

In summary, this study provides real world data based model demonstrating that early ranibizumab intervention is associated with an acceptable incremental cost that is well within the NHS acceptable range to pay for health gain. Thus, the maintenance of better VA in patients who are treated early is not only beneficial clinically but also likely cost effective. This study may help inform future policy decision regarding the routine treatment with ranibizumab at VAs better than 6/12.

8. Valuing The Benefits Of Decision Support Tools

This chapter presents a conceptual framework to assess the value of decision support tools in order to address research aim 2: *Are non-health attributes important in AMD and how can they be incorporated into the cost-utility economic evaluation framework?*

8.1. Measuring the economic benefits of process

Decision support tools are increasingly used within the health care system. Their application may be to enhance the shared doctor-patient decision-making process or to allow patients to access information at their own leisure rather than within the constraint of a time-limited consultation. Alternatively, patients may not need a trained physician to understand some more simple health decisions and their use may allow limited physician resources to be reemployed to more complex, more valuable tasks.

Despite these hypothesised benefits, economically evaluating the use of decision support tools provides a challenge for CUA using QALYs, the dominant framework used to conduct economic evaluation of health technologies. Decision support tools have a cost, but they are rarely implemented with the sole or even primary aim of generating a health benefit, so their impact on QALYs is difficult to quantify.

To date, a small number of evaluations have assessed decision support tools in terms of cost: a systematic review of the impact of decision support tools on costs to the health care system concluded that although patients chose more

conservative disease management options, there was limited evidence , that implementing decision support interventions generated savings for the system.(127)

On the effect side, assessments of the benefits of decision support tools have focused on reporting improved patient knowledge, experience and satisfaction. A review of 86 randomised trials of decision aids found decision aids increase people's involvement, and improve knowledge and realistic perception of outcomes.(128)

Decision support tools are rarely subjected to economic evaluation with a view to their opportunity cost despite having recognised cost-effectiveness implications for the health care system and for patients. This is at odds with increasingly rigorous methods being applied to assess the cost-effectiveness of other health technologies.(2)

A major reason for this is that the current methodological toolkit is unsuited to assessing them. The lack of a directly measurable health benefit may make decision makers wary of exposing decision support tools to the rigors of HTA processes. In a review of the impact of information provision on the HRQoL of cancer survivors, only one of eight studies of interventions to increase health information showed a positive impact on HRQoL.(129) Furthermore, a trial of shared decision-making and risk communication aids found that neither had an impact on patient health outcomes, yet concluded that arguments for the techniques can be made from values and ethical principles set against cost.(130)

In a resource-constrained health care system there is a need for the costs and benefits of interventions to be assessed in a manner that has cross-programme comparability in order to assess the opportunity cost of the forgone alternative in order to make the best use of limited resources.(1) Furthermore, the use of decision support tools may be desirable from an ethical and legal perspective. In the USA, Washington State, a bill was passed that recognises the role of decision aids in facilitating a higher legal standard of obtaining informed consent.(131)

This chapter begins by considering the assessment of benefits of decision support tools within the context of CUA, the dominant framework used by HTA agencies for economic evaluation. Limitations of this framework for the assessment of decision aids are identified. An alternative framework for the economic evaluation of decision support tools is proposed and the issues required to operationalize the approach are discussed.

For the purposes of this chapter we define a decision support tool as a system to help patients understand their disease management options in order to make an informed health care decision with their physician, either for the patient alone or for the patient and physician to use together. An example of the former is the *CatInfo*, which is a computer program for prospective cataract surgery patients to use prior to the informed consent process. *CatInfo* has been shown to increase patient knowledge of cataract surgery.(132)

 Decision support tools may also refer to systems for physicians to better interact with patients and raise relevant issues. While these may have similar benefits for the patient in terms of improved decision making, these tools are related to improving the effectiveness of physicians themselves, and can be

viewed as a separate concept falling within the context of physician training. From a measurement point of view, a patient will find it harder to distinguish between the performance of a physician using the tool and their performance without it.

8.1.1. Current framework: health benefits

Within QALY-based CUA, health benefit can be achieved through improvements in quality of life or length of life. The purpose of a decision support tool is generally to improve the decision making process to enable a physician and their patient to come to the best choice among management options with uncertain outcomes.

The increased understanding of relative risks and benefits associated with each management option can be expected to result in proportionally more patients choosing the decision that is associated with the largest health gain. Such a situation will show up in CUA as a greater QALY gain:

$$EU = a\,(uncertainty)\,x\,b\,(health\,gain)$$

Where EU = expected utility and the decision support tool influences the level of uncertainty through a.

Robinson & Thomson developed an expected utility approach for use within a decision analysis framework in order to integrate patient preferences with probabilistic information, which builds on the above methodology. They lay out

the standard gamble as a technique for eliciting preferences for atrial fibrillation and warfarin anticoagulation.(133)

8.1.2. Limitations with current framework

1. Non-health benefits:

The above framework appears to lead the definition of a good decision towards the one that produces the greatest health gain. However, the outcomes associated with use of a decision support tool are broader.

Of 86 studies of decision support tools identified in the review, 63 assessed one or more of knowledge scores (51); accurate risk perceptions (16); and informed value-based choice (12); feeling informed (30) and feeling clear about values (18). The impact of the decision aids on general or condition-specific health was only measured in 7 and 9 of the 86 trials respectively and decision aids did not appear to have an effect on health attributes. None of the 86 studies identified in a recent review included preference-based health outcomes.(128)

A focus on health gain alone is not necessarily consistent with the broader aims of physicians employed in the agency relationship. Agents are there to reduce the information gap present when patients make health care decisions or to act on patients behalf by assuming their values.(134) These two concepts have been articulated in the decision making literature by *Bekker et al.* who considered an informed decision to be one "using relevant information about the advantages and disadvantages of all possible courses of action" (informed) and "in accordance with personal beliefs" (based on the patient's values).(135)

Vick & Scott highlighted the complexity of the agency relationship. They identified that being able to talk to the doctor was the most important attribute. Patients tended to prefer more information to less, but only females and highly qualified respondents wanted to choose their own treatment.(136)

In the current framework, the role of the decision tool is to reduce uncertainty in order to realise a greater QALY gain. As discussed, it is unclear that the objective of health gain is the only or even the main aim of the tool. By excluding other benefits within the broad umbrella of process of care, the utility of decision support tools are likely to be undervalued.

2. Measuring uncertainty:

The above framework is grounded in expected utility theory (vNM utility theorem), which is considered to be a realistic representation of how health care decisions are made in practice.(4)

The long-term objective of health gain through reduced uncertainty is challenging to measure and associate with the decision. While a treatment and health effect are easy to correlate, the initial decision choice between disparate treatment options is harder to associate with the health effect. The extra step may make ex ante uncertainty-based utility a less reliable proxy of realised utility in the context of deciding a treatment, compared with the treatment itself.

8.1.3. New framework: consultation time

A new approach to measuring the benefits of decision support tools should address the issues of the difficulty measuring the uncertainty and the additional objectives of decision support tools.

A more suitable approach is to consider what activity is displaced in the health care system. A decision support tool may be seen as a substitute for physician time. The aims of a physician are broader than maximising health and it is unlikely that a physician consultation would be fully assessed in a formula of reducing uncertainty to increase realised QALYs. As well as improving the health of a patient in the long term, in the short term, they are a provider of information and a reducer of anxiety regardless of the potential for health gain. Indeed, the agency model of the doctor-patient relationship assumes that physicians are employed by a patient to reduce the information gap between the patient and the disease management options.(136)

By considering the decision support tool in terms of the opportunity cost of physician consultation and as a substitute for physician time, an approach of valuing the tool against the next best alternative is likely to capture a more direct measure of the benefit and include more attributes than health uncertainty. Applying this to decision making gives:

EU = a (Physician consultation) + b (Decision support tool)

Where EU is the expected utility of the consultation process and physician time and the decision support tool are perfect substitutes.

The Consultation Time Trade-Off (CTTO) requires the patient to choose between use of the decision support tool and varying lengths of consultation time with a physician before they reach the point of indifference. A ping-pong technique within a hypothetical ten-minute consultation may be used as described in **Figure 8.25**. Ten minutes has been chosen as a length that patients will be familiar with for a consultation. The output of the CTTO will be a number of minutes that the patient would be willing to trade for use of the tool, equivalent to the opportunity cost of the tool expressed by its displaced alternative: physician consultation time.

I would like you to imagine a situation in which you are about to undergo [your treatment decision] for the first time. You are given the choice of either having a consultation with your doctor for a maximum of 10 minutes or alternatively using the [decision support tool] for all or part of this process.

Please imagine that 10 minutes with your doctor is the amount of time required to explain the treatment options and answer any questions you may have to your satisfaction.

Based on your knowledge of [the decision support tool], you have the choice of a shorter consultation with your doctor or to use the [decision support tool] for as long as you would like.

1.

Choice A

Doctor consultation

0 1 2 3 4 5 6 7 8 9 10

Minutes

Choice B

As much time using the decision support tool as you would like

Followed by informed consent.

Would you prefer to use the decision support tool for as long as you need, or to have a 10 minute discussion with a doctor, or are they the same?

2. *If doctor consultation chosen*

Choice A

Doctor consultation

0 1 2 3 4 5 6 7 8 9 10

0 minutes

Choice B

As much time using the decision support tool as you would like

Followed by informed consent.

Would you prefer to use the decision support tool for as long as you need, or to have no discussion with a doctor, or are they the same?

3. If decision tool chosen

Choice A

Doctor consultation

0 1 2 3 4 5 6 7 8 9 10

5 minutes

Choice B

As much time using the decision support tool as you would like

Followed by informed consent.

Would you prefer to use the decision support tool for as long as you need, or to have a 5 minute discussion with a doctor, or are they the same?
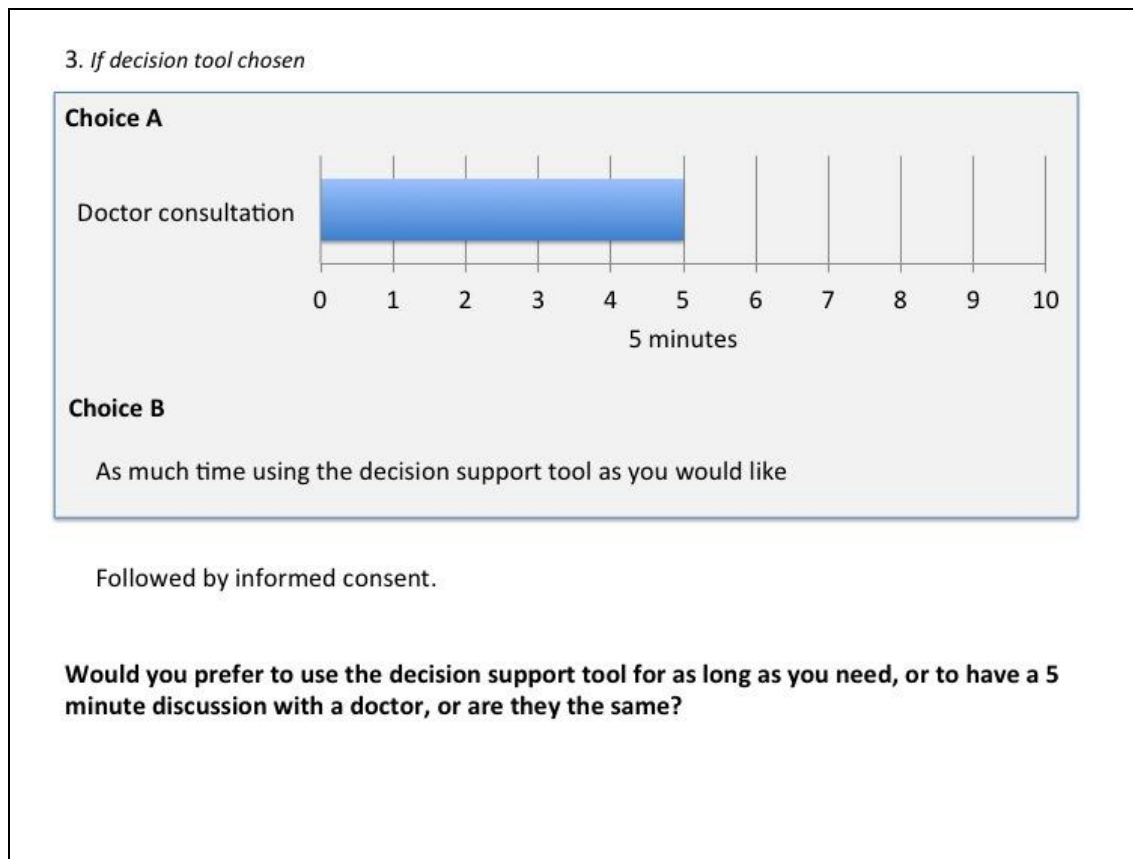
Figure 8.25. Consultation time trade-off: Introduction and first three questions.

The approach follows the widely used TTO,(137) which is commonly used to elicit health preferences and forms the basis of the EQ-5D utility scale.(18)

8.1.4. Application to economic evaluation

The number of minutes can be assessed against the cost of the tool (likely to be calculated as cost of use and an appropriate proportion of implementation). Such a value may be informative to give an indication of the amount of physician time that can be saved and re-deployed to more complex tasks elsewhere in the health care system.

216

Alternatively, the number of physician minutes saved can be converted to a monetary value using the local wage rate of the physician that would have been employed on the task. This can then be put against cost in a cost benefit analysis that is comparable across health care programmes.

The preferences derived from the CTTO are those of the patient. Due to the unique combination of attributes of each decision support tool, direct user experience is required to make an accurate trade-off. In contrast economic evaluation of health technologies is often recommended from the public perspective using general public preferences for health states expressed from behind a 'veil of ignorance'.(7) This difference may limit the direct comparability of economic evaluation of decision support tools using the CTTO with those using other measures that take the public perspective.

8.1.5. Further questions to refine new framework

Converting to a monetary value has implications in terms of the marginal value of a consultation to a patient. The cost to the health care system of a physician consultation is constant, so from the health care system perspective, the monetary value of the consultation is constant. However, it may be the case that, from the patient perspective, the ideal consultation should have a diminishing marginal utility because the patient should have their most important questions answered first. However, constraint on consultation time may make this less likely. Further work would be recommended on the marginal value of a consultation if the monetary measure is to be described as a patient value.

The time at which the CTTO is asked requires consideration in relation to ex-ante and ex post utility. By asking soon after the decision support tool has been used, patients are likely to have the clearest recollection of it. Having said this, the full evaluation of the tool may incorporate the implications of the decision, for example after the patient has undergone the elective surgical procedure and the health consequences have been realised. The former, ex ante, application would be recommended for consistency with expected utility theory. Use of the CTTO after the health consequences have been realised would derive experience utilities,(138) which cannot be considered consistent with expected utility used in other health care decision making contexts.

The value of the use of decision support tools is likely to be influenced by the patient's own attitude towards making their own health care decisions compared with delegating the decision to their physician agent. The Degner scale may be a useful measure to prospectively determine if the patient is likely to benefit from use of a decision support tool or retrospectively stratify cost benefit results of the tool into subgroups of patients.(139)

8.1.6. Conclusion

The framework of QALYs is ill-suited to the economic evaluation of health care decision making due to non-health attributes of the decision making process and the gap between a decision and the future health gain (or loss). A new approach based around physician consultation time allows decision support tools to be assessed within the framework of opportunity cost, which has the

potential to support a more effective allocation of resources within the health

care system.

9. Conclusion

The significant and progressive impact on health-related quality of life of the disease makes the accurate calculation of utility values for economic evaluation important. This thesis has investigated approaches for the measurement and valuation of health in AMD. Four research aims were identified to investigate current methods for measuring and valuing health and develop improved methods:

1.How do widely used methods for deriving health state utility values in AMD perform and how can these methods be improved?

2.Are non-health attributes important in AMD and how can they be incorporated into the cost-utility economic evaluation framework?

3.How is visual function associated with utility in AMD and how can the association be applied to economic evaluation?

4.What is the economic impact of treating AMD patients with good starting vision?

Findings

- **How do widely used methods of deriving utility values in AMD perform and how can these methods be improved?**

Chapter 3 reported the valuation of the performance of commonly used PROMs and health state valuation techniques. It identified limitations in the utility values used to estimate QALYs in AMD. Patient preferences for health states associated with AMD were found to differ substantially from public tariffs. Using simulation contact lenses to inform the public about the impact of AMD prior to valuation was found to be invalid as the contact lenses did not generate a central scotoma characteristic of AMD.

Chapter 4 reported a study augmenting the EQ-5D descriptive system with AMD disease descriptions. It demonstrated that different utility values may be elicited for health states when using different information and framing in the TTO valuation task.

- **Are non-health attributes important in AMD and how can they be incorporated into the cost-utility economic evaluation framework?**

Chapter 5 developed weightings for utilities by other attributes and shown that members of the public value non-health attributes such as severity and process of care and are willing to forgo some health gain to prioritise these attributes.

Chapter 8 developed a theoretical framework for the evaluation of decision support tools for treatment choices in vision.

- **How is visual function associated with utility in AMD and how can the association be applied to economic evaluation?**

Chapter 6 investigated the association between different aspects of visual function and utility values in AMD. It demonstrated that using contrast sensitivity in economic modelling results in different cost-effectiveness estimates to visual acuity, which has been most commonly used to date.

It also showed the potential for a mapping algorithm between visual function and utility that could be applied to perform cost effectiveness analysis using trials that have not recorded utility values.

- **What is the economic impact of treating AMD patients with good starting vision?**

Chapter 7 employed a CUA model to assess the cost effectiveness of the treatment of early AMD currently outside UK guidance using real world outcomes data. It demonstrated that early treatment is associated with a modest incremental cost per QALY.

Future research

During the course of the thesis, the Euroqol Group has developed a bolt-on for the EQ-5D (the EQ-5+V).(140) Whilst this questionnaire is still to be validated in patients, it may offer a promising alternative to the standard EQ-5D for deriving utilities for vision interventions.

There remain several challenges which need to be addressed in order to accurately assess the cost effectiveness of interventions for vision disorders. Firstly, the association between utility and visual function measures remains important, both for trials that do not contain suitable PROs for deriving utility and for extrapolating outcomes beyond the end of the trial for vision disorders that are life-long conditions. Further work on this may be done with a larger sample than used in this thesis.

Secondly, the measurement and valuation of non-health benefits for interventions that may have significant process benefits is increasingly important for decision makers as evidence continues to emerge that the public are willing to forgo health gain for improvements in other attributes. Further work on defining the relevant attributes and incorporating these into economic evaluation is warranted.

Novel contribution of this thesis to the field of Health Economics

This thesis demonstrates the lack of validity of widely used methods to derive utility values in AMD and therefore suggests that previous economic evaluations may have not accurately assessed the economic value of treatments for AMD.

The thesis provides methodological contributions to the augmentation of health state descriptions for preference elicitation. It also develops methods for incorporating non-health attributes into economic evaluation by the external weighting of QALYs. These may better measure preferences for health states in AMD and therefore enable more valid economic valuations of health technologies for the condition.

In terms of impact on patients and practice, as well as developing methods to better measure preferences, the thesis demonstrates that the initiation of anti-VEGF therapy earlier in disease than current guidance is likely to be a cost-effective use of resources.

Bibliography

1.   Drummond MF. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford ; New York: Oxford University Press; 2005. 379 p. p.
2.   NICE. Guide to the methods of technology appraisal. National Institute for Health and Clinical Excellence, 2013.
3.   Brazier J. Measuring and valuing health benefits for economic evaluation. Oxford ; New York: Oxford University Press; 2007. xi, 344 p. p.
4.   Torrance GW, Feeny D. Utilities and quality-adjusted life years. Int J Technol Assess Health Care. 1989;5(4):559-75.
5.   Culyer AJ, Evans RG. Mark Pauly on welfare economics: normative rabbits from positive hats. J Health Econ. 1996;15(2):243-51; discussion 53-4.
6.   Brazier J, Akehurst R, Brennan A, Dolan P, Claxton K, McCabe C, et al. Should Patients Have a Greater Role in Valuing Health States? Applied Health Economics and Health Policy. 2005;4(4):201-8.
7.   Gold MR. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996. xxiii, 425 p. p.
8.   Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA. 1996;276(15):1253-8.
9.   The Green Book: Appraisal and Evaluation in Central Government. HM Treasury; 2003.
10.   Mehrez A, Gafni A. Quality-adjusted life years, utility theory, and healthy-years equivalents. Med Decis Making. 1989;9(2):142-9.
11.   Murray CJ. Quantifying the burden of disease: the technical basis for disability-adjusted life years. Bull World Health Organ. 1994;72(3):429-45.
12.   Salomon JA. New disability weights for the global burden of disease. Bull World Health Organ. 2010;88(12):879.
13.   van Oyen H, Van der Heyden J, Perenboom R, Jagger C. Monitoring population disability: evaluation of a new Global Activity Limitation Indicator (GALI). Sozial- und Praventivmedizin. 2006;51(3):153-61.
14.   Tosh J, Brazier J, Evans P, Longworth L. A review of generic preference-based measures of health-related quality of life in visual disorders. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(1):118-27.
15.   Fryback DG, Lawrence WF, Jr. Dollars may not buy as many QALYs as we think: a problem with defining quality-of-life adjustments. Medical decision making : an international journal of the Society for Medical Decision Making. 1997;17(3):276-84.
16.   Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. Health Econ. 2004;13(9):873-84.
17.   Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53-72.
18.   Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-108.
19.   Dolan P, Gudex C, Kind P, Williams A. The time trade-off method: results from a general population study. Health Econ. 1996;5(2):141-54.
20.   van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value

sets. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(5):708-15.

21.	Rasanen P, Roine E, Sintonen H, Semberg-Konttinen V, Ryynanen OP, Roine R. Use of quality-adjusted life years for the estimation of effectiveness of health care: A systematic literature review. Int J Technol Assess Health Care. 2006;22(2):235-41.

22.	Health and Social Care Information Centre. Health Survey for England; Health, social care and lifestyles [13/05/2014]. Available from: http://www.hscic.gov.uk/article/3741/Health-Survey-for-England-Health-social-care-and-lifestyles.

23.	Economic and Social Research Council. Understanding Society: The UK Household Longitudinal Study [13/05/2014]. Available from: https://www.understandingsociety.ac.uk/.

24.	Health and Social Care Information Centre. [15/08/2014]. Available from: http://www.hscic.gov.uk/proms.

25.	Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2001;119(7):1050-8.

26.	Misajon R, Hawthorne G, Richardson J, Barton J, Peacock S, Iezzi A, et al. Vision and quality of life: the development of a utility measure. Investigative ophthalmology & visual science. 2005;46(11):4007-15.

27.	Peacock S, Misajon R, Iezzi A, Richardson J, Hawthorne G, Keeffe J. Vision and quality of life: development of methods for the VisQoL vision-related utility instrument. Ophthalmic Epidemiol. 2008;15(4):218-23.

28.	Mortimer D, Segal L. Comparing the incomparable? A systematic review of competing techniques for converting descriptive measures of health status into QALY-weights. Med Decis Making. 2008;28(1):66-89.

29.	Swamy BN, Chia EM, Wang JJ, Rochtchina E, Mitchell P. Correlation between vision- and health-related quality of life scores. Acta Ophthalmol. 2009;87(3):335-9.

30.	Loftus JV, Sultan MB, Pleil AM. Changes in Vision- and Health-Related Quality of Life in Patients with Diabetic Macular Edema Treated with Pegaptanib Sodium or Sham. Investigative ophthalmology & visual science. 2011;52(10):7498-505.

31.	Fenwick EK, Pesudovs K, Rees G, Dirani M, Kawasaki R, Wong TY, et al. The impact of diabetic retinopathy: understanding the patient's perspective. Br J Ophthalmol. 2011;95(6):774-82.

32.	Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995;273(1):59-65.

33.	Brazier J, Tsuchiya A. Preference-based condition-specific measures of health: what happens to cross programme comparability? Health Econ. 2010;19(2):125-9.

34.	Tsuchiya A, Brazier, J, McColl, E, Parkin, d. Deriving preference-based single indicies from non-preference based condition-specific instruments: Converting AQLQ into EQ5D indicies. Sheffield Health Economics Group Discussion Paper Series. 2002.

35.   Dakin H. Review of studies mapping from quality of life or clinical measures to EQ-5D: an online database. Health Qual Life Outcomes. 2013;11:151.

36.   Torrance GW, Thomas WH, Sackett DL. A utility maximization model for evaluation of health care programs. Health Serv Res. 1972;7(2):118-33.

37.   Arnesen T, Trommald M. Are QALYs based on time trade-off comparable?--A systematic review of TTO methodologies. Health Econ. 2005;14(1):39-53.

38.   Morimoto T, Fukui T. Utilities measured by rating scale, time trade-off, and standard gamble: review and reference for health care professionals. Journal of epidemiology / Japan Epidemiological Association. 2002;12(2):160-78.

39.   Torrance GW, Feeny D, Furlong W. Visual analog scales: do they have a role in the measurement of preferences for health states? Med Decis Making. 2001;21(4):329-34.

40.   Robinson A, Spencer A. Exploring challenges to TTO utilities: valuing states worse than dead. Health Econ. 2006;15(4):393-402.

41.   Devlin NJ, Tsuchiya A, Buckingham K, Tilling C. A uniform time trade off method for states better and worse than dead: feasibility study of the 'lead time' approach. Health Econ. 2011;20(3):348-61.

42.   Aspinall PA, Hill AR, Dhillon B, Armbrecht AM, Nelson P, Lumsden C, et al. Quality of life and relative importance: a comparison of time trade-off and conjoint analysis methods in patients with age-related macular degeneration. Br J Ophthalmol. 2007;91(6):766-72.

43.   Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics. 2008;26(8):661-77.

44.   Ryan M, Gerard, K., Amaya-Amaya, M. Using discrete choice experiments to value health and health care: Springer; 2008.

45.   Rubin G, Bate A, George A, Shackley P, Hall N. Preferences for access to the GP: a discrete choice experiment. Br J Gen Pract. 2006;56(531):743-8.

46.   Kymes SM, Lee BS. Preference-based quality of life measures in people with visual impairment. Optom Vis Sci. 2007;84(8):809-16.

47.   Dolan P, Olsen JA, Menzel P, Richardson J. An inquiry into the different perspectives that can be used when eliciting preferences in health. Health Econ. 2003;12(7):545-51.

48.   Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. Archives of ophthalmology. 2000;118(1):47-51.

49.   Mitchell P, Annemans L, White R, Gallagher M, Thomas S. Cost effectiveness of treatments for wet age-related macular degeneration. Pharmacoeconomics. 2011;29(2):107-31.

50.   Congdon N, O'Colmain B, Klaver CC, Klein R, Munoz B, Friedman DS, et al. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol. 2004;122(4):477-85.

51.   Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. Am J Ophthalmol. 2004;137(3):486-95.

52.   Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004;82(11):844-51.

53.   Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. The British journal of ophthalmology. 2012;96(5):752-6.

54.   Ferris FL, 3rd, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol. 1984;102(11):1640-2.

55.   Mitchell J, Bradley C. Quality of life in age-related macular degeneration: a review of the literature. Health Qual Life Outcomes. 2006;4:97.

56.   NHS Choices. Macular Degeneration [updated 08/11/2013; cited 2014 15/08/2014]. Available from: http://www.nhs.uk/conditions/macular-degeneration/Pages/Introduction.aspx.

57.   Thiagarajan M, Evans JR, Smeeth L, Wormald RP, Fletcher AE. Cause-specific visual impairment and mortality: results from a population-based study of older people in the United Kingdom. Arch Ophthalmol. 2005;123(10):1397-403.

58.   Espallargues M, Czoski-Murray CJ, Bansback NJ, Carlton J, Lewis GM, Hughes LA, et al. The impact of age-related macular degeneration on health status utility values. Invest Ophthalmol Vis Sci. 2005;46(11):4016-23.

59.   Bansback N, Czoski-Murray C, Carlton J, Lewis G, Hughes L, Espallargues M, et al. 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. Qual Life Res. 2007;16(3):533-43.

60.   Bansback N, Davis S, Brazier J. Using contrast sensitivity to estimate the cost-effectiveness of verteporfin in patients with predominantly classic age-related macular degeneration. Eye (Lond). 2007;21(12):1455-63.

61.   The prescribing year: 2011. Prescriber. 2011;22(23-24):16-7.

62.   Hernandez-Pastor LJ, Ortega A, Garcia-Layana A, Giraldez J. Cost-effectiveness of ranibizumab compared with photodynamic treatment of neovascular age-related macular degeneration. Clin Ther. 2008;30(12):2436-51.

63.   Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364(20):1897-908.

64.   Nguyen NX, Weismann M, Trauzettel-Klosinski S. Improvement of reading speed after providing of low vision aids in patients with age-related macular degeneration. Acta Ophthalmol. 2009;87(8):849-53.

65.   Brauer CA, Rosen AB, Greenberg D, Neumann PJ. Trends in the measurement of health utilities in published cost-utility analyses. Value Health. 2006;9(4):213-8.

66.   CRD Y. Undertaking Systematic Reviews of Research on Effectiveness CRD's Guidance for those Carrying Out or Commissioning Reviews. University of York, 2001.

67.   Matchar DB SI, Samsa GP, McCrory DC, Cline K, Lee PP. Measuring quality of life for patients with age-related macular degeneration. Agency for Healthcare Research and Quality (AHRQ), 2006.

68.   Neumann PJ, Fang CH, Cohen JT. 30 years of pharmaceutical cost-utility analyses: growth, diversity and methodological improvement. Pharmacoeconomics. 2009;27(10):861-72.

69.   Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.

70.   Stein JD, Brown MM, Brown GC, Hollands H, Sharma S. Quality of life with macular degeneration: perceptions of patients, clinicians, and community members. Br J Ophthalmol. 2003;87(1):8-12.

71.   Payakachat N, Summers KH, Pleil AM, Murawski MM, Thomas J, 3rd, Jennings K, et al. Predicting EQ-5D utility scores from the 25-item National Eye Institute Vision Function Questionnaire (NEI-VFQ 25) in patients with age-related macular degeneration. Qual Life Res. 2009;18(7):801-13.

72.   Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. Value Health. 2009;12(5):793-9.

73.   NICE. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. 2012.

74.   Javitt JC, Zlateva GP, Earnshaw SR, Pleil AM, Graham CN, Brogan AJ, et al. Cost-effectiveness model for neovascular age-related macular degeneration: comparing early and late treatment with pegaptanib sodium based on visual acuity. Value Health. 2008;11(4):563-74.

75.   Rowen D, Brazier J, Tsuchiya A, Young T, Ibbotson R. It's all in the name, or is it? The impact of labeling on health state values. Medical decision making : an international journal of the Society for Medical Decision Making. 2012;32(1):31-40.

76.   Albrecht GL, Devlieger PJ. The disability paradox: high quality of life against all odds. Soc Sci Med. 1999;48(8):977-88.

77.   Torrance GW. Social preferences for health states: An empirical evaluation of three measurement techniques. Socio-Economic Planning Sciences. 1976;10(3):129-36.

78.   Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20(10):1727-36.

79.   Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. Journal of health economics. 2002;21(2):271-92.

80.   Measurement and Valuation of Health Group. The Measurement and Valuation of Health: Final Report on the Modelling of Valuation Tariffs. Centre for Health Economics, University of York, 1995.

81.   Mitchell J. Measuring quality of life in macular disease: What use are utilities? International Congress Series. 2005;1282:654-8.

82.   Nord E. The trade-off between severity of illness and treatment effect in cost-value analysis of health care. Health Policy. 1993;24(3):227-38.

83.   Baker R, Bateman I, Donaldson C, Jones-Lee M, Lancsar E, Loomes G, et al. Weighting and valuing quality-adjusted life-years using stated preference methods: preliminary results from the Social Value of a QALY Project. Health technology assessment. 2010;14(27):1-162.

84.   NICE. Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237). 2012.

85. Mainster MA, Timberlake GT, Webb RH, Hughes GW. Scanning laser ophthalmoscopy. Clinical applications. Ophthalmology. 1982;89(7):852-7.

86. Alavi Y, Jofre-Bonet M, Bunce C, Wormald RP, Viswanathan A, Foster A, et al. Developing an algorithm to convert routine measures of vision into utility values for glaucoma. Ophthalmic Epidemiol. 2011;18(5):233-43.

87. Brown GC. Vision and quality-of-life. Trans Am Ophthalmol Soc. 1999;97:473-511.

88. Cummins E, Waugh, N., Lois, N., Shyangdan, D. Ranibizumab for diabetic macular oedema: report for NICE rapid review. 2012.

89. Culham L, Fitzke, F.W., Timberlake, G.T., Marshall, J. Assessment of fixation stability in normal subjects and patients using a scanning laser ophthalmoscope. Clin Vision Sci. 1993;8:551-61.

90. Crossland MD, Culham LE, Rubin GS. Fixation stability and reading speed in patients with newly developed macular disease. Ophthalmic Physiol Opt. 2004;24(4):327-33.

91. Macedo AF, Crossland MD, Rubin GS. Investigating unstable fixation in patients with macular disease. Investigative ophthalmology & visual science. 2011;52(3):1275-80.

92. Scherlen AC, Bernard JB, Calabrese A, Castet E. Page mode reading with simulated scotomas: oculo-motor patterns. Vision Res. 2008;48(18):1870-8.

93. Butt T. The impact of disease information on general public preferences for health states: Comparing labeling, disease-‐‐ specific, and adaptation information. Health Economist Study Group; Oxford2012.

94. Williams RA, Brody BL, Thomas RG, Kaplan RM, Brown SI. The psychosocial impact of macular degeneration. Archives of ophthalmology. 1998;116(4):514-20.

95. CNIB. Age-related macular degeneration: Take a closer look before it's too late:A journalist's guide to AMD. 2007.

96. Norman R. Does mode of administration matter? Comparison of online and face-to-face administration of a time trade-off task. Qual Life Res. 2010;19:499-508.

97. Damschroder LJ, Zikmund-Fisher BJ, Ubel PA. The impact of considering adaptation in health state valuation. Soc Sci Med. 2005;61(2):267-77.

98. Dolan P. Effect of age on health state valuations. J Health Serv Res Policy. 2000;5(1):17-21.

99. Department of Health. The Cancer Drugs Fund: Guidance to support operation of the Cancer Drugs Fund in 2012-13. 2012.

100. Department of Health. A new value-based approach to the pricing of branded medicines: A consultation. 2010.

101. Lancsar E, Wildman J, Donaldson C, Ryan M, Baker R. Deriving distributional weights for QALYs through discrete choice experiments. Journal of health economics. 2011;30(2):466-78.

102. Linley WG, Hughes DA. Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritising medicines: a cross-sectional survey of 4118 adults in Great Britain. Health Econ. 2013;22(8):948-64.

103. Green C, Gerard K. Exploring the social value of health-care interventions: a stated preference discrete choice experiment. Health economics. 2009;18(8):951-76.

104.   Salisbury C, Purdy S. Providing care closer to home. BMJ. 2007;335(7625):838.
105.   Rubin G. Assessment of visual function in eyes with visual loss. Ophthalmol Clin North Am. 1989;2:357-67.
106.   Brown GC, Brown MM, Sharma S, Brown HC. Patient perceptions of quality-of-life associated with bilateral visual loss. Int Ophthalmol. 1998;22(5):307-12.
107.   Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD. Model Parameter Estimation and Uncertainty: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(6):835-42.
108.   Tufail A, Patel PJ, Egan C, Hykin P, da Cruz L, Gregor Z, et al. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. BMJ. 2010;340:c2459.
109.   Patel PJ, Chen FK, Da Cruz L, Rubin GS, Tufail A. Contrast sensitivity outcomes in the ABC Trial: a randomized trial of bevacizumab for neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52(6):3089-93.
110.   Legge GE. Binocular contrast summation--II. Quadratic summation. Vision Res. 1984;24(4):385-94.
111.   Statistics OfN. Mortality statistics: Deaths registered in 2009. 2010.
112.   Patel JJ, Mendes MA, Bounthavong M, Christopher ML, Boggie D, Morreale AP. Cost-utility analysis of bevacizumab versus ranibizumab in neovascular age-related macular degeneration using a Markov model. J Eval Clin Pract. 2010.
113.   Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics. 2000;17(5):479-500.
114.   Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. Br J Psychiatry. 2005;187:106-8.
115.   Jackson TL, Kirkpatrick L. Cost comparison of ranibizumab and bevacizumab. BMJ. 2011;343:d5058.
116.   Thomas M, Mousa SS, Mousa SA. Comparative effectiveness of aflibercept for the treatment of patients with neovascular age-related macular degeneration. Clin Ophthalmol. 2013;7:495-501.
117.   Longworth L, Rowen D. Mapping to obtain EQ-5D utility values for use in NICE health technology assessments. Value Health. 2013;16(1):202-10.
118.   Kwong TQ, Mohamed M. Anti Vascular Endothelial Growth Factor therapies in Ophthalmology: Current Use, Controversies and the Future. Br J Clin Pharmacol. 2014.
119.   Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1432-44.
120.   Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1419-31.
121.   Writing Committee for the U. K. Age-Related Macular Degeneration E. M. R. Users Group. The neovascular age-related macular degeneration database:

multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. Ophthalmology. 2014;121(5):1092-101.

122.   Datapharm. Electronic Medicines Compendium [01/03/2014]. Available from: http://www.medicines.org.uk/emc/.

123.   Health and Social Care Information Centre. Hospital Episode Statistics 2011/12 [01/03/2014]. Available from: http://www.hscic.gov.uk/hes.

124.   NICE. TA294 Macular degeneration (wet age-related) - aflibercept: costing template 2013. Available from: http://www.nice.org.uk/guidance/ta294/resources/ta294-macular-degeneration-wet-agerelated-aflibercept-costing-template.

125.   McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. Pharmacoeconomics. 2008;26(9):733-44.

126.   Canan H, Sizmaz S, Altan-Yaycioglu R, Sariturk C, Yilmaz G. Visual outcome of intravitreal ranibizumab for exudative age-related macular degeneration: timing and prognosis. Clinical interventions in aging. 2014;9:141-5.

127.   Walsh T, Barr PJ, Thompson R, Ozanne E, O'Neill C, Elwyn G. Undetermined impact of patient decision support interventions on healthcare costs and savings: systematic review. BMJ. 2014;348:g188.

128.   Stacey D, Bennett CL, Barry MJ, Col NF, Eden KB, Holmes-Rovner M, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2011(10):CD001431.

129.   Husson O, Mols F, van de Poll-Franse LV. The relation between information provision and health-related quality of life, anxiety and depression among cancer survivors: a systematic review. Ann Oncol. 2010.

130.   Edwards A, Elwyn G, Hood K, Atwell C, Robling M, Houston H, et al. Patient-based outcome results from a cluster randomized trial of shared decision making skill development and use of risk communication aids in general practice. Fam Pract. 2004;21(4):347-54.

131.   Blue Ribbon Commission on Health Care Costs and Access, E2S S.B. 5930 (2007).

132.   Wollinger C, Hirnschall N, Findl O. Computer-based tutorial to enhance the quality and efficiency of the informed-consent process for cataract surgery. J Cataract Refract Surg. 2012;38(4):655-9.

133.   Robinson A, Thomson RG. The potential use of decision analysis to support shared decision making in the face of uncertainty: the example of atrial fibrillation and warfarin anticoagulation. Quality in Health Care. 2000;9(4):238-44.

134.   Gafni A, Charles C, Whelan T. The physician-patient encounter: the physician as a perfect agent for the patient versus the informed treatment decision-making model. Soc Sci Med. 1998;47(3):347-54.

135.   Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, et al. Informed decision making: an annotated bibliography and systematic review. Health technology assessment. 1999;3(1):1-156.

136.   Vick S, Scott A. Agency in health care. Examining patients' preferences for attributes of the doctor-patient relationship. Journal of health economics. 1998;17(5):587-605.

137.   Torrance GW. Measurement of health state utilities for economic appraisal. J Health Econ. 1986;5(1):1-30.

138.   Kahneman D, Wakker PP, Sarin R. Back to Bentham? Explorations of Experienced Utility. The Quarterly Journal of Economics. 1997;112(2):375-406.
139.   Degner LF, Sloan JA. Decision making during serious illness: what role do patients really want to play? J Clin Epidemiol. 1992;45(9):941-50.
140.   Longworth L, Yang Y, Young T, Mulhern B, Hernández Alava M, Mukuria C, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess. 2014;18(9).
141.   Butt T, Dunbar HM, Morris S, Orr S, Rubin GS. Patient and public preferences for health states associated with AMD. Optom Vis Sci. 2013;90(8):855-60.
142.   Butt T, Crossland MD, West P, Orr SW, Rubin GS. Simulation contact lenses for AMD health state utility values in NICE appraisals: a different reality. Br J Ophthalmol. 2015;99(4):540-4.
143.   Butt T, Patel PJ, Tufail A, Rubin GS. Modelling Cost Effectiveness in Neovascular Age-Related Macular Degeneration: The Impact of Using Contrast Sensitivity vs. Visual Acuity. Appl Health Econ Health Policy. 2014;12(3):289-97.
144.   Butt T, Lee A, Lee C, Tufail A, Group UAES. The cost-effectiveness of initiating ranibizumab therapy in eyes with neovascular AMD with good vision: an economic model using real-world outcomes. BMJ Open. 2015;5(5):e006535.
145.   Raftery J, Clegg A, Jones J, Tan SC, Lotery A. Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness. Br J Ophthalmol. 2007;91(9):1244-6.
146.   Smith DH, Fenn P, Drummond M. Cost effectiveness of photodynamic therapy with verteporfin for age related macular degeneration: the UK case. Br J Ophthalmol. 2004;88(9):1107-12.
147.   Neubauer AS, Holz FG, Sauer S, Wasmuth T, Hirneiss C, Kampik A, et al. Cost-effectiveness of ranibizumab for the treatment of neovascular age-related macular degeneration in Germany: Model analysis from the perspective of Germany's statutory health insurance system. Clin Ther. 2010;32(7):1343-56.
148.   Gower EW, Cassard SD, Bass EB, Schein OD, Bressler NM. A cost-effectiveness analysis of three treatments for age-related macular degeneration. Retina. 2010;30(2):212-21.
149.   Fletcher EC, Lade RJ, Adewoyin T, Chong NV. Computerized model of cost-utility analysis for treatment of age-related macular degeneration. Ophthalmology. 2008;115(12):2192-8.
150.   Brown MM, Brown GC, Brown HC, Peet J. A value-based medicine analysis of ranibizumab for the treatment of subfoveal neovascular macular degeneration. Ophthalmology. 2008;115(6):1039-45 e5.
151.   Karnon J, Czoski-Murray C, Smith K, Brand C, Chakravarthy U, Davis S, et al. A preliminary model-based assessment of the cost-utility of a screening programme for early age-related macular degeneration. Health Technol Assess. 2008;12(27):iii-iv, ix-124.
152.   Bojke L, Claxton K, Sculpher MJ, Palmer S. Identifying research priorities: the value of information associated with repeat screening for age-related macular degeneration. Med Decis Making. 2008;28(1):33-43.
153.   Earnshaw SR, Moride Y, Rochon S. Cost-effectiveness of pegaptanib compared to photodynamic therapy with verteporfin and to standard care in

the treatment of subfoveal wet age-related macular degeneration in Canada. Clin Ther. 2007;29(9):2096-106; discussion 4-5.

154.   Wolowacz SE, Roskell N, Kelly S, Maciver FM, Brand CS. Cost effectiveness of pegaptanib for the treatment of age-related macular degeneration in the UK. Pharmacoeconomics. 2007;25(10):863-79.

155.   Brown GC, Brown MM, Campanella J, Beauchamp GR. The cost-utility of photodynamic therapy in eyes with neovascular macular degeneration--a value-based reappraisal with 5-year data. Am J Ophthalmol. 2005;140(4):679-87.

156.   Hopley C, Salkeld G, Mitchell P. Cost utility of photodynamic therapy for predominantly classic neovascular age related macular degeneration. Br J Ophthalmol. 2004;88(8):982-7.

157.   Hopley C, Salkeld G, Wang JJ, Mitchell P. Cost utility of screening and treatment for early age related macular degeneration with zinc and antioxidants. Br J Ophthalmol. 2004;88(4):450-4.

158.   Busbee BG, Brown MM, Brown GC, Sharma S. CME review: A cost-utility analysis of laser photocoagulation for extrafoveal choroidal neovascularization. Retina. 2003;23(3):279-87; ; quiz 443-4.

159.   Sharma S, Brown GC, Brown MM, Hollands H, Shah GK. The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology. 2001;108(11):2051-9.

160.   Hurley SF, Matthews JP, Guymer RH. Cost-effectiveness of ranibizumab for neovascular age-related macular degeneration. Cost Eff Resour Alloc. 2008;6:12.

161.   Hurley SF, Matthews JP, Guymer RH. Cost-effectiveness of smoking cessation to prevent age-related macular degeneration. Cost Eff Resour Alloc. 2008;6:18.

Contributions

Chapter 3
Dr Hannah Dunbar: Recruitment of patients and administration of questionnaires

Dr Michael Crossland: Visual function testing

Chapter 7
Mr Aaron Lee: Manipulation of the EMR dataset to enable CUA

Appendices

Appendix A: Published papers

Appendix B: Survey instruments and review of models

Appendix A

Published papers

At the time of writing, the following four papers relating to this thesis have been published in peer-reviewed journals:

Chapter 3

Butt T, Dunbar H, Morris S, Orr S, Rubin G (2013). Public and patient preferences for health states associated with AMD. *Optometry and Vision Science* 90(8):855-60.(141)

Butt T, Crossland MD, West P, Orr SW, Rubin GS (2015). Simulation contact lenses for AMD health state utility values in NICE appraisals: a different reality. *British Journal of Ophthalmology* 99:540-544.(142)

Chapter 6

Butt T, Patel P, Tufail A, Rubin G (2014). Modelling cost effectiveness in neovascular age-related macular degeneration: the impact of using contrast sensitivity versus visual acuity. *Applied Health Economics and Health Policy* 12(3):289-97.(143)

Chapter 7

Butt T, Lee A, Lee C, Tufail A (2015). The cost-effectiveness of initiating ranibizumab therapy in eyes with neovascular AMD with good vision: an economic model using real-world outcomes. *BMJ Open* 5.(144)

Conference presentations

The following conference papers relating to this thesis have been presented:

Chapter 3

- Comparing Patient and Public Preferences for Health States Associated with Age-Related Macular Degeneration. *Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting*. Seattle, USA. May 2013. Invest Ophthalmol Vis Sci 2013;54: E-Abstract 4419. *(Recipient of Envision-Atwell Award for Low Vision Research).*

Chapter 4

- Butt T., Morris S., Orr S., Rubin G. The impact of disease information on general public preferences for health states: Comparing labeling, disease-specific, and adaptation information. *International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 15th Annual European Congress*. Berlin, Germany. November 2012. Value in Health 2012 Vol. 15, Issue 7,Page A280. *(recipient of Best Student Podium Presentation award).*

- Butt T., Morris S., Orr S., Rubin G. The impact of disease information on general public preferences for health states. *Health Economists' Study Group (HESG)*. Oxford UK. June 2012.

Chapter 5

- Butt T. New Methods for Valuing Benefits of Low Vision Interventions *Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting*. Florida, USA (invited symposium). May 2014.

- Butt T., Orr S. Discrete Choice Experiments for Societal Weighting of QALYs for Value-based Pricing. *Sheffield University School of Health and Related Research, ScHARR* (invited seminar) March 2014.

Chapter 6

- Butt T., Rubin G. Estimating Health State Utility Values Associated With AMD Using A Combined Visual Function Algorithm. *Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting*. Florida, USA. May 2014. Invest Ophthalmol Vis Sci 2014;55: E-Abstract 180.

- Butt T., Rubin G. Visual function algorithm for estimating health state utility values associated with age-related macular degeneration (AMD). *European Society for Low Vision Research and Rehabilitation, Bi-annual Meeting*. Oxford, UK. September 2013.

- Butt T., Patel P., Tufail A., Morris S., Rubin G. Cost effectiveness of bevacizumab (Avastin) for AMD: A comparison of visual acuity and contrast sensitivity outcomes. *Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting*. Florida, USA. May 2012.

Chapter 8

- Butt T., Findl O., Orr S., Rubin G. The Value of a good decision: Assessing the economic benefits of decision aids. *International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 18th Annual*

International Meeting. New Orleans, USA. May 2013. Value in Health

2013. Vol. 16, Issue 3 , Pages A52-A53. *(Recipient of ISPOR Student Travel*

Grant award).

Clinical science

OPEN ACCESS

Simulation contact lenses for AMD health state utility values in NICE appraisals: a different reality

Thomas Butt,[1] Michael D Crossland,[1,2] Peter West,[1] Shepley W Orr,[3] Gary S Rubin[1,4]

[1]UCL Institute of Ophthalmology, London, UK
[2]Moorfields Eye Hospital, London, UK
[3]UCL Department of Civil, Environmental and Geomatic Engineering, London, UK
[4]NIHR Moorfields Biomedical Research Centre for Ophthalmology, London, UK

Correspondence to
Thomas Butt, UCL Institute of Ophthalmology, 11-43 Bath Street, London EC1V 9EL, UK; thomas.butt.10@ud.ac.uk

Received 8 July 2014
Revised 23 September 2014
Accepted 26 September 2014

ABSTRACT

Background/aims The National Institute for Health and Care Excellence (NICE) has recommended the use of ranibizumab for neovascular age-related macular degeneration (AMD) and for diabetic macular oedema (DMO) as part of its health technology appraisal process. In the economic evaluations of both interventions, utility values were derived from members of the general public wearing contact lenses with a central opacity that was meant to simulate the blind spot experienced by many patients with advanced retinal disease. This paper tests the validity of the contact lens simulation, and finding it to be invalid, explores the impact on prior economic evaluations.
Methods Visual acuity, contrast sensitivity and visual fields were assessed with and without simulation lenses in five healthy subjects with normal vision.
Results We identified important differences between the contact lens simulation and vision loss experienced by patients with AMD. The contact lens simulator did not cause the central scotoma which is characteristic of late-stage AMD and which leads to severe difficulty with everyday activities such as reading or recognising faces and objects. The contact lens instead caused a reduction in retinal illumination experienced by the subjects as a general dimming across the retina.
Conclusions A contact lens with a central opacity does not simulate a central scotoma. The clinical differences between simulated and actual AMD suggest there has been an underestimation of the severity of AMD health states. This brings into question the validity of the economic evaluations of treatments for AMD and DMO used by NICE.

INTRODUCTION

The National Institute for Health and Care Excellence (NICE) makes recommendations on the use of new and existing treatments within the English National Health Service (NHS) based on clinical and economic evidence. Quality-adjusted life year (QALY)-based cost-utility analysis forms a key component of NICE's health technology appraisal process.[1]

Treatments for neovascular age-related macular degeneration (AMD) and diabetic macular oedema (DMO)[2 3] have been appraised in recent years.[2 3] Both of these conditions can, in advanced cases, lead to the development of an absolute scotoma (a complete absence of retinal function) in the central retina. AMD and DMO have a serious impact on health-related quality of life (HRQoL),[4] but no direct impact on length of life making the utility component of the QALY particularly important to the cost-effectiveness calculation. Indirectly, AMD can mediate lower life expectancy and the disease has been estimated to be associated with a decrease in life expectancy of 2 years.[5]

NICE recommends that the general public value health states to derive utility values for economic evaluation.[1] The standard methodology recommended is for the general public to value health state profiles derived from a generic HRQoL Questionnaire such as the EQ-5D.[1 6]

Generic HRQoL instruments have been shown to be relatively insensitive to vision disorders.[7 8] This has led NICE to deviate from its reference case. Appraisals of treatments for AMD and DMO were based on utilities from *Czoski-Murray et al*[9] which conducted a contact lens simulation of AMD. In the study, members of the general public wore a contact lens with a central opacity that was meant to simulate the patient's view of the world through a central scotoma. Participants then completed a series of HRQoL questionnaires and the time trade-off to produce utility values associated with different levels of AMD severity. These health state utility values were applied to health economic models based on levels of visual acuity (which represents a person's ability to resolve fine detail).

NICE Multiple Technology Appraisal 155 recommended ranibizumab for the treatment of AMD.[10] Following appeal and rapid review of Single Technology Appraisal 237, ranibizumab was recommended as an option for treating visual impairment due to DMO if the eye has a central retinal thickness of 400 μm or more at the start of treatment and the manufacturer provides ranibizumab with the discount agreed in the revised patient access scheme (PAS).[3]

Concern over the validity of this simulation led us to assess the performance of a contact lens occluder. Broadly speaking, scotomas caused by AMD, DMO and similar diseases are a consequence of abnormalities at a retinal level. In advanced cases, these retinal abnormalities lead to dysfunction of the rod and cone photoreceptors in a confined area of the retina (the macula), which results in a blind spot at or near fixation. This blind spot greatly interferes with reading and recognising faces and objects. In contrast, a contact lens sits on the cornea, in front of the nodal point of the eye. Opacities on a contact lens would not be expected to cause a blind spot. This is illustrated in figure 1, which demonstrates image formation in an eye focused at infinity. Ray tracing of image formation for two points in the object plane is shown in Figure 1A. To simulate the effect of the contact lens, an opaque spherical surface which partially fills the pupil is placed into the simulation immediately adjacent to the corneal surface. Figure 1B shows the ray paths with the opacity. It is clear that although fewer rays now contribute to the formation of the retinal images, none the less the images are formed. This can be intuitively understood by considering that rays from all points in the object fall upon all points on the cornea,

To cite: Butt T, Crossland MD, West P, et al. Br J Ophthalmol Published Online First: [please include Day Month Year] doi:10.1136/bjophthalmol-2014-305802

249

Figure 1 Ray diagram illustrating the optical effect of a contact lens with an opaque centre. In figure 1A the object (an arrow, left) is focused on the retina (right) with a plus lens (the crystalline lens and cornea, centre). Rays from all points in the object will be imaged onto the retina. In figure 1B, a contact lens is placed in front of the cornea. The contact lens has an opaque central zone which blocks some rays emanating from the object reaching the image. But some rays from all parts of the object still reach the retina. The retinal image is darker with the occluder and the image is blurred somewhat, because the optics at the edge of the crystalline lens have worse aberrations than the central optics, but the retinal image is complete and there is no scotoma.
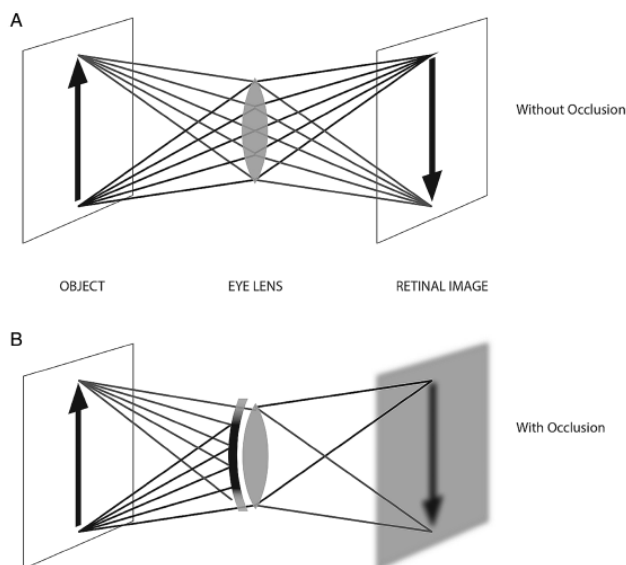
thus an image will be formed even if most of the cornea is occluded. The image is darker because some of the rays are blocked from reaching the retina, and blurred because image formation by the periphery of the lens and cornea is more affected by aberrations than images formed by rays passing through the centre of the lens.

To illustrate the formation of a complete image, ray tracing was conducted with Zemax optical design software (Radiant Zemax LLC, Redmond, Washington, USA). The Zemax image bitmap analysis tool was used to visualise the retinal image with and without the occluder. In our simulation, the image was subdivided into 200×200 pixels and 200 rays were aimed at each pixel using a single simulation wavelength of 550 nm and the number of rays incident on each pixel is displayed as a greyscale image. The object bitmap was a LogMAR visual acuity test chart. Figure 2A shows the resulting image without occlusion; figure 2B with the occluder. Although 35% of the light falling on the cornea has been occluded, the contrast of the retinal image is more than sufficient for the entire chart to be resolved. While the occluder does shadow the centre of the chart to a greater extent than the periphery, there is no clearly demarcated central area in which rays are entirely occluded as would be consistent with a scotoma.

These illustrations show that the occluder would be expected to cause an overall reduction in the amount of light that reaches the retina, but not to cause a blind spot. While this reduction in retinal illumination may affect vision, the impairment is far less debilitating than that caused by a blind spot on the visual axis.

We measured the effect of the opaque contact lenses on five healthy volunteers who underwent a standard battery of vision tests, comparing their performance with the performance of actual AMD patients with real central scotomas.

METHODS

Five control subjects with good visual acuity and no history of eye disease were recruited from colleagues and staff of the UCL Institute of Ophthalmology. Three of the authors (TB, MDC and SWO) acted as participants.

The study was approved by the University College London ethics committee, informed consent was obtained from all participants prior to data collection and the study conformed to the Declaration of Helsinki.

A soft contact lens with an opaque pupil was selected for all participants based on keratometry readings. The lens design was similar to that used in the *Czoski-Murray et al* study. In all cases, the lens was a 67% water content afocal soft contact lens of diameter 14.5 mm, with a 6 mm black central pupil (Ultravision CLPL, Leighton Buzzard, UK).

All vision tests were performed monocularly with and without the contact lens in place. The test eye was selected by each participant.

The vision tests included distance visual acuity (measured at 4 m using a standard ETDRS acuity chart (Lighthouse Low Vision products, New York, USA)) and contrast sensitivity (measured using either the MARS chart at 40 cm or the Pelli–Robson chart at 1 m).

Microperimetry was performed using the MAIA microperimeter (CenterVue, Padova, Italy). This is a scanning laser ophthalmoscope-based perimetry system which performs visual field testing while simultaneously imaging the retina, enabling the retinal location of each visual field position to be controlled.[11] Sixty-eight points were tested over the central 10° of retina, spaced at 2° intervals. Retinal sensitivity was measured using white Goldmann III targets, presented for 200 ms, and thresholds were calculated using an adaptive staircase algorithm. Fixation stability was measured as the area of a bivariate contour ellipse encompassing 95% of fixation points.

RESULTS

The contact lens reduced visual acuity by an average of 17 letters (median logMAR=−0.34; p<0.01) and reduced contrast

250

Figure 2 A simulated image of a logMAR visual acuity test is shown without (A) and with (B) an occluder showing a reduction in luminance of the test chart, but no central opacity.
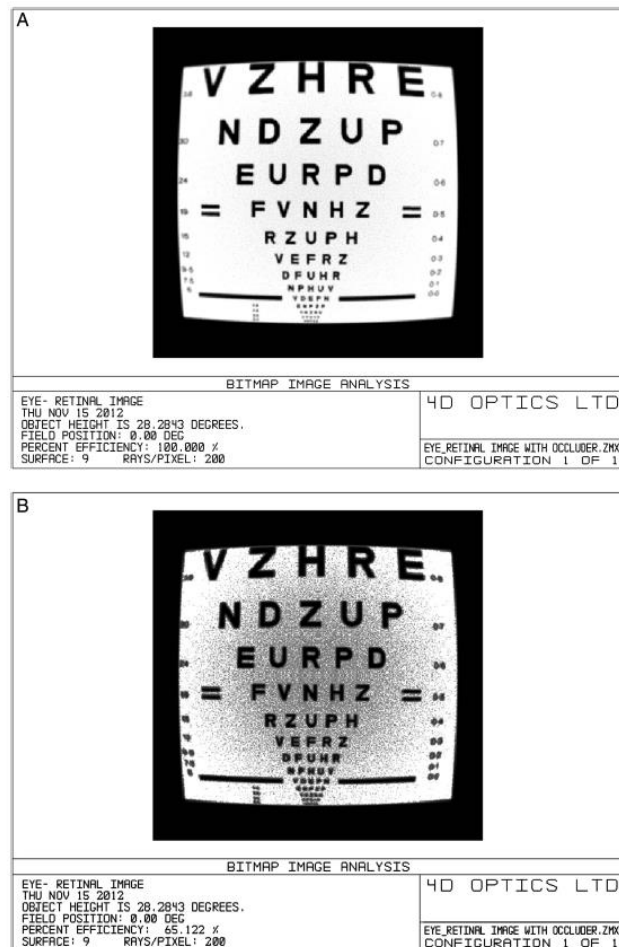

Table 1 Results of visual tests for each participant, with and without simulation contact lens

Subjects	Visual acuity (logMAR)			Contrast sensitivity (log units)			Retinal sensitivity			Fixation stability (degrees^2)		
	With CL	No CL	Diff.	With CL	No CL	Diff.	With CL	No CL	Diff.	With CL	No CL	Diff.
1	0.50	−0.20	0.70	1.04	1.72	0.68	18.1	27.5	−9.4	0.2	0.1	0.1
2	0.22	−0.12	0.34	1.28	1.64	0.36	18.2	26.5	−8.3	2.9	3.4	−0.5
3	0.18	−0.08	0.26	1.52	1.72	0.20	20.4	28.3	−7.9	0.1	0.1	0.0
4	0.24	−0.08	0.32	1.35	1.65	0.30	18.0	27.0	−9.0	0.0	0.0	0.0
5	0.20	−0.18	0.38	1.16	1.82	0.66	17.3	24.9	−7.6	0.1	0.1	0.0
Median			0.34			0.36			−8.3			0.0
IQR			0.32 to 0.38			0.30 to 0.66			−9.0 to −7.9			0.0 to 0.0

CL, contact lens.

Clinical science

sensitivity by an average of 7 letters (median logCS=0.36; p<0.01) (table 1). Fixation stability was not affected by the contact lens (p>0.2).

Figure 3 shows a Nidek MP-1 microperimetry map superimposed onto an infrared image of the retina. Blue dots show the retinal locations corresponding to the centre of the fixation cross during the test. The density of these points indicates fixation stability. Coloured circles indicate retinal sensitivity. Green circles show better sensitivity (targets seen even when the luminance

was reduced by 16–20 dB from a maximum of 127 cd/m²). Yellow, orange and filled red circles show areas of reduced sensitivity (luminance reduced by less than 16 dB). Open red squares show a dense scotoma (not visible at maximum intensity). It can be seen that the contact lens reduces retinal function over the central retina but does not produce any central region of absolute scotoma (with sensitivity less than 0 dB). Median retinal sensitivity without the contact lens was 27.0 dB, and 18.1 dB with the contact lens. The median difference was −8.3 dB.

For comparison, a microperimetry plot for a subject with AMD is shown in figure 4. It can be seen that this individual has a large area with no retinal function (sensitivity less than 0 dB, black circles on figure 3).

DISCUSSION

A contact lens with central opacity reduces retinal illumination across the macula leading to a reduction in visual acuity and contrast sensitivity. It causes a general reduction in retinal sensitivity and increases retinal blur but importantly does not create any area of absolute scotoma. Therefore, a contact lens with a central opacity does not accurately simulate the effects of advanced AMD.

Whether this will impact on the accuracy of the derived utility values is dependent on the strength of the association between visual acuity and utility across eye conditions.

Most studies of vision and utility have shown that utility values worsen as visual impairment increases, although different conditions may affect vision differently; for example some conditions impact on visual field, whereas others affect visual acuity.[7] While some studies have correlated utility and visual acuity.[12] Others have shown that visual acuity is weakly associated with utility and that other aspects of visual function such as contrast sensitivity and visual field have a large impact on utility.[13 14]

Brown reported utility values using the time trade-off in AMD, cataract and diabetic retinopathy by levels of visual acuity. For the same level of vision (20/70–20/100), patients with AMD reported a mean utility of 0.62, patients with cataract reported a mean utility of 0.71 and patients with diabetic retinopathy reported a mean utility of 0.78.[15]
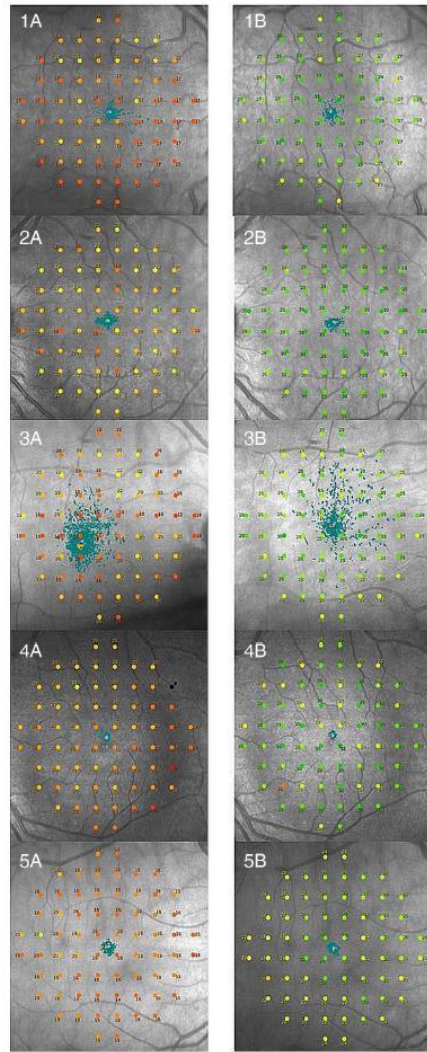

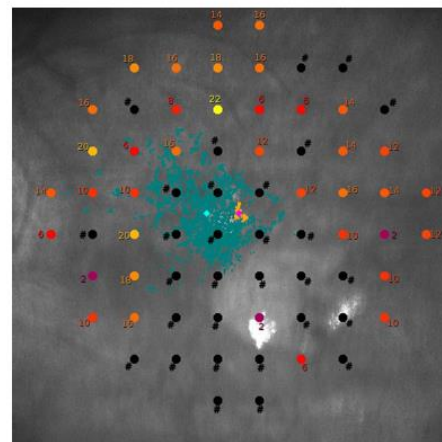**Figure 3** Microperimetry images for each participant with and without simulation contact lens.

Figure 4 Microperimetry image for a subject with age-related macular degeneration.

Given the more severe impact of reduced acuity on utility in patients with AMD compared with cataract, it can be expected that a true simulation of AMD would lead the public to rate AMD more severely than predicted by a contact lens.

An error of the magnitude of 0.09 on the utility scale is a major shift in a disease that impacts on QALYs through long-term decrease in utility, although the impact on the incremental cost-effectiveness ratio (ICER) of this difference is difficult to quantify.

Evidence from the DMO Evidence Review Group report suggests the ICER is sensitive to the utility values used. ICERs ranged from £16 585 to £39 712 in sensitivity analysis based around the *Czoski-Murray et al* utility values, compared with £21 504 to £50 879 for the same sensitivity analysis based around *Brown* utility values. The cost-effectiveness threshold is generally considered to be between £20 000 and £30 000 per QALY for NICE evaluations. Both analyses included the Novartis PAS discount, so represented the actual cost to the NHS.[16]

Although the contact lens occluder causes a generalised reduction in sensitivity, it does not cause a localised defect characteristic of an absolute central scotoma. Further, at the stage of AMD associated with reduced visual acuity, some absolute central scotoma is to be expected.

A well-reported functional consequence of AMD is reduced fixation stability.[17] Poor fixation stability is known to be associated with poorer visual function, particularly for reading.[18] Reduced fixation stability was not identified by the contact lens simulation, further limiting its applicability to true macular disease.

This study was conducted in a sample of five participants. Although the sample size was small, the results were consistent, with all observers showing a drop in acuity and contrast sensitivity, but no scotoma. The use of 'forced-choice' testing procedures increases the reliability of the tests and reduces the opportunity for subjects to consciously influence the results.

How should central vision loss be simulated? Spectacles with opacities on are not a valid option as eye movements will alter the retinal position of the opacity. Although contact lenses seem like an attractive option to simulate vision loss, we have shown that this does not create a central scotoma. The most appropriate way of simulating a scotoma in people with good vision is to use feedback from an eye tracking system. These devices display an image on a computer screen while simultaneously measuring the position of the eye. Software can produce a scotoma at the region of the image corresponding to the centre of gaze. These systems have been used in research settings[19 20] but have not, to our knowledge, been used to elicit utility values for AMD states in a public sample.

Alternatively, one could return to the reason for the use of the simulation. The deviation from generic HRQoL questionnaires to derive utilities was due to concern that standard questionnaires were not sensitive to changes in visual function due to limitations with the descriptive system. Future work to enhance the sensitivity of generic questionnaires may again place vision disorders on a common health state utility scale required for economic evaluation.

CONCLUSION

A contact lens with a central opacity does not simulate a retinal scotoma that is characteristic of diseases of the central vision like AMD. Opaque contact lenses reduce retinal illumination which leads to a reduction in visual acuity and contrast sensitivity, but the overall dimming effect bears little resemblance to a central scotoma, which is the hallmark of AMD.

The association with a lower level of visual acuity is not AMD specific and contact lens utilities could represent many causes of visual impairment. The visual acuity association has

been shown to be different across disorders; therefore, public valuations using this method may misinform the public.

The use of these utility values in economic evaluations such as those used to inform NICE decision making may lead to an incorrect estimation of the cost effectiveness of treatments for AMD and other eye diseases that cause central scotomas.

REFERENCES

1 NICE. Guide to the methods of technology appraisal. 2013.
2 NICE. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. 2012.
3 NICE. Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237). 2012.
4 Mitchell J, Bradley C. Quality of life in age-related macular degeneration: a review of the literature. *Health Qual Life Outcomes* 2006;4:97.
5 Bandello F, Lafuma A, Berdeaux G. Public health impact of neovascular age-related macular degeneration treatments extrapolated from visual acuity. *Invest Ophthalmol Vis Sci* 2007;48:96–103.
6 Brazier J. *Measuring and valuing health benefits for economic evaluation*. Oxford, New York: Oxford University Press, 2007. xi, 344 p. p.
7 Tosh J, Brazier J, Evans P, *et al.* A review of generic preference-based measures of health-related quality of life in visual disorders. *Value Health* 2012;15:118–27.
8 Longworth L, Yang Y, Young T, *et al.* Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. *Health Technol Assess* 2014;18:1–224.
9 Czoski-Murray C, Carlton J, Brazier J, *et al.* Valuing condition-specific health states using simulation contact lenses. *Value Health* 2009;12:793–9.
10 NICE. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. 2008.
11 Mainster MA, Timberlake GT, Webb RH, *et al.* Scanning laser ophthalmoscopy. Clinical applications. *Ophthalmology* 1982;89:852–7.
12 Reeves BC, Langham J, Walker J, *et al.* Verteporfin photodynamic therapy cohort study: report 2: clinical measures of vision and health-related quality of life. *Ophthalmology* 2009;116:2463–70.
13 Bansback N, Czoski-Murray C, Carlton J, *et al.* 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. *Qual Life Res* 2007;16:533–43.
14 Alavi Y, Jofre-Bonet M, Bunce C, *et al.* Developing an algorithm to convert routine measures of vision into utility values for glaucoma. *Ophthalmic Epidemiol* 2011;18:233–43.
15 Brown GC. Vision and quality-of-life. *Trans Am Ophthalmol Soc* 1999;97:473–511.
16 Cummins E, Waugh N, Lois N, *et al.* Ranibizumab for diabetic macular oedema: report for NICE rapid review. 2012.
17 Culham L, Fitzke FW, Timberlake GT, *et al.* Assessment of fixation stability in normal subjects and patients using a scanning laser ophthalmoscope. *Clin Vision Sci* 1993;8:551–61.
18 Crossland MD, Culham LE, Rubin GS. Fixation stability and reading speed in patients with newly developed macular disease. *Ophthalmic Physiol Opt* 2004;24:327–33.
19 Macedo AF, Crossland MD, Rubin GS. Investigating unstable fixation in patients with macular disease. *Invest Ophthalmol Vis Sci* 2011;52:1275–80.
20 Scherlen AC, Bernard JB, Calabrese A, *et al.* Page mode reading with simulated scotomas: oculo-motor patterns. *Vision Res* 2008;48:1870–8.

253

ORIGINAL RESEARCH ARTICLE

Modelling Cost Effectiveness in Neovascular Age-Related Macular Degeneration: The Impact of Using Contrast Sensitivity vs. Visual Acuity

Thomas Butt · Praveen J. Patel · Adnan Tufail ·
Gary S. Rubin

Abstract

Background The cost utility of treatments of age-related macular degeneration (AMD) is commonly assessed using health state transition models defined by levels of visual acuity. However, there is evidence that another measure of visual function, contrast sensitivity, may be better associated with utility than visual acuity. This paper investigates the difference in cost effectiveness resulting from models based on visual acuity and contrast sensitivity using the example of bevacizumab (Avastin) for neovascular AMD. The implications of the choice of outcome on structural uncertainty in the model are investigated.

Method Health state transition Markov models based on levels of visual acuity and contrast sensitivity are used to represent the costs, health utilities and outcomes of the Avastin for choroidal neovascular age-related macular degeneration (ABC) trial. Health states are associated with costs and utilities based on literature values. Treatment outcomes from the ABC trial are used to predict transitions between states in both models. Total costs and quality-adjusted life-years (QALYs) are calculated for a cohort of patients treated over a defined number of model cycles.

Results Over a 5-year time horizon, a contrast sensitivity model predicts a statistically significant ($p < 0.05$) 25 % greater QALY gain than the visual acuity model based on 10,000 Monte Carlo simulations. Bevacizumab is more effective and less costly than the comparator in the contrast sensitivity model and the visual acuity model.

Conclusion There is considerable structural uncertainty associated with the choice of outcome for modelling the cost effectiveness of AMD treatments. Bevacizumab has a higher incremental QALY gain and more favourable incremental cost-effectiveness ratio when cost effectiveness is assessed using contrast sensitivity outcomes compared with using visual acuity outcomes. Previous cost-effectiveness analyses may have underestimated the cost effectiveness of anti-vascular endothelial growth factor (anti-VEGF) therapy.

Key Points for Decision Makers

A model based on contrast sensitivity outcomes results in a significantly greater quality-adjusted life-year gain than a model based on visual acuity outcomes

The finding has implications for cost-effectiveness decisions for anti-vascular endothelial growth factor therapies, which have previously been based on visual acuity models

T. Butt (✉) · G. S. Rubin
Institute of Ophthalmology, University College London,
11-43 Bath Street, London, EC1V 9EL, UK
e-mail: thomas.butt.10@ucl.ac.uk

P. J. Patel · A. Tufail
Moorfields Eye Hospital, London, UK

P. J. Patel · A. Tufail · G. S. Rubin
NIHR Moorfields Biomedical Research Centre, London, UK

1 Introduction

Age-related macular degeneration (AMD) causes the progressive and irreversible loss of central vision. Patients may find it harder to read, recognise faces or make out fine detail, which can have a severe impact on their quality of

Adis

life [1]. Late-stage AMD is the third largest cause of blindness [2]. In the UK, there are currently estimated to be 513,000 cases of AMD and this number is predicted to increase to 679,000 cases by 2020 [3].

Neovascular (wet) AMD is caused by the development of new blood vessels in the macular. Treatment of neovascular AMD with anti-vascular endothelial growth factor (VEGF) therapy is current clinical practice in the UK National Health Service (NHS). Spending on the anti-VEGF ranibizumab (Lucentis®, Novartis AG, Switzerland) accounted for £129 million of the NHS prescribing budget in 2010, making it the third most costly drug [4].

Economic evaluations of treatments for AMD have concluded that the two anti-VEGF therapies used within the NHS, approved ranibizumab and off-label bevacizumab (Avastin®, Roche Holdings AG, Switzerland), are cost effective at commonly applied thresholds when compared with photodynamic therapy with verteporfin (vPDT) [5, 6]. A recent head-to-head comparison found no significant difference between the two drugs in terms of effectiveness [7].

Previous health economic models, including those used to develop the UK National Institute for Health and Care Excellence (NICE)'s guidelines on ranibizumab and pegaptanib for AMD, have relied on the association between visual acuity (VA) and health utility to construct Markov models [8]. Yet there is evidence that anti-VEGF therapy is also effective in reducing the deterioration in contrast sensitivity (CS), another measure of visual function.

A cost-effectiveness model based on CS outcomes may offer advantages over previous modelling techniques. First, no single visual function outcome captures health-related quality of life (HRQoL) in AMD and interventions may have a differential impact on each outcome. CS has an independent impact on health utility and has been shown to be more closely associated with HRQoL than VA. Bansback et al. [9] found CS remained a statistically significant predictor of utility even when VA was included in a regression model. VA measures the eye's ability to resolve fine detail at high contrast, while CS measures the ability to perceive differences between light and dark [10].

Second, utility values for CS have been reported for binocular vision, so a model based on this outcome takes account of visual function in both eyes. Models based on VA outcomes alone have considered only visual function in the better-seeing eye, while the impact of the worse-seeing eye on health utility is uncertain [11]. In clinical practice, the eye with the disease will be treated, whether this is the better- or worse-seeing eye, therefore, taking account of vision in both eyes more closely reflects clinical practice.

There has only been one previous economic evaluation published that used CS. Bansback et al. investigated the cost effectiveness of vPDT and estimated an incremental

Table 1 Baseline summary of patient demographics in the ABC trial

	Bevacizumab ($n = 65$)	Comparator ($n = 66$)
Gender		
Male	26	25
Female	39	41
Mean age (years)	79	81
Mean ETDRS visual acuity in study eye (logMAR)	0.68	0.64
Mean binocular contrast sensitivity (log units)	1.26	1.22

cost effectiveness of approximately GBP 20,996 per quality-adjusted life-year (QALY) over 10 years compared with best supportive care [12].

From the previous model, it was not possible to compare the implications of using CS or VA on the cost effectiveness of treatments for AMD because there was no directly comparable VA model. Furthermore, in recent years, vPDT has been replaced by anti-VEGF therapy as standard clinical practice to treat AMD, so there is no estimate of the cost effectiveness of current clinical practice using CS.

The aim of this paper is to investigate how developing state transition models build around CS health states or VA health states impacts on the cost utility of treatments for AMD.

The choice of using VA or CS in the model is a case of structural uncertainty, the impact of which can only be tested by redesign of the model [13]. In this paper, two Markov models are developed based on the Avastin (bevacizumab) for choroidal neovascular age-related macular degeneration (ABC) trial, which assessed VA and CS outcomes in AMD patients (Table 1). Bevacizumab was compared with standard NHS treatment at the time of the trial, which was a mixture of vPDT, pegaptanib (Macugen®, Pfizer, USA), an alternative anti-VEGF and no treatment (sham injection) depending on the clinical diagnosis. The trial demonstrated that bevacizumab was an effective treatment in terms of both outcomes [14, 15].

2 Methods

2.1 Model Structure

State transition Markov models were constructed to simulate the progression of the disease in terms of VA and CS. The VA model had four states of VA in the better-seeing eye and a death state. The CS had four states of binocular CS and a death state (Fig. 1). States were chosen that represented clinically relevant levels of visual function and had associated health utilities.
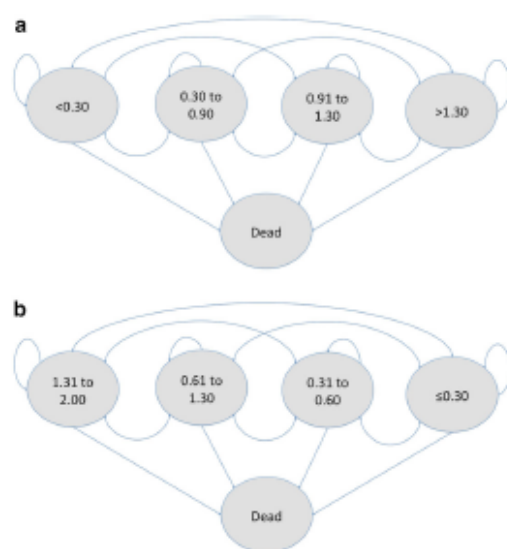
Fig. 1 Markov models. **a** Visual acuity states (better seeing eye logMAR). **b** Contrast sensitivity states (binocular log units)

In the models, patients were allowed to move forwards to a better health state, move backwards to a worse health state, remain in their current health state or die at each model cycle. Death was an absorbing state, meaning that patients could not leave the state.

2.2 Transition Probabilities

Transition probabilities were calculated from patient level data on VA and CS from the ABC trial ($n = 131$, Table 2). Better-seeing eye VA transition rates were approximated from the study eye. The use of the better-seeing eye to assess cost effectiveness reflects that quality of life is most strongly impacted by vision in the better-seeing eye. In the trial, the study eye was the better-seeing eye for 30 % of participants. CS measurement was measured monocularly in the trial, therefore binocular CS transition rates were estimated using a published algorithm, which estimates binocular CS to be the square root of the sum of the square of each eye [16]. Age-specific mortality rates were taken from the Office for National Statistics rates for England and Wales for 2009 [17]. The rates were adjusted to take account of the sex of the cohort using the ratio of participants in the ABC trial.

The trial measured VA every 6 weeks and CS every 12 weeks for 54 weeks. The cycle length was 6 weeks for the VA model and 12 weeks for the CS model, reflecting the ABC trial protocol.

Table 2 Transition probabilities between Markov states for bevacizumab and comparator

		From			
		1.31–2.00	0.61–1.30	0.31–0.60	≤0.30
Visual acuity (better seeing eye logMAR)					
To	Bevacizumab				
	1.31–2.00	0.62	0.03	0.00	0.01
	0.61–1.30	0.33	0.80	0.10	0.00
	0.31–0.60	0.00	0.16	0.72	0.24
	≤0.30	0.05	0.01	0.17	0.76
	Comparator				
	1.31–2.00	0.85	0.06	0.03	0.00
	0.61–1.30	0.11	0.84	0.22	0.05
	0.31–0.60	0.04	0.10	0.69	0.63
	≤0.30	0.00	0.00	0.07	0.32

		From			
		<0.30	0.30–0.90	0.91–1.30	>1.30
Contrast sensitivity (binocular log units)					
To	Bevacizumab				
	<0.30	1.00	0.06	0.00	0.00
	0.30–0.90	0.00	0.44	0.04	0.00
	0.91–1.30	0.00	0.50	0.77	0.11
	>1.30	0.00	0.00	0.19	0.89
	Comparator				
	<0.30	1.00	0.03	0.00	0.00
	0.30–0.90	0.00	0.67	0.10	0.01
	0.91–1.30	0.00	0.31	0.69	0.29
	>1.30	0.00	0.00	0.20	0.70

2.3 Utility

SF-6D utility values reported by Espallargues et al. [18] were applied to the health states in the model. 209 patients with unilateral or bilateral AMD at a hospital in Sheffield, UK were asked a series of preference-based questionnaires and the derived utility values were associated with their visual function. The SF-6D showed greater sensitivity than the EQ-5D, but less sensitivity than the HUI-3 to changes in vision. The SF-6D-derived utilities were chosen over the HUI-3 because the HUI-3 showed little agreement with other measures and gave extremely low utility scores compared with other measures. The HUI-3 reported a utility of just 0.10 for the worst VA state, compared with 0.63, 0.63 and 0.47 for the EQ-5D, SF-6D and time trade-off (TTO), respectively. TTO utilities were applied as sensitivity analyses. The utility values associated with levels of VA and CS were applied to the model health states (Table 3).

Table 3 Utility values assigned to Markov states

	SF-6D utility, mean (SD)	TTO utility, mean (SD)
Visual acuity (better-seeing eye, logMAR)		
1.31–2.00	0.65 (0.11)	0.60 (0.33)
0.61–1.30	0.66 (0.14)	0.64 (0.30)
0.31–0.60	0.67 (0.14)	0.67 (0.31)
≤0.30	0.70 (0.18)	0.73 (0.30)
Contrast sensitivity (binocular, log units)		
<0.30	0.65 (0.11)	0.58 (0.32)
0.30–0.90	0.64 (0.14)	0.56 (0.32)
0.91–1.30	0.68 (0.14)	0.70 (0.28)
>1.30	0.73 (0.16)	0.83 (0.25)

Utilities calculated by Espallargues et al. [18]

SD standard deviation, *TTO* time trade-off

Table 4 Unit costs

Item	Units per cycle (6-week/12-week)	Unit cost (£)	Cost source
Bevacizumab	0.8/1.6	242.66	BNF
Pegaptanib	1.0/2.0	514.00	BNF
First PDT with verporfin	0.4/0.8	1,181.00	Bansback et al. [12]
Subsequent PDT with verporfin	0.4/0.8	1,113.00	Bansback et al. [12]
Ophthalmic antibiotic	0.8/1.6	2.17	BNF
Anaesthetic	0.8/1.6	0.45	BNF
Dilating drops	1.0/2.0	0.45	BNF
Initial consultation	1.0/2.0	179.63	Patel et al. [19]
Subsequent consultation	1.0/2.0	49.98	Patel et al. [19]
Eye examination	1.0/2.0	51.00	Patel et al. [19]
Optical coherence tomography	1.0/2.0	44.00	Patel et al. [19]

BNF British National Formulary, *PDT* photodynamic therapy

2.4 Cost

Resource use was estimated from the ABC trial protocol and presented in British Pounds for a cost year of 2009 (Table 4). Treatment rates were calculated from the trial to reflect that patients were not treated at every time point. If treated, costs were incurred from the drug, the examination and the consultation. Otherwise, only costs associated with the examination and consultation were incurred. A higher cost was applied to the first consultation to reflect a more extensive first visit (Table 5).

Unit costs for drugs were obtained from the British National Formulary and adjusted for the volumes used in

Table 5 Cycle costs

	First cycle (£)	Subsequent cycle (£)
Visual acuity (6-week cycle)		
Bevacizumab		
Drug	208	208
Examination	95	95
Consultation	180	50
Total	483	353
Comparator		
Drug	374	367
Examination	95	95
Consultation	180	50
Total	649	512
Contrast sensitivity (12-week cycle)		
Bevacizumab		
Drug	416	416
Examination	191	191
Consultation	230	100
Total	836	707
Comparator		
Drug	747	733
Examination	191	191
Consultation	230	100
Total	1,168	1,024

the ABC trial. Consultation and examination costs were obtained from other published AMD models [12, 19].

2.5 Perspective

The perspective of the model was the UK NHS and personal social services (PSS) as recommended in the NICE Guide to the Methods of Technology Appraisal reference case [20]. Each model had a time horizon of 5 years, which represented an extension of the 54-week trial follow-up and captures the long-term costs and effects of the treatments. Because there is no evidence on the long-term outcomes of anti-VEGF therapy on either VA or CS, it was assumed that transition rates estimated from the 54-week trial were maintained to 5 years. A discount rate of 3.5 % for costs and QALYs was applied as recommended by the UK HM Treasury [21].

The model compared bevacizumab (1.25 mg in 0.05 mL per injection) with a comparator of mixed standard care in the UK in 2009 (16 patients received PDT, 38 patients received pegaptanib, 12 patients received sham injection) based on clinical assessment in the ABC trial.

2.6 Sensitivity Analysis

Appropriate probability functions were fitted to model parameters to incorporate uncertainty. Probabilistic

sensitivity analysis was performed using a Monte Carlo simulation to randomly sample each parameter [22]. Utilities were characterised by a beta distribution, with alpha and beta parameters defined by the means and standard deviations of the utilities. Costs were characterised by a gamma distribution with alpha and beta parameters defined by the means and standard deviations of the costs. Standard deviations were not available for costs, therefore they were assumed to be 10 % of the mean in line with recommended practice for health economic models [22]. Transition probabilities were characterised by a Dirichlet distribution.

Table 6 Central cost-effectiveness results: average of Monte Carlo analysis (5-year time horizon, 3.5% discount rate for costs and QALYs)

	Comparator	Bevacizumab	Incremental
Visual acuity			
Cost (£)	21,258	14,714	−6,545
QALYs	3.028	3.089	0.061
ICER	Bevacizumab dominates		
Contrast sensitivity			
Cost (£)	20,931	14,490	−6,441
QALYs	3.114	3.190	0.076
ICER	Bevacizumab dominates		

QALYs quality-adjusted life-years, *ICER* incremental cost-effectiveness ratio

A cost-effectiveness acceptability curve was constructed to represent the probability of the treatment proving cost effective at a given value of health effect [23]. One-way sensitivity analysis was employed to test structural uncertainty within the model.

3 Results

A higher incremental QALY gain is obtained from the CS model compared with the VA model. The central estimates of the probabilistic sensitivity analysis are 0.076 in the CS model and 0.061 in the VA model, which indicates that bevacizumab is 25 % more effective using CS outcomes than the VA outcomes (Table 6). This difference was statistically significant ($p < 0.05$) when 10,000 Monte Carlo simulations of the model were assessed using an unpaired *t* test.

The models indicate that bevacizumab is less costly and more effective than the comparator treatment over 5 years using either VA or CS outcomes (bevacizumab dominates the comparator).

The results remain robust when parameters were varied in sensitivity analysis. Bevacizumab dominates the comparator in all model assumptions varied in the one-way sensitivity analysis (Table 7). The CS model generates a higher incremental QALY gain than the VA model in all

Table 7 One-way sensitivity analysis

Parameter	Base case	Sensitivity	Costs (£)			QALYs			Change in ICER (%)	Difference in QALYs VA vs. CS (%)
			Comparator	Bevacizumab	Difference	Comparator	Bevacizumab	Difference		
Visual acuity										
Base case	–	–	21,005	14,529	−6,477	2.995	3.053	0.058	–	
Utilities	SF-6D	TTO	21,005	14,529	−6,477	2.905	3.055	0.150	−61	
Discount rate	3.5 %	0 %	22,947	15,868	−7,078	3.273	3.338	0.064	−1	
		5 %	20,243	14,003	−6,240	2.886	2.942	0.056	0	
Time frame	5 years	2 years	8,911	6,184	−2,727	1.260	1.281	0.021	+17	
		10 years	39,345	27,183	−12,162	5.625	5.740	0.115	−5	
Starting age	65 years	80 years	29,342	20,281	−9,061	4.191	4.275	0.084	−3	
Contrast sensitivity										
Base case	–	–	20,972	14,500	−6,471	3.125	3.199	0.075	–	+29
Utilities	SF-6D	TTO	20,972	14,500	−6,471	3.273	3.484	0.211	−65	+41
Discount rate	3.5 %	0 %	22,950	15,866	−7,084	3.421	3.503	0.082	−1	+28
		5 %	20,197	13,966	−6,231	3.009	3.081	0.072	0	+28
Time frame	5 years	2 years	8,900	6,171	−2,729	1.316	1.344	0.027	+15	+30
		10 years	39,288	27,139	−12,149	5.869	6.009	0.140	0	+22
Starting age	65 years	80 years	29,312	20,255	−9,057	4.374	4.478	0.104	+1	+23

VA visual acuity, *CS* contrast sensitivity, *TTO* time trade-off, *QALYs* quality-adjusted life-years, *ICER* incremental cost-effectiveness ratio

△ Adis

258

Fig. 2 Cost-effectiveness plane
of incremental costs and
quality-adjusted life-years
(QALYs) for bevacizumab vs.
comparator. a Visual acuity.
b Contrast sensitivity

259

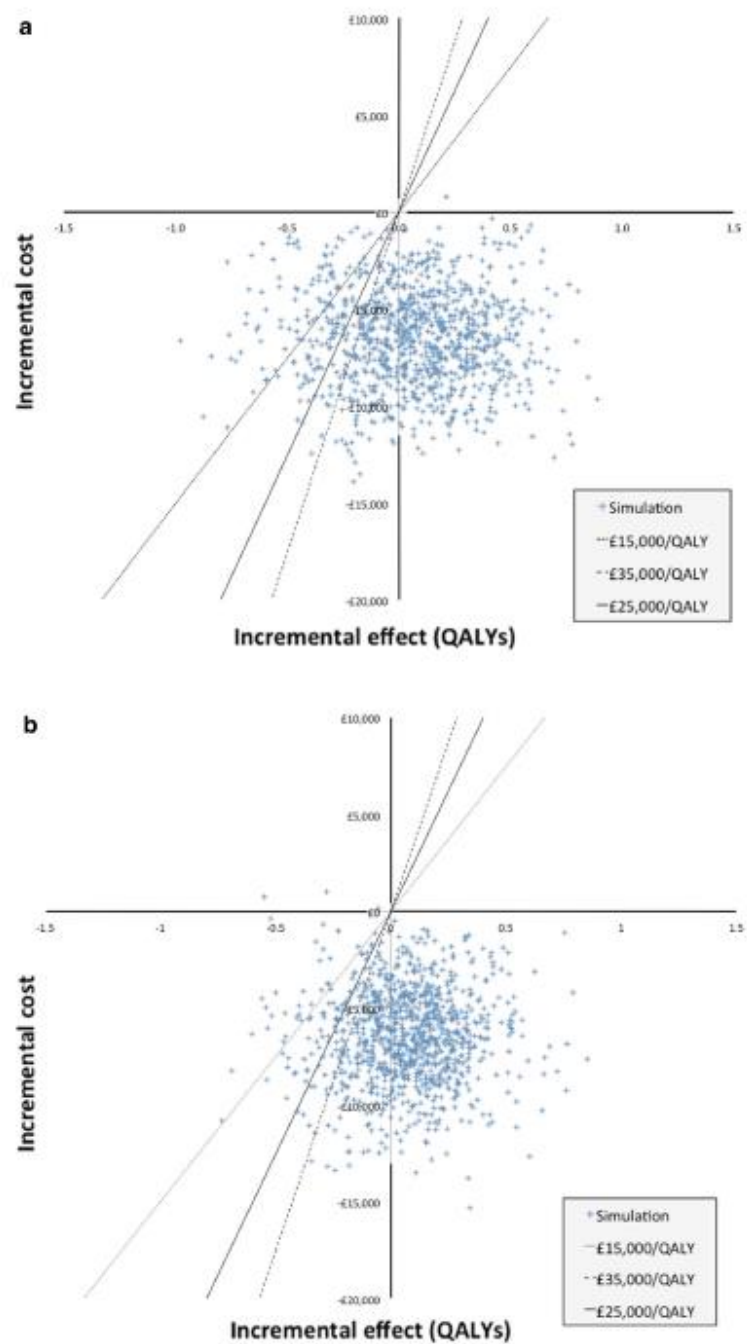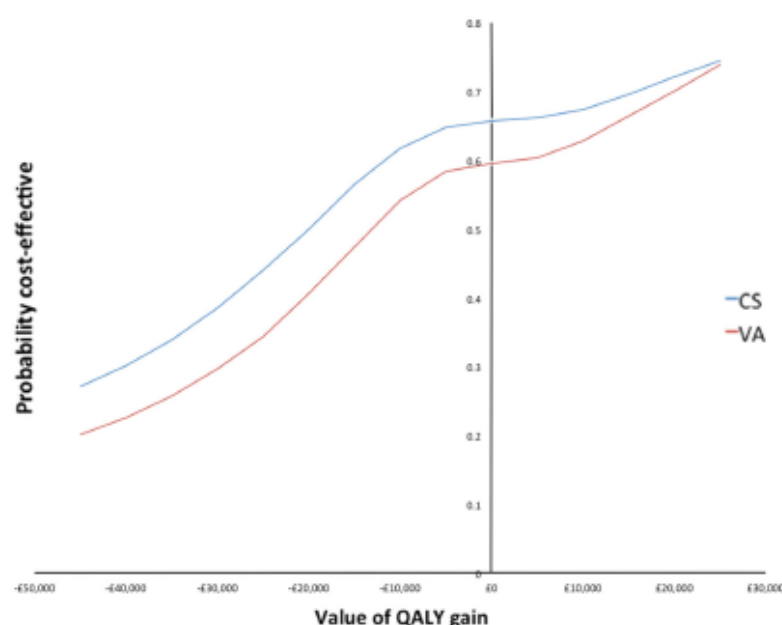Fig. 3 Cost-effectiveness
acceptability curve for
bevacizumab vs. comparator.
CS contrast sensitivity,
VA visual acuity

4 Discussion/Conclusion

The choice of outcome represents a major source of structural uncertainty when constructing models to assess the cost effectiveness of treatments for AMD and has been shown to have a large impact on cost-effectiveness estimates.

Bevacizumab appears more cost effective when assessed using CS outcomes rather than VA outcomes. In this trial, as bevacizumab dominates the comparator, the decision on the use of bevacizumab in AMD would not be altered by the choice of outcome used in the model.

scenarios. The model is most sensitive to the choice of utility set.

Bevacizumab remains cost effective when a probabilistic sensitivity analysis is applied to utilities, costs and transition probabilities. Figure 2 shows the probabilistic sensitivity analysis on a cost-effectiveness plane.

The cost-effectiveness acceptability curve (CEAC) highlights that for the same cost as the comparator, bevacizumab has a probability of being cost effective of more than 60 % when assessed using VA and 65 % when assessed using CS (Fig. 3). At most values of QALY gain there is a higher probability of bevacizumab being cost effective in the CS model than in the VA model.

The difference in incremental QALY gain between the CS and VA models when assessing the cost effectiveness of anti-VEGF therapy is potentially significant in health-care decision making, particularly in decisions close to the cost-effectiveness threshold.

Another anti-VEGF therapy, ranibizumab, is currently recommended for the treatment of AMD patients within the NHS [8]. It has been shown to be equally effective to bevacizumab, but is more costly [7, 24]. In NICE's economic evaluation of ranibizumab for AMD, the assessment group used a state transition model based on VA. The base-case incremental cost-effectiveness ratios (ICERs) over a 10-year time horizon for predominantly classic lesions were £15,638 per QALY gained compared with PDT, and £11,412 per QALY gained compared with best supportive care. For minimally classic lesions and occult no classic lesions, assuming 2 years of treatment, the ICER was £25,098 per QALY gained compared with best supportive care [5].

Although a direct comparison between the appraisal results and this study is not possible because of a different intervention and comparator, an improvement in cost effectiveness of 25 % could have implications on decision making at a threshold of £20,000–£30,000 per QALY, particularly in subgroups with minimally classic lesions and occult no classic lesions.

Traditionally, a CEAC such as that shown in Fig. 3 would only show positive values of health effects.

However, the negative value of health effect is shown to allow inferences to be made about how the two outcomes may impact on the cost effectiveness of a more costly drug. The CEAC demonstrates that for a given value of health effect, the CS model predicts bevacizumab to be more likely to be considered cost effective.

There are two potential reasons for the different QALY estimates from the two models. First, the closer association between CS and HRQoL may mean that the CS model is more accurately representing the utility gain of the treatment than the VA model. Alternatively, the intervention may have a differential effect on VA and CS and anti-VEGF therapy may improve CS more than VA in terms of relative utility.

There are a number of limitations with this study. The comparator treatment (a mixture of pegaptanib, PDT and no treatment) as used in the ABC trial is no longer standard NHS practice because of the approval of ranibizumab. This limits interpretation of the absolute ICERs. A comparison of bevacizumab with ranibizumab based on CS outcomes would be a valuable area for future research. Furthermore, another anti-VEGF therapy, aflibercept (Eylea ®Bayer), is approved for the treatment of AMD in the US and has been shown to be equally effective compared with ranibizumab [25].

Both VA and CS have limitations when measuring very poor vision. Both measures rely on patients reading letters on a chart, so when patients cannot read the first letter, patients are assumed to have the most severe health state in the model.

Transition rates were based on trial data and allowed patients' vision to worsen, remain the same or improve at each cycle. Anti-VEGF therapy is generally believed to maintain or reduce deterioration in vision rather than improve it. However, the nature of VA and CS as performance measures means there may be variation in the exact scores achieved by patients on each visit.

These models do not include adverse events. Of the 131 patients enrolled in the ABC trial, five patients did not complete the study because of adverse events, loss to follow-up or death. The ocular safety profiles for the two treatment groups showed no overall imbalance in serious and non-serious ocular adverse events. Given the incidence of any adverse events in the two models would be the same, their exclusion from the models should not impact on the difference between VA and CS identified.

Generally, these results highlight that the choice of clinical outcome on which a model is based can have a large impact on the cost-effectiveness estimates of the model. The uncertainty associated with the choice of clinical variable to associate with utility cannot be assigned a distribution and tested using a probabilistic sensitivity analysis, as is frequently done for costs, utilities and

transition rates. Attention should be paid to the association between clinical disease states and HRQoL when developing health economic models. The clinical outcome that is best associated with HRQoL in the condition should be used where practical. If there is uncertainty over the most suitable clinical outcome for defining model states, the alternatives could be presented in a one-way sensitivity analysis.

References

1. Mitchell J, Bradley C. Quality of life in age-related macular degeneration: a review of the literature. Health Qual Life Outcomes. 2006;4:97. doi:10.1186/1477-7525-4-97.
2. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004;82(11):844–51 (pii S0042-96862004001100009).
3. Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. Br J Ophthalmol. 2012;96(5):752–6. doi:10.1136/bjophthalmol-2011-301109.
4. The prescribing year: 2011. Prescriber. 2011;22:16–7. doi:10.1002/psb.844
5. National Institute for Health and Care Excellence. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. TA155. London: National Institute for Health and Care Excellence. 2008.
6. Hernandez-Pastor LJ, Ortega A, Garcia-Layana A, Giraldez J. Cost-effectiveness of ranibizumab compared with photodynamic treatment of neovascular age-related macular degeneration. Clin Ther. 2008;30(12):2436–51. doi:10.1016/j.clinthera.2008.12.025.
7. Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364(20):1897–908. doi:10.1056/NEJMoa1102673.
8. National Institute for Health and Care Excellence. Ranibizumab and pegaptanib for the treatment of age-related macular

degeneration. TA155. London: National Institute for Health and Care Excellence. 2012.

9. Bansback N, Czoski-Murray C, Carlton J, Lewis G, Hughes L, Espallargues M, et al. 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. Qual Life Res. 2007;16(3):533–43. doi:10.1007/s11136-006-9126-8.

10. Rubin G. Assessment of visual function in eyes with visual loss. Ophthalmol Clin N Am. 1989;2:357–67.

11. Brown GC, Brown MM, Sharma S, Brown HC. Patient perceptions of quality-of-life associated with bilateral visual loss. Int Ophthalmol. 1998;22(5):307–12.

12. Bansback N, Davis S, Brazier J. Using contrast sensitivity to estimate the cost-effectiveness of verteporfin in patients with predominantly classic age-related macular degeneration. Eye (Lond). 2007;21(12):1455–63. doi:10.1038/sj.eye.6702636.

13. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM modeling good research practices task force-6. Value Health J Int Soc Pharmacoecon Outcomes Res. 2012;15(6):835–42. doi:10.1016/j.jval.2012.04.014.

14. Tufail A, Patel PJ, Egan C, Hykin P, da Cruz L, Gregor Z, et al. Bevacizumab for neovascular age related macular degeneration (ABC trial): multicentre randomised double masked study. BMJ. 2010;340:c2459. doi:10.1136/bmj.c2459.

15. Patel PJ, Chen FK, Da Cruz L, Rubin GS, Tufail A. Contrast sensitivity outcomes in the ABC trial: a randomized trial of bevacizumab for neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52(6):3089–93. doi:10.1167/iovs.10-6208.

16. Legge GE. Binocular contrast summation: II. Quadratic summation. Vis Res. 1984;24(4):385–94.

17. Office for National Statistics. Mortality statistics: deaths registered in 2009. 2010. Available from http://www.ons.gov.uk/ons/rel/vsob1/mortalitystatistics–deaths-registered-in-england-and-wales–series-dr-/2009/index.html. Accessed 27 Feb 2014.

18. Espallargues M, Czoski-Murray CJ, Bansback NJ, Carlton J, Lewis GM, Hughes LA, et al. The impact of age-related macular degeneration on health status utility values. Invest Ophthalmol Vis Sci. 2005;46(11):4016–23. doi:10.1167/iovs.05-0072.

19. Patel JJ, Mendes MA, Bounthavong M, Christopher ML, Boggie D, Morreale AP. Cost-utility analysis of bevacizumab versus ranibizumab in neovascular age-related macular degeneration using a Markov model. J Eval Clin Pract. 2010. doi:10.1111/j.1365-2753.2010.01546.x.

20. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. London: National Institute for Health and Care Excellence. 2013.

21. The Green Book: Appraisal and Evaluation in Central Government. HM Treasury, UK. 2003.

22. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics. 2000;17(5):479–500.

23. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. Br J Psychiatry. 2005;187:106–8. doi:10.1192/bjp.187.2.106.

24. Jackson TL, Kirkpatrick L. Cost comparison of ranibizumab and bevacizumab. BMJ. 2011;343:d5058. doi:10.1136/bmj.d5058.

25. Thomas M, Mousa SS, Mousa SA. Comparative effectiveness of aflibercept for the treatment of patients with neovascular age-related macular degeneration. Clin Ophthalmol. 2013;7:495–501. doi:10.2147/OPTH.S29974.

262

BMJ Open The cost-effectiveness of initiating ranibizumab therapy in eyes with neovascular AMD with good vision: an economic model using real-world outcomes

Thomas Butt,[1] Aaron Lee,[2] Cecilia Lee,[2,3] Adnan Tufail,[1,2] on behalf of the UK AMD EMR Study Group

[1]Institute of Ophthalmology, University College London, London, UK
[2]Moorfields Eye Hospital, London, UK
[3]University of Washington, Seattle, WA, USA

Correspondence to
Adnan Tufail;
Adnan.Tufail@moorfields.nhs.uk

ABSTRACT

Objectives: To evaluate the cost-effectiveness of immediate treatment with ranibizumab in patients with neovascular age-related macular degeneration (nAMD) with good (better than 6/12) starting visual acuity compared with current UK clinical guidance of waiting until vision falls below 6/12 to begin treatment, using real-world outcomes data.

Design: A patient-level health economic state transition model based on levels of visual acuity in the better seeing eye was constructed to simulate the costs and consequences of treating patients with nAMD with ranibizumab.

Setting: The model took the perspective of the UK National Health Service (NHS).

Participants: The model was populated with real-world outcomes and resource use from a prospective multicentre national nAMD database study containing 92 976 ranibizumab treatment episodes.

Interventions: Two treatment approaches were compared: immediate intervention with 0.5 mg ranibizumab pro re nata, PRN (on detection of nAMD) or delayed intervention (waiting until vision fell to 6/12 before beginning treatment).

Main outcome measures: Quality-adjusted life years (QALYs) for health states and healthcare costs were accrued for each strategy, and an incremental cost-effectiveness ratio (ICER) was calculated. One-way and probabilistic sensitivity analyses were employed to test the uncertainty of the model.

Results: Over a 2-year time horizon, based on 10 000 Monte Carlo simulations, the early treatment arm accumulated 1.59 QALYs and £8469.79 cost. The delayed treatment arm accumulated 1.35 QALYs and £7460.21 cost. The central ICER estimate was £4251.60.

Conclusions: A model based on real-world data is likely to be a realistic reflection of the health gains and resource use of ranibizumab for nAMD in the UK NHS. Initiating treatment immediately with ranibizumab PRN regimen is a cost-effective strategy compared with current guidance of initiating treatment at a level of 6/12 or worse vision.

Strengths and limitations of this study

- This is the first cost-effectiveness analysis of initiating ranibizumab treatment of age-related macular degeneration (AMD) in patients with good vision. Immediate treatment of neovascular AMD (nAMD) with ranibizumab in patients with good starting vision (>6/12) is compared with delayed treatment until vision falls below 6/12.
- This model, based on a large real-world data set, is likely to better reflect treatment patterns and outcomes in clinical practice than trial-based models.
- The results suggest that it would be cost-effective to extend the National Institute for Health and Care Excellence (NICE) guidance to treat nAMD immediately.
- The study required some assumptions to be made about changes in vision that occur before patients begin treatment, which we derived from natural history data from the fellow eyes of patients in the electronic medical record (EMR) data set.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of severe visual loss in patients over the age of 50 years in Europe and North America.[1][2] Neovascular AMD (nAMD) is characterised by choroidal neovascularisation (CNV), which is the growth of abnormal, choroidal blood vessels beneath the macula, which causes severe loss of vision and is responsible for the majority of visual loss due to AMD.[3] One of the key mediators implicated in the pathogenesis of CNV in nAMD is vascular endothelial growth factor-A (VEGF). Treatments for CNV target VEGF are administered by injection into the vitreous cavity with high binding specificity to VEGF (anti-VEGF agents). These agents are administered by intraocular (intravitreal)

263

injections with repeat injections as necessary depending on the agent.

Intravitreal injection of anti-VEGF drugs such as ranibizumab (Lucentis, Novartis) is an established therapy to treat nAMD and is the most commonly performed retinal procedure in the UK National Health Service (NHS).[4]

The National Institute for Health and Care Excellence (NICE) issued guidance recommending the use of ranibizumab for nAMD England in August 2008, leading to almost exclusive usage of ranibizumab for nAMD in the UK NHS.[5]

Clinical and economic evidence was initially informed by the Anti-vascular endothelial growth factor Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related Macular Degeneration (ANCHOR) and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) studies, which demonstrated that ranibizumab prevents central vision loss and improves mean visual acuity (VA) at 2 years when given at monthly intervals in eyes with subfoveal nAMD.[6] [7]

Consistent with these pivotal studies, NICE recommended that ranibizumab for nAMD should be funded in eyes presenting with VAs between 6/12 and 6/96, which parallels the entry criteria of the pivotal studies. Owing to the trials' exclusion criteria, no direct evidence exists from phase 3 randomised controlled clinical trials to assess the clinical effectiveness and cost-effectiveness of treating patients presenting with early lesions resulting in vision better than 6/12.

However, patients have been presenting with nAMD to treating centres with better visions since NICE initially supported ranibizumab reimbursement on the NHS in 2008. Current guidance is to wait until vision worsens to below 6/12 before treating. Our group has previously shown that if ranibizumab therapy is initiated in eyes with good visual acuities, the treated eye is more likely to maintain good vision,[8] and this is consistent with the indirect evidence from the pivotal trials that eyes are more likely to maintain vision than recover lost vision at initiation of treatment.[6] [7]

The purpose of this work is to evaluate whether immediate intervention with ranibizumab in the better seeing eye of patients presenting with nAMD with good vision is cost-effective compared with the delayed intervention approach that is currently recommended.

A health economic model with health states based on levels of VA in the better seeing eye was developed. The intervention considered is the initiation of ranibizumab (0.5 mg) treatment using three loading injections+a pro re nata (PRN) protocol for patients with a confirmed diagnosis of nAMD and vision better than 6/12: *immediate treatment*. The comparator is the current standard of care for patients with nAMD, which is no treatment for patients with a confirmed diagnosis of nAMD with vision better than 6/12 and treatment with ranibizumab using three loading injections of ranibizumab at approximately monthly intervals followed by a PRN (3 loading injections+PRN) protocol when vision falls below 6/12: *delayed treatment* (current NHS practice). Effectiveness and resource use was derived from real-life outcomes from treated and untreated (fellow) eyes in 14 centres using ranibizumab for AMD in the UK.[8]

This analysis is the first to assess the cost-effectiveness of treating VA better than 6/12 in nAMD compared with treating only when vision is worse than 6/12 with ranibizumab. Furthermore, the work demonstrates how real-world outcomes and resource use associated with the use of ranibizumab therapy may be used to assess the cost-effectiveness of treating nAMD. These results may be more generalisable to routine clinical practice than models based on randomised controlled trial (RCT) data, and therefore more appropriate to assess the cost-effectiveness of routine use treatment protocol in the NHS.

METHODS
Model structure
A Markov patient-level simulation model was developed with an initial 3-month cycle followed by monthly cycles. The model consisted of six health states: five health states defined by declining VA ranging from 6/12 or better (least severe) to less than 3/60 (most severe), and an additional absorbing state, death, which was accessible from all levels of vision (figure 1). This model structure was consistent with the model developed by the Evidence Review Group (ERG) in the original NICE appraisal of ranibizumab for nAMD.[5]

On entering the model, a patient was assigned an age and gender based on the distribution of these characteristics among patients with a starting vision of better than 6/12 in the data set.

For *immediate treatment*, a patient was simulated to be treated straightaway on confirmed diagnosis of nAMD with three initial monthly ranibizumab injections followed by PRN for 2 years. For *delayed treatment*, a patient was assigned a time from diagnosis to vision falling below 6/12. In the initial period (>6/12), a patient received no treatment. After reaching 6/12, treatment began and a patient progressed to a state of vision assigned according to a distribution based on the visions of patients beginning treatment in the data set (ie, many eyes with nAMD will initially present with a vision in the NICE guidance allowing immediate treatment but the vision may be any value between 6/12 and 6/96, and not just 6/12). A patient was then treated with three initial monthly ranibizumab injections followed by PRN and continued through the model for 2 years including the starting delay. The simulation was run for 10 000 patients.

Perspective
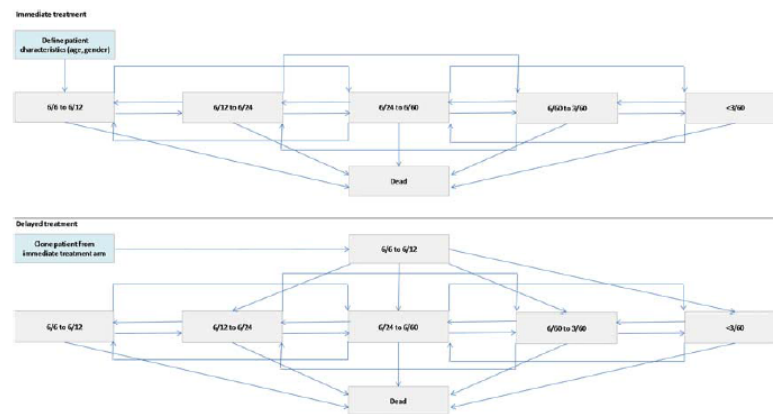The perspective of the model was the UK NHS and Personal Social Services (PSS) as recommended in the

264

Figure 1 Model structure.

NICE Guide to the Methods of Technology Appraisal reference case.[8] The model had a 2-year time horizon, which represented the time horizon used in pivotal trials. Owing to the short time horizon, costs and benefits were not discounted.

Transition probabilities

Transition matrices were calculated from the electronic medical record (EMR) data set (table 1). For treatment, transitions were calculated from visual acuities recorded for treated eyes. For no treatment of eyes better than 6/12, transitions were calculated from visual acuities recorded for fellow (untreated) eyes.

In the immediate treatment arm, all patients began in state >6/12 with a 3-month loading dose cycle. Patients then received ranibizumab PRN with monthly transitions for the remainder of the 2 years.

For the delayed treatment arm, patients followed a time-to-event survival curve to define the time in state >6/12 before dropping below 6/12 and beginning treatment. Once their vision dropped below 6/12, they entered the 3-month loading dose cycle in the following distribution (state 1: 0, state 2: 0.434484, state 3: 0.3891544, state 4: 0.1456472, state 5: 0.0307501 (based on the distribution of patients beginning treatment in the data set)). Patients then received ranibizumab PRN with monthly transitions for the remainder of the 2 years.

Utility

Benefits were measured in quality-adjusted life years (QALYs). VA was converted to utility for the calculation of QALYs using Brown et al,[9] which elicited utilities in 80 patients with AMD using the time trade-off method and grouped these by the VA health states defined in the model. The health state utility values used in the model

are reported in table 2[10] and are consistent with those applied to the model used by the ERG in the original NICE appraisal of ranibizumab for nAMD.[5]

Cost

Resource use and costs were applied to reflect UK clinical practice. Resource use consisted of monthly assessment visits and ranibizumab injection. On initiation of treatment, patients received three loading doses of ranibizumab as recommended by clinical guidance followed by PRN injections at a frequency calculated from the data set.

UK unit costs were assigned for a cost year of 2012. A cost of ranibizumab of £742.17 per injection, an assessment cost of £255.00 and a monitoring cost of £60.00 was used.[11 12] These costs were consistent with the NICE costing template for aflibercept (July 2013).

Sensitivity analysis

Appropriate probability functions were fitted to model parameters to incorporate uncertainty. Probabilistic sensitivity analysis was performed using a Monte Carlo simulation to randomly sample each parameter. Utilities were characterised by a β distribution, with α and β parameters defined by the means and SDs of the utilities. Costs were characterised by a γ distribution with α and β parameters defined by the means and SDs of the costs. SDs were not available for costs, therefore they were assumed to be 10% of the mean in line with recommended practice for health economic models. Transition probabilities were characterised by a Dirichlet distribution. A cost-effectiveness acceptability curve (CEAC) was constructed to represent the probability of the treatment proving cost-effective at a given value of health effect. One-way sensitivity analysis was employed to test structural uncertainty within the model.

Open Access

Table 1 Transition probabilities

Immediate treatment

		To state				
		6/6 to >6/12	6/12 to 6/24	6/24 to 6/60	6/60 to 3/60	<3/60
First 3 months (months 0–2), probability for 3-month cycle						
From state	6/6 to >6/12	0.7240	0.2222	0.0335	0.0108	0.0096
Remainder of 2 years (months 3–24), probability for 1-month cycle						
From state	6/6 to >6/12	0.8778	0.1163	0.0046	0.0006	0.0008
	6/12 to 6/24	0.2937	0.6243	0.0783	0.0032	0.0005
	6/24 to 6/60	0.0359	0.2355	0.6747	0.0479	0.0060
	6/60 to 3/60	0.0219	0.0146	0.1533	0.7007	0.1095
	<3/60	0.0588	0.0147	0.0147	0.2059	0.7059

Delayed treatment

		To state				
		6/6 to >6/12	6/12 to 6/24	6/24 to 6/60	6/60 to 3/60	<3/60
First 3 months (months after drop to state 2), probability for 3-month cycle						
From state	6/6 to >6/12	0.0	0.0	0.0	0.0	0.0
	6/12 to 6/24	0.3300	0.4993	0.1506	0.0139	0.0062
	6/24 to 6/60	0.0699	0.3049	0.4923	0.1057	0.0272
	6/60 to 3/60	0.0157	0.0927	0.3795	0.4123	0.0999
	<3/60	0.0203	0.0541	0.2432	0.4257	0.2568
Remainder of 2 years (+3 from months after reaching state 2), probability for 1-month cycle						
From state	6/6 to >6/12	0.7366	0.2408	0.0139	0.0026	0.0062
	6/12 to 6/24	0.1433	0.7161	0.1341	0.0054	0.0011
	6/24 to 6/60	0.0081	0.1414	0.7369	0.1068	0.0068
	6/60 to 3/60	0.0047	0.0093	0.2018	0.7045	0.0797
	<3/60	0.0380	0.0087	0.0459	0.2985	0.6089

EMR data set

We have previously described the methodology of obtaining the large data set of 92 976 ranibizumab injections,[10] which covered data from the approval of ranibizumab in August 2008 until April 2012. In brief, 14 NHS hospitals that deliver ranibizumab AMD treatment services in England and Northern Ireland submitted data to this study. Each site is the only NHS provider of nAMD care to their local population and very few patients switch between providers. Following NICE approval for the use of ranibizumab for nAMD in the NHS in August 2008, all sites used this drug almost exclusively. The lead clinician and Caldicott Guardian (who oversees data protection) at each centre gave written approval for the data extraction. Patient identifiers were completely stripped out, and site and clinician data were pseudo-anonymised, and on this basis an ethics committee determined that formal ethics approval was not required. This study was conducted in accordance with the declaration of Helsinki and the UK's Data Protection Act.

The 14 sites entered their first treatment episodes into the EMR system during the following years: 2006 (n=2 sites), 2007 (n=5), 2008 (n=4), 2009 (n=1) and 2010 (n=2). The first recorded ranibizumab injection was dated November 2006.

Over the period of data collection, anti-VEGF treatment was performed in 13 774 patients, of whom 2639 received anti-VEGF for reasons other than nAMD or received bevacizumab. Thus, this study analyses data on

Table 2 Utility values for model health states

Visual acuity	Utility, mean (SD)
From 6/6 to 6/12	0.89 (0.16)
6/12 to 6/24	0.81 (0.20)
6/24 to 6/60	0.57 (0.17)
6/60 to 3/60	0.52 (0.24)
<3/60	0.40 (0.12)

Source: Brown *et al*.[9]

Table 3 Demographic details of patients used to develop model

Variable	Male (n=4071)	Female (n=7062)	Not specified (n=1)	Total (n=11 135)
Age (years)				
Mean	78.8	80.1	79	79.7
Median	80	81	79	81
IQR	74–84	76–86	–	75–85
Range	55–103	55–108	–	55–108

266

Open Access

Table 4 Central cost-effectiveness results: average of Monte Carlo analysis

	Comparator (delayed intervention)	Intervention (immediate intervention)	Incremental
Cost (£)	7460.21	8469.79	1009.58
QALYs	1.35	1.59	0.24
ICER (£)			4251.60

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

12 951 eyes of 11 135 patients who received a total of 92 976 ranibizumab injections during 317 371 clinic visits at 14 UK hospitals. In total, 16.3% (n=1816) of these patients required treatment to both eyes during the follow-up period. The demographics of the patients included have previously been described and are summarised in table 3.[10]

'Best-measured VA' was the best VA with refraction or habitual correction and/or pinhole as measured on an Early Treatment Diabetic Retinopathy Study (ETDRS) chart and expressed as ETDRS letters and LogMAR vision in this study.

Missing data

For patients whose data were not available for a particular visit or had been lost to follow-up, no missing value substitutions were performed. The only exception to this rule was baseline VA, as some treatment centres brought patients back for a two stop service—assessment on first visit followed by injection on second visit, and did not repeat VA measurements on the date of the first injection (n=1670), which was always performed within 3 weeks. This was therefore not missing data per se but reflects variation in treatment delivery. In the model, we assumed no differences between centres for resource use associated with service delivery.

RESULTS

The central ICER estimate from PSA was £4251.60 per QALY for immediate intervention compared with delayed intervention (table 4). In the immediate intervention group, patients accumulated on average 1.59 QALYs and £8469.79 costs over 2 years versus 1.35 QALYs and £7460.21 costs in the delayed intervention group.

Figure 2 shows the cost-effectiveness plane with 10 000 simulations. The majority of the distributions are located to the lower right of a £20 000 willingness to pay threshold. The results are disaggregated into the incremental cost per QALY of immediate intervention and delayed intervention in figure 3.

Figure 4 shows the CEAC. Immediate treatment has a 50% chance of being cost-effective compared with current treatment practice if the NHS were willing to
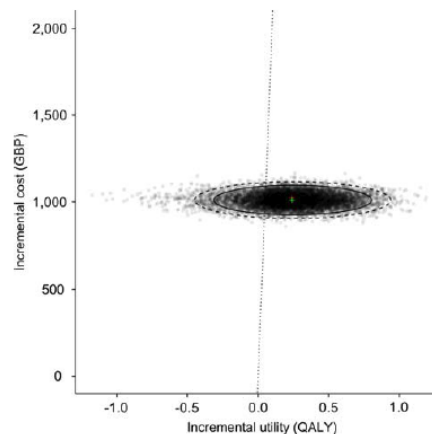
Figure 2 Cost-effectiveness plane (GBP, British Pounds; QALY, quality-adjusted life year).

pay £4251.60 per QALY. At a willingness to pay threshold of £20 000 per QALY, immediate treatment has a >90% chance of being cost-effective.

One-way sensitivity analysis is reported in table 5. The model was sensitive to time horizon. Running the model for 5 years rather than 2 resulted in a lower ICER of £1773.21 (58% lower than the base case). Over a longer time horizon, the early intervention arm accumulated more QALYs for a marginally higher cost than the
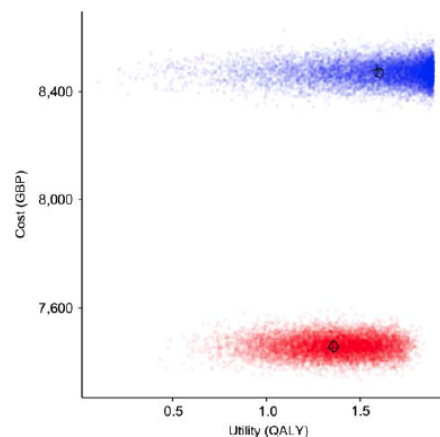
Figure 3 Costs and QALYs accumulated over 2 years by patients treated with ranibizumab according to current NHS practice (red) and with early intervention (blue). GBP, British Pounds; NHS, National Health Service; QALY, quality-adjusted life year.
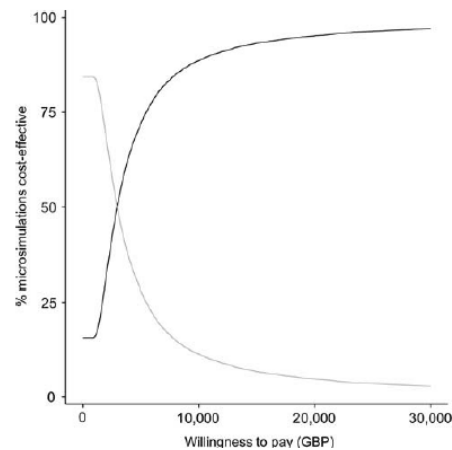
267

Open Access

Figure 4 Cost-effectiveness acceptability curve of immediate treatment of nAMD with ranibizumab (dark grey) compared with current NHS practice of delayed treatment (light grey). GBP, British Pounds; nAMD, neovascular age-related macular degeneration; NHS, National Health Service.

delayed intervention arm. A younger starting age had a marginal impact on the ICER, with a starting age of 60 years generating an ICER of £3909.36 (8% lower than the base case). Including only drug cost (no visit cost) led to an ICER of £3697.82 (13% lower than the base case). The ICER was also impacted by the choice of health state utility values. Using values elicited by Brown *et al* using the standard gamble technique generated an ICER of £5126.51 (21% higher than the base case using time trade-off values from the same source).

DISCUSSION

Immediate intervention in nAMD is likely to be a cost-effective strategy. Over 2 years, patients received an average of one more injection and gained 0.24 QALYs compared with current practice of delayed intervention.

The ICER of £4251.60 of treating early versus current treatment practice is substantially below a threshold of £20 000 per QALY, which is often considered the NHS's willingness to pay for health gain.[8]

This is, to our knowledge, the first assessment of the cost-effectiveness of treating patients with vision better than 6/12. We believe that the recommendation of treating patients with vision worse than 6/12 was based on the absence of evidence in patients with better vision due to the exclusion criteria in clinical trials of ranibizumab. Therefore, NICE currently does not recommend funding for eyes with good VA, which may result in some patients having to drop below 6/12 to initiate therapy. From a patient perspective, what is more important is

Table 5 One-way sensitivity analysis

Parameter	Base case	Sensitivity	Cost (£)			QALY			ICER	Change in ICER (%)
			Comparator	Intervention	Difference	Comparator	Intervention	Difference		
Base case	–	–	7460.21	8469.79	1009.58	1.35	1.59	0.24	4251.60	–
Utility	Brown et al TTO	Brown et al SG	7460.21	8469.79	1009.58	1.54	1.73	0.19	5126.51	+21
Cost	Drug and visit	Drug only	6232.08	7110.14	878.06	1.35	1.59	0.24	3697.82	–13
Time horizon	2 years	5 years	15 000.16	15 998.43	998.27	3.01	3.57	0.56	1773.21	–58
Starting age	78.8*	60†	7771.01	8768.44	997.43	1.42	1.67	0.25	3909.36	–8

Source: Brown et al.[9]
*Distribution defined by characteristics of data set.
†Fixed starting age for cohort.
ICER, incremental cost-effectiveness ratio; SG, standard gamble; TTO, time trade-off; QALY, quality-adjusted life year.

6

268

maintaining a good functional visual state that allows continuing to be able to read and drive; waiting until vision falls below 6/12 can be anxiety provoking and delayed treatment can result in worse clinical outcome.[13] This paper provides evidence that early ranibizumab treatment is associated with a small incremental cost per QALY within the range that the NHS is typically willing to pay for health gain.[8]

The database shows that patients are presenting at centres with AMD with good starting vision. In order to determine the budget impact of extending ranibizumab treatment to visions better than 6/12, the full incidence of early AMD in the population, and the availability and effectiveness of screening, need to be examined. Rates of clinical presentation and screening effectiveness were identified as major areas of uncertainty in a model assessing the cost-utility of a screening programme for early AMD.[14]

It is also possible that earlier treatment could have a different effect on vision. For example, treating AMD at an earlier stage when lesions are smaller could mean that fewer injections may be needed to maintain vision. Further work investigating the cost to the healthcare system of earlier detection and treatment would be valuable future research.

As the first assessment of the cost-effectiveness of treating a broader range of visual acuities with ranibizumab, the results cannot be directly compared with other models. In NICE's economic evaluation of ranibizumab for AMD, the assessment group used a similar state transition model.[5] The base case ICERs over a 10-year time horizon for predominantly classic lesions were £15 638 per QALY gained compared with photodynamic therapy with verteporfin, and £11 412 per QALY gained compared with best supportive care. For minimally classic lesions and occult lesions, assuming 2 years of treatment, the ICER was £25 098 per QALY gained compared with best supportive care. In terms of clinical effectiveness, VA outcomes from the database previously reported that outcomes do not match the results achieved in most randomised trials, but they were delivered with substantially fewer injections and hospital visits.[8]

This paper synthesises outcomes from routine NHS treatment, which is likely to better reflect real-world effectiveness and resource use than RCT evidence. Beyond the limited range of visual acuities included in pivotal trials, the use of RCT data for assessing cost-effectiveness suffers from limitations of inclusion/exclusion criteria and protocol-driven treatment patterns. Thus, the outcomes and treatment practices derived from RCT data may not reflect today's clinical practice. By contrast, the use of real-world data requires robust methods to deal with non-standardised aspects such as missing data.

There are a number of limitations to this study. First, the study required some assumptions to be made about changes in vision that occur between patients not being treated, which we derived from natural history data, and

patients beginning treatment, which we derived from the EMR data set. Once the delayed treatment group initiates therapy, they immediately fall to the starting VA of any person starting on treatment. Meaning that once they fall below the 6/12 line their VA state changes to match the distribution of starting VA in the data set of anyone beginning treatment. We believe that this is realistic in clinical practice, since most lesions are likely to go through subtle changes that can be seen clinically before the patient notices them or before the lesions qualify for treatment. The survival curve on which the model is based uses the fellow eye's structural optical coherence tomography data in the EMR data set. Once the lesion causes the vision to fall below 6/12, patients could realistically end up with any possible vision, clinically.

Second, due to the limited number of VA states, a significant number of patients in the treat-early group remain in the best VA state for the lifetime of the model. Such a situation is perhaps not surprising: Ranibizumab treatment is generally associated with a maintenance of vision rather than an improvement (recovery of lost vision due to nAMD). Therefore, in the model initiating treatment early, patients maintained a better VA state and accumulated more QALYs.

In summary, our study provides a real-world data based model demonstrating that early ranibizumab intervention is associated with an acceptable incremental cost that is well within the NHS acceptable range to pay for health gain. Thus, the maintenance of better VA in patients who are treated early is not only beneficial clinically but also likely cost-effective. This study may help inform future policy decision regarding the routine treatment with ranibizumab in patients having visual acuities better than 6/12.

269

Open Access

REFERENCES

1. Congdon N, O'Colmain B, Klaver CCW, *et al.*, Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol* 2004;122:477–85.
2. Klein R, Peto T, Bird A, *et al.* The epidemiology of age-related macular degeneration. *Am J Ophthalmol* 2004;137:486–95.
3. Ferris FL, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 1984;102:1640–2.
4. Kwong TQ, Mohamed M. Anti vascular endothelial growth factor therapies in ophthalmology: current use, controversies and the future. *Br J Clin Pharmacol* 2014;78:699–706.
5. National Institute of Clinical Excellence (NICE) technology appraisal guidance 155. Ranibizumab and pegaptanib for the treatment of agerelated macular degeneration. http://www.nice.org.uk/TA155
6. Brown DM, Kaiser PK, Michels M, *et al.*, ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432–44.
7. Rosenfeld PJ, Brown DM, Heier JS, *et al.*, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419–31.

8. National Institute for Health and Care Excellence (NICE). Guide to the Methods of Technology Appraisal 2013. http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9
9. Brown GC, Sharma S, Brown MM, *et al.* Utility values and age-related macular degeneration. *Arch Ophthalmol* 2000;118:47–51.
10. Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. The Neovascular Age-related Macular Degeneration Database: multicenter study of 92976 ranibizumab injections: report 1: visual acuity. *Ophthalmology* 2014;121:1092–101.
11. Health and Social Care Information Centre. Hospital Episode Statistics 2011/12. http://www.hscic.gov.uk/hes
12. Electronic Medicines Compendium. http://www.medicines.org.uk/emc/
13. Canan H, Sizmaz S, Altan-Yaycioglu R, *et al.* Visual outcome of intravitreal ranibizumab for exudative age-related macular degeneration: timing and prognosis. *Clin Interv Aging* 2014;9:141–5.
14. Karnon J, Czoski-Murray C, Smith K, *et al.* A preliminary model-based assessment of the cost-utility of a screening programme for early age-related macular degeneration. *Health Technol Assess* 2008;12:iii–iv, ix-124.

270

Appendix B

Survey instruments

Chapter 3

EQ-5D 5L sample

EQ-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

273

- We would like to know how good or bad your health is

  TODAY.

- This scale is numbered from 0 to 100.

- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the
  box below.

YOUR HEALTH TODAY =

100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

3

Modified from RAND 36-Item Short Form Health Survey based on Brazier et al. The estimation of a preference-based measure of health from the SF-36. Journal of Health Economics 21 (2002) 271-292. This survey contains the items of the SF-36 that are used in the SF-6D utility algorithm.

_____

<u>*This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.*</u>

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
*3. **Vigorous activities**, such as running, lifting	[1]	[2]	[3]

heavy objects, participating in strenuous sports

*4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
6. Climbing **several** flights of stairs	[1]	[2]	[3]
*12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle One Number on Each Line)

	Yes	No
14. **Accomplished less** than you would like	1	2
*15. Were limited in the **kind** of work or other activities	1	2

During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

	Yes	No
*18. **Accomplished less** than you would like	1	2
19. Did work or other activities less carefully than usual (Didn't do work	1	2

or other activities as **carefully** as usual)

*21. How much **bodily** pain have you had during the **past 4 weeks**?

(Circle One Number)

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

*22. During the **past 4 weeks,** how much did **pain** interfere with your normal work

(including both work outside the home and housework)?

(Circle One Number)

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks** . . .

(Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
*24. Have you been a very nervous person?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
*27. Did you have a lot of energy?	1	2	3	4	5	6
*28. Have you felt downhearted and *depressed (blue)*?	1	2	3	4	5	6

*32. During the **past 4 weeks,** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle One Number)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

Thank you for completing this survey

*: goes into SF-6D algorithm

Red: additional question from SF-36

Underline: Modified wording

I am going to ask you some theoretical questions, which require careful thought. Please take your time to think about your answer. I would like you to compare living in two quality of life states for a maximum period of 10 years after which you must assume you will die.

Please consider your **overall health** today. Imagine that you know with certainty that your level of health would remain the same as it is today for **10 years** after which point you would die.

Instead of spending 10 years in your current health state, you may instead choose to spend **a lesser number of years, between 0 and 10,** with perfect health and then die.

(After script, see end for Q9 vision question)

Script i

1. If you were given the choice to live for 10 years in your current state of health or to live for 10 years in perfect health, which would you prefer?
 	
    a.   Perfect health (go to 2)
 	
    b.   Current health (stop)
 	
    c. Same (stop)	

2. If you were given the choice to live for 10 years in your current state of health or to die immediately (0 years in perfect health), which would you prefer? a. Immediate death **(go to script iiia)**	

b. Current health (go to 3) c. Same (stop)	
3. If you were given the choice to live for 10 years in your current state of health or to live for 5 years in perfect health, which would you prefer? a. Perfect health **(go to script ii)** b. Current health (go to 4) c. Same (stop)	
4. If you were given the choice to live for 10 years in your current state of health or to live for 6 years in perfect health, which would you prefer? a. Perfect health (go to 4a) b. Current health (go to 5) c. Same (stop)	4a. If you were given the choice to live for 10 years in your current state of health or to live for 5.5 years in perfect health, which would you prefer? a. Perfect health (stop) b. Current health (stop) c. Same (stop)
5. If you were given the choice to live for 10 years in your current state of health or to live for 7 years in perfect health, which would you prefer? a. Perfect health (go to 5a) b. Current health (go to 6) c. Same (stop)	5a. If you were given the choice to live for 10 years in your current state of health or to live for 6.5 years in perfect health, which would you prefer? a. Perfect health (stop) b. Current health (stop) c. Same (stop)

6. If you were given the choice to live for 10 years in your current state of health or to live for 8 years in perfect health, which would you prefer? a. Perfect health (go to 6a) b. Current health (go to 7) c. Same (stop)	6a. If you were given the choice to live for 10 years in your current state of health or to live for 7.5 years in perfect health, which would you prefer? a. Perfect health (stop) b. Current health (stop) c. Same (stop)
7. If you were given the choice to live for 10 years in your current state of health or to live for 9 years in perfect health, which would you prefer? a. Perfect health (go to 7a) b. Current health (go to 8) c. Same (stop)	7a. If you were given the choice to live for 10 years in your current state of health or to live for 8.5 years in perfect health, which would you prefer? a. Perfect health (stop) b. Current health (stop) c. Same (stop)
8. If you were given the choice to live for 10 years in your current state of health or to live for 10 years in perfect health, which would you prefer? a. Perfect health (go to 8a) b. Current health (stop) c. Same (stop)	8a. If you were given the choice to live for 10 years in your current state of health or to live for 9.5 years in perfect health, which would you prefer? a. Perfect health (stop) b. Current health (stop) c. Same (stop)

Script ii

4. If you were given the choice to live for 10 years in your current state of health or to live for 4 years in perfect health, which would you prefer?
 	
   a. Perfect health (go to 4a)
 	
   b. Current health (go to 5)
 	
   c. Same (stop)
	4a. If you were given the choice to live for 10 years in your current state of health or to live for 4.5 years in perfect health, which would you prefer?
	
	   a. Perfect health (stop)
	
	   b. Current health (stop)
	
	   c. Same (stop)

5. If you were given the choice to live for 10 years in your current state of health or to live for 3 years in perfect health, which would you prefer?
 	
   a. Perfect health (go to 5a)
 	
   b. Current health (go to 6)
 	
   c. Same (stop)
	5a. If you were given the choice to live for 10 years in your current state of health or to live for 3.5 years in perfect health, which would you prefer?
	
	   a. Perfect health (stop)
	
	   b. Current health (stop)
	
	   c. Same (stop)

6. If you were given the choice to live for 10 years in your current state of health or to live for 2 years in perfect health, which would you prefer?
 	
   a. Perfect health (go to 6a)
 	
   b. Current health (go to 7)
 	
   c. Same (stop)
	6a. If you were given the choice to live for 10 years in your current state of health or to live for 2.5 years in perfect health, which would you prefer?
	
	   a. Perfect health (stop)
	
	   b. Current health (stop)
	
	   c. Same (stop)

7. If you were given the choice to live for	7a. If you were given the choice to live for

10 years in your current state of health or to live for 1 year in perfect health, which would you prefer?
 	
   a. Perfect health (go to 7a)
 	
   b. Current health (go to 8)
 	
   c. Same (stop)
	10 years in your current state of health or to live for 1.5 years in perfect health, which would you prefer?
	
	   a. Perfect health (stop)
	
	   b. Current health (stop)
	
	   c. Same (stop)

8. If you were given the choice to live for 10 years in your current state of health or to die immediately (0 years perfect health), which would you prefer?
 	
   a. Perfect health (go to 8a)
 	
   b. Current health (stop)
 	
   c. Same (stop)
	8a. If you were given the choice to live for 10 years in your current state of health or to live for 0.5 years in perfect health, which would you prefer?
	
	   a. Perfect health (stop)
	
	   b. Current health (stop)
	
	   c. Same (stop)

Script iiia

3. If you were given the choice to live for 5 years in perfect health followed by 5 years in your current state of health or to die immediately, which would you prefer? a. 5 perfect, 5 current **(go script iiib)** b. Die immediately (go to 4) c. Same (stop)	
4. If you were given the choice to live for 6 years in perfect health followed by 4 years in your current state or to die immediately, which would you prefer? a. 6 perfect, 4 current (go to 4a) b. Immediate death (go to 5) c. Same (stop)	4a. If you were given the choice to live for 5.5 years in perfect health followed by 4.5 years in your current state or to die immediately, which would you prefer? a. 5.5 perfect, 4.5 current (stop) b. Die immediately (stop) c. Same (stop)
5. If you were given the choice to live for 7 years in perfect health followed by 3 years in your current state or to die immediately, which would you prefer? a. 7 perfect, 3 current (go to 5a) b. Die immediately (go to 6) c. Same (stop)	5a. If you were given the choice to live for 6.5 years in perfect health followed by 3.5 years in your current state or to die immediately, which would you prefer? a. 6.5 perfect, 3.5 current (stop) b. Die immediately (stop) c. Same (stop)
6. If you were given the choice to live for 8 years in perfect health followed by 2 years in your current state or to die	6a. If you were given the choice to live for 7.5 years in perfect health followed by 2.5 years in your current state or to die

immediately, which would you prefer?
 	
   a. 8 perfect, 2 current (go to 6a)
 	
   b. Die immediately (go to 7)
 	
   c. Same (stop)
	immediately, which would you prefer?
	
	   a. 7.5 perfect, 2.5 current (stop)
	
	   d. Die immediately (stop)
	
	   e. Same (stop)

7. If you were given the choice to live for 9 years in perfect health followed by 1 years in your current state or to die immediately, which would you prefer?
 	
   a. 9 perfect, 1 current (go to 7a)
 	
   b. Die immediately (go to 8)
 	
   c. Same (stop)
	7a. If you were given the choice to live for 8.5 years in perfect health followed by 1.5 years in your current state or to die immediately, which would you prefer?
	
	   a. 8.5 perfect, 1.5 current (stop)
	
	   b. Die immediately (stop)
	
	   c. Same (stop)

8. If you were given the choice to live for 10 years in perfect health or to die immediately, which would you prefer?
 	
   a. 10 perfect health (go to 8a)
 	
   b. Die immediately (stop)
 	
   c. Same (stop)
	8a. If you were given the choice to live for 9.5 years in perfect health followed by 0.5 years in your current state or to die immediately, which would you prefer?
	
	   a. 9.5 perfect, 0.5 current (stop)
	
	   b. Die immediately (stop)
	
	   c. Same (stop)

Script iiib

4. If you were given the choice to live for 4 years in perfect health followed by 6 years in your current state or to die immediately, which would you prefer?
 	
   a. 4 perfect, 6 current (go to 4a)
 	
   b. Die immediately (go to 5)
	4a. If you were given the choice to live for 4.5 years in perfect health followed by 5.5 years in your current state or to die immediately, which would you prefer?
	
	   a. 4.5 perfect, 5.5 current (stop)
	
	   b. Die immediately (stop)

c. Same (stop)	c. Same (stop)

5. If you were given the choice to live for 3 years in perfect health followed by 7 years in your current state or to die immediately, which would you prefer?
 	
    a. 3 perfect, 7 current (go to 5a)
 	
    b. Die immediately (go to 6)
 	
    c. Same (stop)
	5a. If you were given the choice to live for 3.5 years in perfect health followed by 6.5 years in your current state or to die immediately, which would you prefer?
	
	    a. 3.5 perfect, 6.5 current (stop)
	
	    b. Die immediately (stop)
	
	    c. Same (stop)

6. If you were given the choice to live for 2 years in perfect health followed by 8 years in your current state or to die immediately, which would you prefer?
 	
    a. 2 perfect, 8 current (go to 6a)
 	
    b. Die immediately (go to 7)
 	
    c. Same (stop)
	6a. If you were given the choice to live for 2.5 years in perfect health followed by 7.5 years in your current state or to die immediately, which would you prefer?
	
	    a. 2.5 perfect, 7.5 current (stop)
	
	    b. Die immediately (stop)
	
	    c. Same (stop)

7. If you were given the choice to live for 1 years in perfect health followed by 9 years in your current state or to die immediately, which would you prefer?
 	
    a. 1 perfect, 9 current (go to 7a)
 	
    b. Die immediately (go to 8)
 	
    c. Same (stop)
	7a. If you were given the choice to live for 1.5 years in perfect health followed by 8.5 years in your current state or to die immediately, which would you prefer?
	
	    a. 1.5 perfect, 8.5 current (stop)
	
	    b. Die immediately (stop)
	
	    c. Same (stop)

8. If you were given the choice to live for 10 years in your current health state or to die immediately, which would you prefer?
 	
    a. 10 current health (go to 8a)
 	
    b. Die immediately (stop)
	8a. If you were given the choice to live for 0.5 years in perfect health followed by 9.5 years in your current state or to die immediately, which would you prefer?
	
	    a. 0.5 perfect, 9.5 current (stop)

| c. Same (stop) | b. Die immediately (stop) |
| | c. Same (stop) |
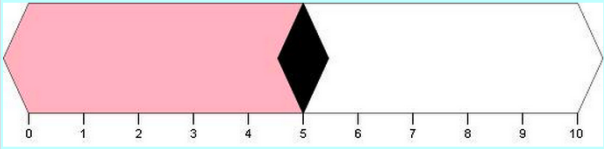
Online TTO developed with Accent Marketing and Research Ltd.

Example screenshot:

If you were given the choice to live for 5 years in life A and then die or to live for 10 years in life B and then die, which would you prefer?

Perfect Health

- I have no problems in walking about
- I have no problems washing or dressing myself
- I have no problems doing my usual activities
- I have no pain or discomfort
- I am not anxious or depressed

LIFE A

Age related macular degeneration

- I have moderate problems in walking about
- I have no problems washing or dressing myself
- I have slight problems doing my usual activities
- I have no pain or discomfort
- I am not anxious or depressed

LIFE B

○ 1. Life A preferred   ○ 2. Life B preferred   ○ 3. Same

DCE choices

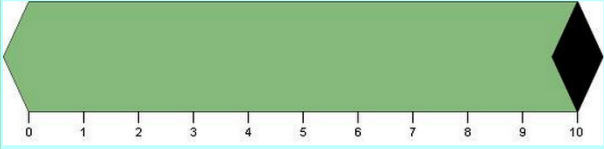| Task		1	2	3	4	5	6	7	8	9
Choice A										
Current HRQoL		20%	20%	20%	20%	40%	40%	40%	40%	60%
HRQoL gain		5%	10%	15%	20%	5%	10%	15%	20%	5%
Unmet need		Existing treatment available (new	No adequate treatment available	Existing treatment available (new	No adequate treatment available	No adequate treatment available	Existing treatment available (new	No adequate treatment available	Existing treatment available (new	Existing treatment available (new
Process		Monthly home-based self-administered	One-off hospital appointment for injection	Monthly hospital appointment for injection	Monthly home visit by nurse for injection	Monthly home visit by nurse for injection	Monthly hospital appointment for injection	One-off hospital appointment for injection	Monthly home-based self-administered	One-off hospital appointment for injection
Choice B										
Current HRQoL		40%	40%	40%	40%	60%	60%	60%	60%	80%
HRQoL gain		10%	15%	20%	5%	10%	15%	20%	5%	10%
Unmet need		No adequate treatment available	Existing treatment available (new	No adequate treatment available	Existing treatment available (new	Existing treatment available (new	No adequate treatment available	Existing treatment available (new	No adequate treatment available	No adequate treatment available
Process		Monthly home visit by nurse for injection	Monthly hospital appointment for injection	Monthly home-based self-administered	One-off hospital appointment for injection	One-off hospital appointment for injection	Monthly home-based self-administered	Monthly hospital appointment for injection	Monthly home visit by nurse for injection	Monthly hospital appointment for injection

Task								
10	60%	10%	No adequate treatment available	Monthly home-based self-administered	80%	15%	Existing treatment available (new	Monthly home visit by nurse for injection
11	60%	15%	Existing treatment available (new	Monthly home visit by nurse for injection	80%	20%	No adequate treatment available	One-off hospital appointment for injection
12	60%	20%	No adequate treatment available	Monthly hospital appointment for injection	80%	5%	Existing treatment available (new	Monthly home-based self-administered
13	80%	5%	No adequate treatment available	Monthly hospital appointment for injection	20%	10%	Existing treatment available (new	Monthly home-based self-administered
14	80%	10%	Existing treatment available (new	Monthly home visit by nurse for injection	20%	15%	No adequate treatment available	One-off hospital appointment for injection
15	80%	15%	No adequate treatment available	Monthly home-based self-administered	20%	20%	Existing treatment available (new	Monthly home visit by nurse for injection
16	80%	20%	Existing treatment available (new	One-off hospital appointment for injection	20%	5%	No adequate treatment available	Monthly hospital appointment for injection
(17)	20%	20%	No adequate treatment available	One-off hospital appointment for injection	5%	80%	Existing treatment available (new	Monthly hospital appointment for injection

Note: task 17 is additional dominant choice added to 16 run main effects design and excluded from analysis

Converting Visual function data to approximate visual field

Method for extracting points seen on microperimeter to approximate a visual field:

1. Extract raw points displayed to patient by microperimeter using x and y coordinates.

2. Convert to distance from centre of vision $[(x^2+y^2)^{0.5}] = d$

3. Censor points with coordinates that were displayed outside of plausible visual field (d>17)

4. Define whether point was seen by the patient (TRUE) or not seen by the patient (FALSE)

5. Calculate proportion of points seen by the patient within the plausible visual field [SEEN/(SEEN+NOT SEEN)]

Review of AMD economic models

Chapter 2

Data extraction from AMD economic models

	Intervention	Comparator	Utilities	Efficacy	Reported ICER
Hernandez-Pastor et al. (2008)(62)	Ranibizumab	PDT with verteporfin	Brown et al. (2000)	VA from ANCHOR	€131,275/QALY (2 year time horizon)
Patel et al. (2010)(112)	Bevacizumab	Ranibizumab	Modified from Brown et al. (2000)	VA from MARINA and ANCHOR	$1,405/QALY (bevacizumab) and $12,177/QALY (ranibizumab)
Raftery et al. (2007)(145)	Ranibizumab	Bevacizumab	Brown et al. (2000)	VA from MARINA and specified range	N/A (efficacy and price ranges modelled)
Smith et al. (2004)(146)	PDT with verteporfin	Placebo	Brown et al. (2000)	VA from TAP	£76,000 (starting VA 20/40, 2 year time horizon)
Bansback et al. (2007)(60)	PDT with verteporfin	BSC	Espallargues et al. (2005)	CS from TAP	£20,996 (10 year time horizon)

	Intervention	**Comparator**	**Utilities**	**Efficacy**	**Reported ICER**
Neubauer et al. (2010)(147)	Ranibizumab	PDT/BSC	Brown et al. (2000) (Bansback for sensitivity analysis)	VA from MARINA and ANCHOR	ranibizumab for occult, minimally classic CNV, and classic CNV were €22,320, €22,538, and €25,036, /QALY respectively, and €3294 for classic CNV compared with PDT
Gower et al. (2010)(148)	Pegaptanib or ranibizumab	PDT with verteporfin	Brown et al. (2000)	Various	Various
Fletcher et al. (2008)(149)	Ranibizumab	BSC	Sharma (2000)	VA from MARINA	$626,938 per QALY
Brown et al. (2008)(150)	Ranibizumab	Sham (no treatment)	Brown et al. (2000)	MARINA	$50 691/QALY
Karnon et al. (2008)(151)	AMD screening	No screening	Espallargues et al. (2005)	Uniform distribution for rate of uptake (no	£15,169 (Annual screening, £2 per screen)

	Intervention	Comparator	Utilities	Efficacy	Reported ICER
				data)	
Bojke et al. (2008)(152)	AMD screening followed by PDT	PDT, no screening (self referral) and no screening, no PDT	Brown et al. (2000)	VA from TAP	N/A (EVPI)
Earnshaw et al. (2007)(153)	Pegaptanib	PDT and standard care	Brown et al. (2000)	VA from VISION and TAP	$49,052 vs PDT and $59,039 vs standard care
Wolowacz et al. (2007)(154)	Pegaptanib	BSC	Not reported	VA	PharmacoEconomics [1170-7690] Wolowacz Year: 2007 Volume: 25 Issue: 10 Page: 863 -79
Brown et al. (2005)(155)	PDT with verteporfin		233 patients	VA from TAP	US$31,103/QALY
Hopley et al. (2004)(156)	PDT with verteporfin	Placebo	Brown et al. (2000)	VA from TAP	£31,607/QALY (6/12 starting VA)
Hopley et	Screening for	No	Sharma et	VA from	£22,722/QALY

	Intervention	Comparator	Utilities	Efficacy	Reported ICER
al. (2004)(157)	early AMD followed by high dose zinc	treatment	al. (2000)	AREDS and Blue Mountains Eye Study	
Busbee et al. (2003)(158)	Laser photocoagulation	Placebo	Brown et al. (2000)	VA from MPS	US$$23,176/QALY
Sharma et al. (2001)(159)	PDT with verteporfin	Placebo	Brown et al. (2000) and physician panel for complications	VA from TAP	US$86,721/QALY (US 3rd party payer perspective, 20/40 starting VA)
Hurley et al. (2008)(160)	Ranibizumab	No treatment	Brown et al. (2000)	VA from MARINA	US$91,900/QALY
Javitt (2008)(74)	Pegaptanib	Usual care	Brown et al. (2000)	VA from VISION	
Hurley (2008)(161)	Smoking cessation	Smoking	Brown et al. (2000)	VA from MARINA	US$$200/QALY