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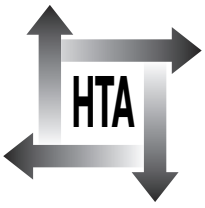

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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 03/06/01. The contractual start date was in April 2004. The draft report began editorial review in March 2006 and was accepted for publication in February 2008. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration

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Objectives: To estimate the cost-effectiveness of screening for age-related macular degeneration (AMD) by developing a decision analytic model that incorporated and assessed all of the National Screening Committee criteria. A further objective was to identify the major areas of uncertainty in the model, and so inform future research priorities in this disease area.
Data sources: Major databases were searched in March 2004 and updated in January 2005.
Review methods: Systematic literature reviews covered the epidemiology and natural history of AMD, the screening and treatment effectiveness and health-related quality of life relating to AMD. A hybrid cohort–individual sampling model was implemented to describe the range of pathways between the incidence of age-related maculopathy (ARM) and death via clinical presentation and treatment at different stages of the disease. As significant shortfalls in the data available from the literature were apparent, so a range of primary data sources were also used to populate the model. To obtain estimates for the value of parameters deemed to be within an expert's remit, data describing some parameters were elicited from relevant experts. The data identified informed probability distributions describing the uncertainty around the model parameters. To incorporate joint parameter uncertainty (i.e. correlations between parameters), the AMD natural history model was calibrated probabilistically. Randomly sampled sets of input parameters were assigned weights representing the accuracy of their predictions of a set of observed model outputs. The analysis of the AMD screening model estimated the costs, numbers of quality-adjusted life-years (QALYs) and cases of blindness in a general population sample of 50-year-olds over the remainder of their lifetime, for 16 alternative screening options (including no screening). The reference case analysis incorporated current treatment options of laser photocoagulation and photodynamic therapy. Sensitivity analyses describing six alternative sets of intervention strategies, based on horizon scanning of potential future treatments for AMD, were also undertaken.
Results: There remains significant uncertainty about whether any form of screening for AMD is cost-effective. However, annual screening from age 60 years seems to provide the highest mean net benefits, but this is based on a cost-effectiveness estimate that has very poor precision (high levels of uncertainty). The probabilistic sensitivity analysis shows that the 95% credible interval for annual screening from age 60 years ranges from this option dominating the previous option to an incremental cost per QALY of over £0.5 million. Plotting a cost-effectiveness acceptability frontier shows that although annual screening from age 60 years has the highest net benefits at a value of QALY of £30,000, the associated probability of this option being the most cost-effective option is only around 20%. The sensitivity analyses around potential future treatment options indicate that screening may become more cost-effective with the new treatments.
Conclusions: The conclusions focus on the interpretation of the results from the perspective of

defining the major areas of uncertainty, which were defined as disease progression, rates of clinical presentation, screening test and optician effectiveness, treatment effectiveness, and costs of blindness. Future research may be best targeted at assessing how routine data may be used to describe clinical presentation rates of ARM. Other potential studies include a pilot study of the effectiveness of screening and opticians' referral patterns for AMD and a costing study of blindness as a continuum of association with deterioration in vision.

Contents

List of abbreviations

AMD	age-related macular degeneration
ANCHOR	ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in AMD
anti-VEGF	anti-vascular endothelial-derived growth factor
AREDS	Age-Related Eye Disease Study
AREDSRG	Age-Related Eye Disease Study Research Group
ARM	age-related maculopathy
ARR	absolute risk reduction
BCVA	best corrected visual acuity
BMD	bilateral macular drusen
BMES	Blue Mountains Eye Study
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CNV	choroidal neovascularisation
CNVPT	CNV Prevention Trial
CS	contrast sensitivity
DARE	Database of Abstracts of Reviews of Effects
DLTV	daily living tasks dependent on vision
EBRT	external beam radiation therapy
EF	extrafoveal
EQ-5D	EuroQol 5 Dimensions
EVI	expected value of information
FOCUS (trial)	RhuFab V2 Ocular Treatment Combining the Use of Verteporfin to Evaluate Safety
GA	geographic atrophy
GAMD	geographical age-related macular degeneration
HRQoL	health-related quality of life
HUI-3	Health Utility Index 3
ICER	incremental cost-effectiveness ratio
IVSI	intra-vitreal steroid injections
JF	juxtafoveal
MC	minimally classic
MPS	Macular Photocoagulation Study
NICE	National Institute for Health and Clinical Excellence
NSC	National Screening Committee
NVAMD	neovascular age-related macular degeneration
OR	odds ratio
PC	predominantly classic

continued

List of abbreviations *continued*

PDT	photodynamic therapy
QALY	quality-adjusted life-year
QoL	quality of life
RAP	retinal angiomatous proliferation
RCT	randomised controlled trial
RPE	retinal pigment epithelium
RR	relative risk
SAILOR	Safety Assessment Intravitreal Ranubizimab for AMD
SCI	Science Citation Index
SF	subfoveal
SF-6D	Short Form 6 Dimensions
SFRADS	SubFoveal Radiotherapy Study
SSCI	Social Sciences Citation Index
TAP	Treatment of AMD with Photodynamic Therapy
TRIP	Turning Research into Practice
TTO	time trade-off
TTT	trans-papillary thermo-therapy
VA	visual acuity
VEGF	vascular endothelial growth factor
VIP	Verteporfin in Photodynamic Therapy
VISION	VEGF Inhibition Study in Ocular Neovascularisation

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in people aged over 60 years in the western world. It is estimated that around 25% of the over-60s in the UK have some degree of visual loss because of AMD. AMD is divided into early and late. In early disease, visual acuity is normal. Late disease consists of choroidal neovascularisation (wet) and geographic atrophy (dry). Treatment options for dry AMD are still at a relatively early stage of evaluation and at present no treatment for dry AMD is routinely available. Wet AMD occurs as a result of bleeding and scarring and leads to more rapid sight loss. Current treatments for wet AMD seek to prevent further visual loss rather than cure or restore vision, although newer interventions have shown promising results that indicate that vision improvement may be possible.

The National Screening Committee have defined a set of criteria to inform the suitability of screening for a condition. The condition must be important, and the natural history and epidemiology must be understood. The screening test should be simple, safe, precise and acceptable to the general population, and there should be a defined diagnostic process following a positive test. Treatment for screen-detected disease should lead to better outcomes than treatment provided at the point of clinical diagnosis.

Aims and objectives

The aim of this study was to estimate the cost-effectiveness of screening for AMD by developing a decision analytic model that incorporated and assessed all of the above criteria. At the outset it was recognised that there was likely to be significant uncertainty in key areas of the model, and an objective of the study was to identify the major areas of uncertainty, and so inform future research priorities in this disease area.

Methods

Systematic literature reviews of the major electronic databases took place in March 2004 and were updated in January 2005. These reviews covered the epidemiology and natural history of AMD, the screening and treatment effectiveness and health-related quality of life relating to AMD. A hybrid cohort–individual sampling model was implemented to describe the range of pathways between the incidence of age-related maculopathy (ARM) and death via clinical presentation and treatment at different stages of the disease.

Significant shortfalls in the data available from the literature were apparent, so a range of primary data sources were also used to populate the model. To obtain estimates for the value of parameters deemed to be within an expert's remit, data describing some parameters were elicited from relevant experts. The data identified informed probability distributions describing the uncertainty around the model parameters.

To incorporate joint parameter uncertainty (i.e. correlations between parameters), the AMD natural history model was calibrated probabilistically. Randomly sampled sets of input parameters were assigned weights representing the accuracy of their predictions of a set of observed model outputs.

The analysis of the AMD screening model estimated the costs, numbers of quality-adjusted life-years (QALYs) and cases of blindness in a general population sample of 50-year-olds over the remainder of their lifetime, for 16 alternative screening options (including no screening). The reference case analysis incorporated current treatment options of laser photocoagulation and photodynamic therapy. Sensitivity analyses describing six alternative sets of intervention strategies, based on horizon scanning of potential future treatments for AMD, were also undertaken.

Results

There remains significant uncertainty about whether any form of screening for AMD is cost-effective. However, annual screening from age 60 years seems to provide the highest mean net benefits, but this is based on a cost-effectiveness estimate that has very poor precision (high levels

of uncertainty). The probabilistic sensitivity analysis shows that the 95% credible interval for annual screening from age 60 years ranges from this option dominating the previous option to an incremental cost per QALY of over £0.5 million. Plotting a cost-effectiveness acceptability frontier shows that although annual screening from age 60 years has the highest net benefits at a value of QALY of £30,000, the associated probability of this option being the most cost-effective option is only around 20%.

The sensitivity analyses around potential future treatment options indicate that screening may become more cost-effective with the new treatments.

Conclusions

The conclusions focus on the interpretation of the results from the perspective of defining the major areas of uncertainty, which were defined as:

- Disease progression (due to the available data, the model was built around progression of visual acuity, despite a preference for contrast sensitivity).
- Rates of clinical presentation (informed by local data from the Sheffield photodynamic therapy (PDT) clinic and responses from a survey of general ophthalmologists). Problems with this approach included a small sample of patients, the fact that the PDT database was not validated, a limited response to the survey of ophthalmologists and inconsistencies in the responses received.
- Screening test and optician effectiveness (elicited data described the probability that individuals undertaking the simple screening test at home who notice an abnormality would then present at an optician's). The model assumes that optometrists accurately refer all cases of dry and wet AMD on to hospital ophthalmologists, while not referring any cases of early ARM.
- Treatment effectiveness (a lack of long-term follow-up data inevitably requires the use of weak assumptions to extrapolate the observed effectiveness data).
- Costs of blindness (a binary threshold for costs associated with blindness was incorporated, but such costs would be more appropriately described on a continuum).

Future research may be best targeted at assessing how routine data may be used to describe clinical presentation rates of ARM. Other potential studies include a pilot study of the effectiveness of screening and opticians' referral patterns for AMD and a costing study of blindness as a continuum of association with deterioration in vision.

Chapter 1
Introduction

Age-related macular degeneration (AMD) is a progressive and degenerative disease of the retina which may ultimately lead to blindness. AMD is divided into early and late. In early disease, visual acuity (VA) is normal. Late disease consists of choroidal neovascularisation (wet) and geographic atrophy (dry).[1] Wet AMD involves the vascular membrane from the choroid sprouting under and through the retinal pigment epithelium (RPE) and Bruch's membrane to spread beneath the retina. The leaking and bleeding from these vessels cause exudative or haemorrhagic retinal detachments or both.[2] The bleeding results in scarring that replaces the outer layers of the retina, which is the cause of the loss of visual function. The cause is still unknown, and most treatment options seek to arrest decline rather than cure or restore vision.

Epidemiology

The Framingham Eye Study in 1980 stated that although only 10% of the cases of AMD were wet, this form of the disease accounted for 80% of cases with severe visual loss.[3] However, Owen and colleagues[4] challenge this view as they estimated the prevalence of wet AMD to be higher than that of dry AMD (245,000 versus 172,000 in the UK). It is thought that studies identifying dry AMD as the more common form of late AMD have usually misidentified early AMD as dry AMD [information provided by one of the authors (AB)].

As the current study is concerned with population-based screening for AMD, we looked mainly for population-based epidemiological studies which were either UK centred or were similar to the UK population. There is some evidence to suggest that AMD is more prevalent in white European populations and less common in black[5] or Chinese[6] populations. These distinctions are less important in the context of screening in the UK, as the prompt to take part in any programme would be related to age and not to ethnicity.

The incidence of AMD increases with the age of the population, and the majority of cases are found in the over-60 age group. It is not uncommon to see changes within the eye in the 50–60 age group, which could indicate that AMD may develop, even though there are no symptoms of vision loss at this stage.

The early stage of this disease is also referred to as age-related maculopathy (ARM). The appearance of drusen, which are deposits found between the RPE and Bruch's membrane, of the hard type is not necessarily associated with worrying pathological changes; indeed, drusen were noted to disappear in the Waterman study.[7] The less defined and less common soft drusen are thought to be more indicative of the development of a more serious maculopathy.[2]

General rationale for screening

The purpose of screening is to identify individuals who have a greater or lesser risk of developing a particular condition. A screening programme should alert those at greater risk to seek further investigation and reassure those with a lower risk. There are well-established criteria for screening programmes,[8] which have been adapted by the UK National Screening Committee (NSC)[9] to guide the provision of screening programmes in general, and also to inform the specification of accepted screening programmes. The criteria address four broad factors: the condition, the test, the treatment and the screening programme.

The condition, it is stated, must be important, and the natural history and epidemiology must be understood. The screening test should be simple, safe, precise and acceptable to the general population, and there should be a defined diagnostic process following a positive test. Treatment for screen-detected disease should lead to better outcomes than treatment provided at the point of clinical diagnosis. Regarding the screening programme as a whole, it is stated that plans for monitoring the programme should be defined, adequate staffing and facilities should be available to cope with expected demand and the programme should provide value for money, as compared with other areas of medical expenditure.

The last criterion states the need for screening to be cost-effective and implicitly, if screening is

cost-effective, that the most cost-effective form of screening should be implemented. Each of the preceding criteria describes factors that must be defined in order to estimate the cost-effectiveness of screening, or that will permit the confirmation of cost-effectiveness, namely monitoring. The criteria recognise the need for cost-effectiveness to be defined in terms of a generic outcome measure to allow comparison with other areas of medical expenditure, which in practice requires the estimation of quality-adjusted life-years (QALYs).

The criteria also state that "there must be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity". If such data were available, one could assess the cost–utility of alternative screening programmes alongside the relevant trials. However, there are areas in which no clinical trial evidence is available, for example, cervical cancer screening, and it is always the case that trial evidence is not available to inform all possible specifications of a screening programme, for example, with respect to the eligible population, the combination of screening tests, the interval between screening rounds and the issues over the generalisability of trial results.

It is necessary, therefore, to use some form of modelling to inform cost–utility analyses of screening programmes.

Rationale for screening for AMD

The purpose of this research was to define, with the attendant uncertainty, the extent to which screening for AMD meets the NSC's criteria. To that end, the research addressed each criterion.

Study aims and objectives

This study aimed to examine the three broad issues around the evaluation of any screening programme, relating to the natural history of the disease, the relative effectiveness of early versus late treatment and the diagnostic accuracy of the screening test in identifying early cases of the disease. In all three of these areas there exists significant uncertainty around AMD.

Our objective was to:

1. Develop a model of natural history for each relevant subcategory of the disease, that is, for dry and wet AMD, in addition to differentiating between the alternative specifications of the wet form of the disease [classic and occult, and subfoveal (SF), juxtafoveal (JF) and extrafoveal (EF)]. The description of natural history required estimates of the likelihood and timing of loss of vision in both eyes, and the impact of AMD (and loss of vision) on people's quality of life (QoL) (utility).
2. Analyse the effectiveness of alternative therapy options for alternative forms of AMD, by estimating the impact of the therapies on preventing progression, and possibly encouraging regression of the disease.
3. Identify a range of potential screening programmes, and with clinical input further evaluate those programmes that appear to be the most viable, effective and cost-effective options using the defined decision analytic modelling framework.

Research methods

The planned methods for the evaluation of a screening programme for early AMD consisted of the following main sections, which are presented in order of their presentation in the report.

Chapter 2 describes the process of development and the final structure of the model used to estimate the cost-effectiveness of screening for AMD. The model structure was iteratively developed based on the findings from the literature review and discussions with expert ophthalmologists. This chapter is presented before the review and elicitation chapters to provide the reader with a reference point for the conduct and analysis of the literature review.

Chapters 3, 4 and 5 present the results of the literature reviews that were undertaken for each of the following areas:

1. observational evidence and no treatment arms of clinical trials to describe the natural history of the different forms of AMD (Chapter 3)
2. trial evidence, clinical guidelines and systematic reviews on the effectiveness of alternative treatment options for AMD (Chapter 4)
3. evidence describing the diagnostic accuracy of alternative screening tests for AMD (Chapter 4)
4. evidence on the acceptability of screening tests in general, and for AMD in particular (Chapter 4)
5. empirical estimates of health-related quality of life (HRQoL) and patient utilities relating to AMD and screening (Chapter 5).

The analysis of the natural history of AMD was significantly enhanced by the availability of several primary datasets that contained more information than available in the secondary literature. These datasets, and their analysis, are also described in Chapter 3.

In addition to the results of the literature review for screening and treatment parameters, Chapter 4 describes the conduct and outputs from a primary elicitation study that obtained parameter estimates from experts in the field of AMD, mainly for the model's screening parameters. The parameters included in the elicitation study were those that were not adequately informed by the literature, but which were absolutely necessary to estimate the cost-effectiveness of screening for AMD.

A full systematic review of treatment effectiveness was not undertaken because the study had access to the patient-level data from the two pivotal trials of the predominant current treatment options for AMD. Data from the Treatment with AMD with Photodynamic Therapy (TAP) and Verteporfin in Photodynamic Therapy (VIP) trials of photodynamic therapy (PDT) were analysed to estimate the effectiveness parameters for PDT. Evidence relating to other current treatment options, primarily laser photocoagulation, was limited to high-quality systematic reviews. Future, potential treatment options were also included in the analysis, which were informed by the ophthalmologist authors of this report, with data obtained through a non-systematic review of key data sources, primarily the Internet.

Chapter 5 describes the utility values used in the model, but also reports on the data sources and assumptions used to populate the model's screening and treatment cost parameters.

Chapter 6 describes the process of implementing and calibrating the model against estimates of some key model outputs (e.g. age-specific numbers of AMD cases presenting clinically). The calibration process accounts for the potential correlation of all the model's input parameters by assigning probabilities to full sets of input parameters, reflecting the likelihood that each set is the most accurate set of parameter values.

Chapter 7 reports the results of the reference case probabilistic analysis, and also a number of sensitivity analyses that incorporate alternative scenarios.

Chapter 8 interprets the methods and results of the study to identify the key areas of uncertainty by identifying the input parameters that had the greatest effect on the results, and at which future research should be targeted.

Literature review methods

Separate systematic reviews of the literature were undertaken in the following areas relating to AMD: natural history, epidemiology, risk factors, screening tests, treatments and QoL. The results of these reviews are reported in separate chapters, but the methodologies for each review were similar and so are described here.

Search strategies

A comprehensive literature search was undertaken during March 2004 (updated in January 2005) to identify relevant literature pertaining to screening for AMD (Appendix 1). Four major searches were conducted which were designed to retrieve:

1. high-level evidence [i.e. guidelines, systematic reviews and randomised controlled trials (RCTs)] concerning AMD
2. papers describing the epidemiology of AMD
3. papers describing the diagnosis and diagnostic tests associated with AMD
4. cost-effectiveness and health utility literature in the field.

The following electronic bibliographic databases were searched:

- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- EMBASE
- MEDLINE
- NHS Database of Abstracts of Reviews of Effects (DARE)
- NHS Health Technology Assessment (HTA) database
- Science Citation Index (SCI)
- Social Sciences Citation Index (SSCI)
- Turning Research into Practice (TRIP) database.

Attempts were also made to identify 'grey' literature by searching appropriate databases (e.g. Health Management Information Consortium, Index to Theses, Dissertation Abstracts), current research registers (e.g. National Research Register, Research Findings Register, Current Controlled Trials) and relevant websites (e.g. Macular Disease

Society, Moorfields Eye Hospital, Royal National Institute for the Blind). The reference lists of included studies and relevant review articles were also checked.

Inclusion and exclusion criteria

The team devised the criteria for inclusion and exclusion. References were retrieved by one reviewer selecting from a specific subject heading and then checked by a second reviewer.

In the first round of sifting the retrieved references, we used the following criteria; as the work progressed, it became apparent that there were significant gaps in the literature in some of these categories, which we will report later.

The searches were conducted as described above. When the team began sifting the papers by category it became evident that there was often a mismatch between the key word description and, for example, the abstract. We made a decision to re-classify where possible as we sifted. The papers which we identified as being potentially useful in this review were separated into the categories listed below. We found this to be the most efficient method of making use of papers which did not match their search criteria or were relevant in more than one category.

1. *Prevalence and incidence*
   (a) Inclusion: primary research, systematic review or high-quality review
   representative population-based sample
   (b) Exclusion: non-AMD

2. *Risk factors*
   (a) Inclusion: primary research, systematic review or high-quality review
   (b) Exclusion: non-AMD
   risk factors not applicable to a screening programme, e.g. genetic risk markers
   pathogenesis studies

3. *Natural history progression*
   (a) Inclusion: primary research, systematic review or high-quality review
   data reported, including baseline measurement and measurement(s) at subsequent time point(s)
   (b) Exclusion: non-AMD
   drusen-based prognosis
   highly selected population

4. *Quality of life studies*
   (a) Inclusion: primary research
   utility data or appropriate HRQoL measures used
   data relates to alternative states of visual impairment

5. *Economic studies*
   (a) Inclusion: screening evaluations
   resource use and cost data presented

6. *Screening studies*
   (a) Inclusion: potential screening test
   data reported on sensitivity and specificity

7. *Diagnostic test studies*
   (a) Inclusion: potential diagnostic test
   data reported: accuracy, cost oftests.

The search resulted in 388 studies. The number of studies identified in each category is presented in Appendix 1. The data were extracted by one reviewer and checked by a second reviewer using specially developed data extraction tables.

Chapter 2

The AMD screening model

Decision modelling is about representing a disease or condition as a number of health states. Important clinical events are demonstrated by transitions between these states. The preferred, and most common, modelling approach to evaluating screening programmes is to describe the progression of disease in a population without screening, that is the natural history of the disease to the point of clinical presentation, followed by the post-diagnosis (and treatment) prognosis of the disease given current treatment options. Disease progression is generally described with respect to factors that influence treatment eligibility and treatment effectiveness. Possible screening programme options are then 'laid on top' of the natural history model in order to predict the effects of screening on disease progression via the potential diagnosis of the condition at earlier stages.

All models are simplifications of reality, which may be due to an incomplete understanding of the process being modelled (e.g. the pathogenesis of a disease) or practical constraints on the level of detail that can be incorporated within a computer-based model. The more complex the model, the more time is required to build, verify and analyse the model. Given a fixed period for a model-based evaluation, the general modelling objective is to develop a feasible model structure that is based on as strong a set of assumptions as possible.

General framework

The development of the model structure for the evaluation of screening for AMD was refined in an iterative process that involved frequent conversation with expert ophthalmologists, improving understanding of the disease area through review of the literature and assessment of optimal methods for incorporating the available data for populating or calibrating the model.

The aim of the AMD model is to describe the progression of both eyes with respect to AMD over the lifetime of a general population. The principal outcome measure for the evaluation of screening for AMD is the QALY, which is estimated as a function of the VA of the best seeing eye. Costs are associated with the act of screening, diagnosis, treatment for ARM and the consequences of blindness. Therefore, the model must describe the VA of both eyes at all ages and differentiate between alternative states of ARM that affect treatment eligibility and treatment effectiveness. It was recognised that current treatment options for AMD are limited, but the developed model was intended to provide a tool for updating estimates of the cost-effectiveness of screening as and when new treatment options become available. A range of baseline assumptions are stated to place a boundary around the scope of the model:

- No-one under the age of 50 years develops any form of ARM.
- All individuals in a population have two eyes that are at risk of developing ARM.
- There are no practical risk factors that could be used to define a population subgroup at whom screening could be targeted.
- Individuals live to a maximum of 100 years.
- ARM does not affect life expectancy; all individuals have the same probability of dying at any given age.
- The model moves forward in cycles of 1 year.

The above assumptions inform a model structure that describes the progression of two eyes in a homogeneous set of individuals from the age of 50 years. The homogeneity refers to the probabilities of disease incidence and progression, not to the actual experience of disease.

Risk factors for AMD are identifiable (e.g. smoking), but it is not practically or ethically feasible to target screening based on risk factors. It may be hypothesised that individuals in different risk factor subgroups may have alternative propensities to screen for AMD, or to comply with treatment, but given the scarcity of data to inform the additional input parameters that would be required to incorporate such hypotheses, the research team decided against their inclusion.

The assumption of constant life expectancy is a conservative assumption, but because the evidence regarding the impact of sight on mortality is not definitive, we felt it to be a suitable assumption.

The model's cycle length of 1 year was chosen for pragmatic reasons to ease the implementation of the model. Although it is recognised that ARM may progress between the defined health states (see the next section) more than once within a year, the model allows for transitions between non-sequential vision states, and the estimated transition probabilities account for the annual cycles. The main impact is that the model may overestimate the time between transitions slightly, but this is unlikely to have a material effect on the model's results.

Lesion states

The next stage of the development of the model structure involved the definition of the disease states to be included. The three broad stages of ARM may be defined as early ARM, dry AMD and wet AMD, although within each of these stages multiple and varying subcategories have been defined in the literature. The following ARM states are described within the model:

- early ARM
- dry AMD
- EF occult wet AMD
- EF minimally classic (MC) wet AMD
- EF predominantly classic (PC) wet AMD
- JF occult wet AMD
- JF MC wet AMD
- JF PC wet AMD
- SF occult wet AMD
- SF MC wet AMD
- SF PC wet AMD.

A range of other options was discussed by the research team, such as the subcategorisation of early ARM, which is commonly disaggregated in the literature; for example, the Rotterdam study defines five separate categories of early ARM, ranging from the presence of soft distinct drusen to the presence of soft, indistinct or reticular drusen with pigmentary irregularities.[2] However, there were few data describing progression rates between substages of early ARM, or between substages of early ARM and the AMD states. Also, the limited evidence around potential treatment options for early ARM did not distinguish between different stages of early ARM.

The main option for subcategorising dry AMD was into two states describing dry AMD affecting the fovea and dry AMD not affecting the fovea. However, few studies differentiate between these states, with respect to disease progression to wet AMD, or with regard to potential treatment options.

The description of alternative wet AMD states is most detailed because the type (occult, MC or PC) and location (EF, JF, or SF) of wet AMD is important in determining treatment options and treatment effectiveness. However, additional subcategories of wet AMD could have been included in the model. Predominantly classic lesions may be defined as either 100% classic or PC, although these lesion types were combined as treatment eligibility and effectiveness is generally defined for the combined group of lesions.

The terms classic and occult are clinical, morphological descriptions defined by fluorescein angiography characteristics. A broader spectrum of occult wet AMD may be defined to include entities such as polypoidal choroidal neovascularisation and retinal angiomatous proliferation (RAP).[10] RAP is associated with proliferation of intraretinal capillaries in the paramacular area and a contiguous telangiectatic response, which itself has three defined stages in a progressive vasogenic sequence. At this stage, no data on differential rates of disease progression and treatment effectiveness for RAP and non-RAP occult lesions were identified, so the model retains the single category of occult lesions.

The primary additional factor that was considered for inclusion in the AMD screening model was lesion size. Lesion size has been defined as a potentially relevant criterion informing treatment effectiveness (PDT may be less effective in larger lesions), and some primary data were identified that described lesion size progression. However, analyses of the data informing disease progression of wet AMD (described in more detail in Chapter 3, 'Visual acuity', pp. 33–34) consistently identified size as a statistically insignificant covariate when estimating deterioration in VA for individuals with wet AMD. A lack of data describing the size of lesions at the point of clinical presentation also reduced the usefulness of including lesion size as a further prognostic indicator in the model and, as the inclusion of size would increase the complexity of the model significantly, the decision was taken to restrict the categorisation of wet AMD to the above-listed states.

Lesion progression

Figure 1 describes the possible pathways of progression between the main categories of ARM

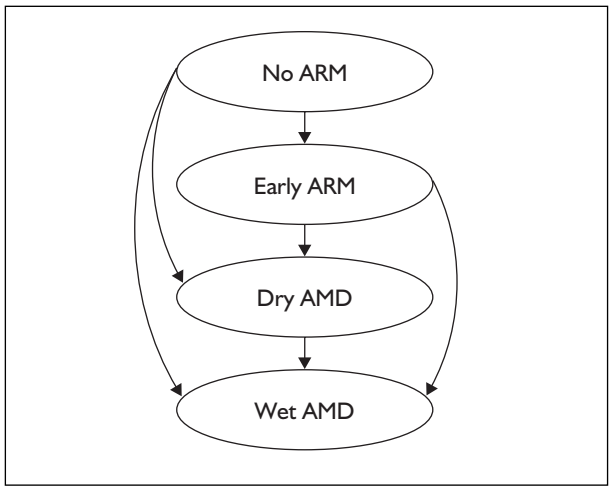

FIGURE 1 *Lesion pathways between broad ARM categories*

states: early ARM, dry AMD and wet AMD. The figure shows that the model does not assume a strict linear pathway where early ARM is the precursor to all subsequent ARM states. This approach is due to theoretical uncertainties about the true pathogenesis of ARM as elaborated by the expert ophthalmologist members of the research team, but also owing to practical considerations due to the format of the data available to populate the model. Even if all dry and wet AMD pass through an early ARM stage, some of these transitions are not observed by prospective studies that examine populations at sequential time points. The reported direct incidence rates for dry and wet AMD are used in the model to represent direct transitions from 'no ARM' to dry or wet AMD. Similarly, direct transitions from early ARM to wet AMD are reported in the literature, and used directly to populate the AMD screening model.

The same lesion pathways are used to describe lesion incidence and progression in both eyes, although incident ARM may only be described in eye 2 from the age at which eye 1 first develops some form of ARM.

Figure 2 describes the model's representation of possible pathways between alternative states of wet AMD. Patients may enter the wet AMD model in any of the nine vision states, from which point the possible pathways that an eye may follow are demonstrated by the presented arrows. The assumptions incorporated in the structure include:

- Lesion location may change from EF to JF or SF or from JF to SF.
- Lesion type may change from occult to MC or PC or from minimally classic to PC.
- Lesion type and location may change separately or simultaneously.

Modelling clinical presentation and screen detection

The model assumes that the impact of any costs and benefits associated with individuals presenting with visual symptoms unrelated to AMD are neutral, that is, the costs equal the benefits. Screening may, for example, lead to an increase in the number of individuals undergoing NHS-funded eye examinations, which would lead to increased resources being spent on providing eye

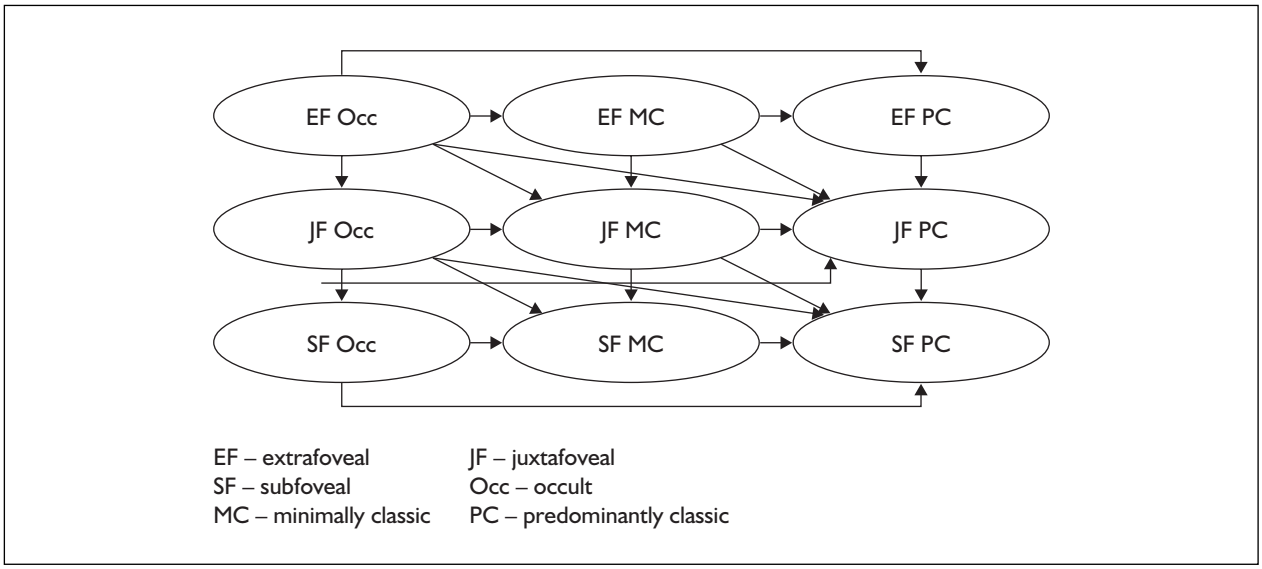

FIGURE 2 *Lesion pathways between wet AMD lesion states*

examinations. However, it is assumed that eye examinations are provided because they lead to some form of benefit to the population. As no readily available data were identified describing the costs and benefits of such interventions, and primary investigation of such effects was beyond the scope of this study, the simplifying assumption of equal costs and benefits was made. Therefore, the clinical presentation of individuals without any form of ARM is not described by the model.

Individuals with one or both eyes with any form of ARM may present in the year of incidence, or in any year in which one or both lesions progress. The simplifying assumption that individuals will not present clinically in years in which existing ARM lesions are no different to the previous year was made, as a year was considered to be a long time to go without noticing symptoms.

In the analyses in which screening programme are included, the model applies a probability that individuals respond to a reminder to screen for AMD (screening intervals of 1, 2, 3 and 5 years are tested). For the proportion of individuals who self-test for AMD, probabilities that screening identifies different states of preclinical ARM in the worst affected eyes are specified for early ARM, dry AMD, EF wet AMD, JF wet AMD and SF wet AMD.

Modelling visual acuity

The principal outcome measure for the evaluation of screening for AMD is QALYs, which are estimated by applying utility weights to the years of life of each individual in the model. The utility weights may be a function of the age of an individual and their VA, so the model must capture VA at each year of life.

VA is measured in logMAR units in the model, where a logMAR score of 0 is assumed to be equivalent to 6/6 vision using the metric version of the Snellen chart. The following assumptions are made in the model with respect to measuring VA:

- The best possible vision is defined as a logMAR score of 0.
- All eyes with no ARM or early ARM have a logMAR score of 0.
- Upon incidence of dry or wet AMD, eyes are assigned a logMAR score worse than 0.
- VA associated with dry AMD may deteriorate over time even without progression to wet AMD.
- VA associated with EF or JF wet AMD deteriorates upon progression to alternative wet AMD states (by either type or location).
- VA associated with SF wet AMD deteriorates over time based on VA and lesion type at the point of incidence of SF wet AMD.

The health impact of changes in VA levels was estimated by converting the VA level into utility values that reflect the HRQoL of the patient, as depicted in *Figure 3*. Utility values are generally described as values between 0 and 1 that are used to weight the remaining lifetime of patients to reflect their QoL; for example, patients living for 10 years with a constant utility value of 0.8 are said to gain 8 (0.8×10) QALYs. Algorithms are available for converting VA scores to utility values (see the section 'Utility values', p. 50 for details of the algorithms).

Modelling treatment

The reference case model describes only treatment options considered to be current practice in the NHS, which limits treatment to PDT for some JF

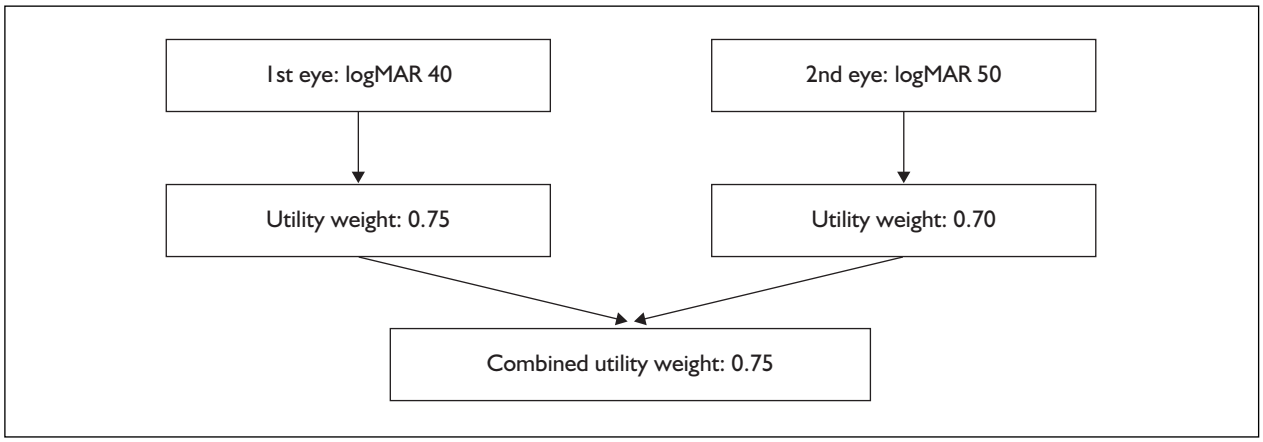

FIGURE 3 *Utility value estimation*

and SF lesions, and laser photocoagulation for a proportion of EF lesions (see the section 'Calibration outputs', p. 53, for more details). For the treatment of JF and SF lesions, a probability distribution describing the probability that treatment maintains VA at the same level at which treatment is instigated was defined for each relevant disease category. For each iteration of the model, a probability is sampled from each treatment effectiveness distribution. This is implemented by having each eye sample a random number between 0 and 1 to determine whether treatment is effective in maintaining VA. If the sampled value is below the sampled probability that VA is maintained, then treatment is effective and VA in that eye is maintained at that level for the remainder of the patient's life. If treatment is ineffective, VA progresses as if treatment had not been received.

For the treatment of EF wet AMD, a similar process to that described in the previous paragraph is defined whereby VA is either maintained for the remainder of the patient's lifetime, or continues as if treatment had not been received. However, if laser photocoagulation is unsuccessful, an eye may receive subsequent intervention with PDT if the eye progresses to a treatable form of JF or SF wet AMD (as determined by the natural history of the disease).

In additional analyses of the model, where potential interventions for ARM are included, the impact of treatment on disease progression is modelled using two basic approaches. First, some interventions are targeted at preventing progression between the broad ARM states, such as from early ARM to dry or wet AMD, or from dry AMD to wet AMD. In these cases, effective treatments (as defined by a similar process to that described for the main model analysis) are assumed to maintain the eye in the state, and at the same level of VA, at which the intervention was implemented.

Other potential interventions are aimed at maintaining or improving VA in eyes with wet AMD, primarily JF or SF. Eyes for which treatment is sampled as being effective are assigned maintained VA or improved VA over the remainder of their lifetime, based on the reported proportions of eyes experiencing either outcome.

Modelling costs

Costs are incurred due to screening, diagnosis and surveillance, treatment and blindness and rapidly deteriorating vision. Further details of the assumptions around the costs included in the model are described in Chapter 7. The costs of screening include only the cost of organising and distributing reminders to individuals aged over 50 years to self-test for AMD. The model attaches a unit cost of screening to each living individual at each age at which a screening reminder is due (e.g. at 3-yearly intervals after the age of 50 years).

Costs associated with diagnosis are attached at the point at which individuals present with ARM, the costs depending on the form of ARM at presentation. If no treatment is offered, the costs of surveillance are applied at each point at which VA deteriorates.

Aggregate (discounted) treatment costs are applied at the point at which treatment is instigated. Eyes treated for EF wet AMD may receive subsequent treatment for JF or SF wet AMD. No further costs are applied to eyes with JF or SF wet AMD until the point at which both eyes have 6/60 vision or worse, at which point the annual costs associated with blindness and rapidly deteriorating vision are applied to the surviving proportion of individuals each year.

Chapter 3

Natural history parameters

This chapter presents the results from the reviews of the literature aimed at informing the model's natural history parameters, including first eye and fellow eye incidence of AMD, and progression from early ARM, from dry AMD and between wet AMD states. Following presentation of the identified data, the relative benefits of the alternative data sources are discussed and the estimation of the relevant model parameters is described.

The first section describes the findings from a review of risk factors for AMD, which was undertaken in order to identify any relevant factors that could be used to define high-risk groups at whom screening could be targeted.

Risk factors

Several studies have been conducted looking at risk factors for the development of AMD. In reviewing these studies, we were interested in identifying risk factors that could be used to (1) identify high-risk groups for targeted screening and (2) identify high-risk activities which needed to be included in the analysis of the model.

Identifying high-risk groups for targeted screening

In adult screening programmes currently in place in the UK, a call and recall service is used to notify and recruit individuals for screening. In this model, routinely identifiable data are used. For example, cervical cancer screening is targeted at women aged 25–50 years and breast cancer screening is targeted at women aged 50 years and over. The population health record includes age and sex, so identification of the target group is easily possible.

Women who have not had penetrative sex are at a much lower risk (some would say no risk at all) of cervical cancer. These women are invited to decline screening based on their sexual history but the invitation is still sent. Similarly, women who have had hysterectomies or breast excision surgery are identified by GPs in the pre-invitation phase.

For AMD screening, we considered a notification system being used to remind people to test their vision (however this would be done). For this we needed to consider which groups within the population register would be notified.

Several large studies have shown the link between advanced age and onset of AMD. In Smith and colleagues' study,[11] the combined analysis of three cohort studies was used to calculate the prevalence of AMD at various ages. This gave a prevalence of 0.2% in the population aged 55–64 years, rising to 13% in those older than 85 years. Most other and subsequent trials have presented data adjusted for age. This same study reported no significant difference by gender.

Identifying high-risk activities for targeted screening

Several high-risk activities were identified through the systematic review, as described in *Table 1*. Recent changes in general practice in the UK have led to the recording of several of these factors as a routine. However, none of the studies quoted relates to a British population. As such, the link between factors identified in the research setting and those identified through routine care within general practice is not clear.

It was decided to model screening as though none of these factors was highlighted on notification. As such, patients with these conditions are modelled as equally likely to screen themselves as others without that factor in the population. This may not be the case, since smoking, raised BMI and hypertension may be suggestive of an individual that would not take up health-promoting activities.[11–19]

However, with no studies looking at uptake of any of the screening methods within the UK population, we contend that such differential uptake will need to be addressed if and when screening is introduced, rather than at this stage.

Since we did not factor in these activities and risks in the uptake stage of the model, we also did not use these factors to determine likely presentation, success of treatment or mortality. For these we applied figures that are appropriate for individuals at that age and sex – some of whom will have the risk factors, whereas others will not. To take one example: a smoker may be seen to be more likely

TABLE 1 *Potential risk factors for the development of AMD*

Activity or risk	OR or RR	Study reference
Smoking (current and past versus never smoked)	OR = 1.7 (95% CI 1.1 to 2.6)[a] OR = 1.3 (95% CI 1.01 to 1.69)[b] OR = 1.91 (95% CI 1.57 to 2.33)[a] (Former vs never) OR = 2.8 (95% CI 1.1 to 6.9)[a] (Former vs never) RR = 2.1 (95% CI 1.1 to 3.9)[c] (Current vs never) OR =3.12 (95% CI 2.10 to 4.64)[a]	Seddon and colleagues[12] Christen and colleagues[13] Age-Related Eye Disease Study Research Group[14] Delcourt and colleagues[15] Vingerling and colleagues[16] Smith and colleagues[11]
BMI	(BMI >30) OR = 2.29 (95% CI 1.00 to 5.23)[c] (BMI >31 vs <23.6) OR = 1.43 (95% CI 1.08 to 1.91)[a]	Delcourt and colleagues[17] Age-Related Eye Disease Study Research Group[14]
Raised blood pressure	(Treated normal) OR = 2.29 (95% CI 1.12 to 4.69)[d] (Treated high) OR = 3.29 (95% CI 1.24 to 8.79)n[d] (Hypertension) OR = 1.45 (95% CI 1.20 to 1.76)[a] (Hypertension) no association	Klein and colleagues[18] Age-Related Eye Disease Study Research Group[14] Klein and colleagues[19]
Lens opacity	OR = 1.32 (95% CI 1.08 to 1.60)[a] (Any cataract) OR = 1.30 (95% CI 1.04 to 1.63)[e] (Lens opacity or previous cataract surgery) OR = 1.44 (95% CI 1.09 to 1.89)[a]	Age-Related Eye Disease Study Research Group[14] Klein and colleagues[20] Chaine and colleagues[21]

BMI, body mass index; CI, confidence interval; OR, odds ratio; RR, relative risk.
[a] Multivariate analysis.
[b] Age and treatment adjusted.
[c] Age and sex adjusted.
[d] Adjusted for age, sex, smoking, drinking, vitamin intake.
[e] Generalised estimating equations.

to develop AMD, but less likely to present. If they were equally likely to self-screen, they would benefit from earlier detection of their lesion and consequent benefits of early treatment. However, if they were less likely to take up screening, this benefit would not be achieved. Similarly, if they continued to smoke, the benefit of treatment in arresting AMD in one eye might be cancelled out by the development of AMD in the other eye as a consequence of smoking.

It is clear that there is a complex relationship between risks and outcomes which the available evidence does not allow us to model for the UK population. We took the view that men and women of advanced age should be targeted for screening, but will allow for various lower age limits to be tested in the model. For the purposes of the model, we applied standard distributions of risk of prevalence, presentation and treatment effectiveness based on age but on no other factor.

Incidence

We retrieved and reviewed 39 studies (summary tables are presented in Appendix 2). With respect to populating the AMD screening model, data were required that described incidence by disease type and by first eye and fellow eye. Single point estimates of disease prevalence were considered of limited applicability as these data do not permit the estimation of age-specific incidence rates, which are also required by the screening model. The following sections describe the studies describing relevant data on the incidence of ARM in the first and fellow eyes, including commentaries on the use of these data to inform age- and stage-specific incidence rates for both eyes.

First eye incidence

Seven studies were identified that presented some form of relevant data to inform the incidence of ARM in a first eye. The data extracted from these studies, and the re-analyses of the reported data, are presented in this section.

The Rotterdam study

The Rotterdam Study was a prospective study of over 10,000 people aged 55 years or older living in a middle-class suburb of Rotterdam, The Netherlands.[2] Individuals were examined at baseline, 2 years and 6.5 years. The exact data are used to estimate the age-specific incidence of early

ARM, and confidence intervals (CIs) are estimated on the basis of person-years at risk. The use of person-years as the denominator informing the CIs will underestimate the true uncertainty, as person-years are estimated from baseline to follow-up for each participant, whereas the events of interest occurred prior to the follow-up point. However, as the proportion of cases is small, the underestimate is assumed to be insignificant. *Table 2* presents the age-specific annual probabilities of early ARM and the associated 95% CIs.

The estimation of the age-specific probabilities for the incidence of AMD (from no ARM) requires the combination of the presented incidence rates for individuals initially in stages 0 and 1. The AMD incidence rate presented in *Table 3* is estimated as a weighted proportion of the separately presented rates for ARM categories 0 and 1, based on the distribution of patients between categories 0 and 1 at follow-up (the distribution of ARM stages at baseline is not presented).

TABLE 2 *Annual incidence of early ARM (per 1000 person-years) in the Rotterdam study*[2]

Age (years)	Person-years	Cases	Mean	95% CI	
				Lower	Upper
55–59	2179	3	1.4	0.4	4.3
60–64	6085	32	5.3	3.7	7.4
65–69	6376	69	10.8	8.6	13.7
70–74	5102	97	19.0	15.6	23.2
75–79	3212	102	31.8	26.2	38.6
80+	2159	110	50.9	42.3	61.4

TABLE 3 *Annual incidence of AMD (per 1000 person-years) in persons with no ARM*

Age (years)	Person-years	Cases[a]	Mean[b]	95% CI	
				Lower	Upper
60–69	12461	3.6	0.289	0.1	0.7
70–79	8314	6.5	0.78	0.3	1.6
80+	2159	3.0	1.399	0.3	4.1

[a] The numbers of cases are estimated from the reported mean rate and implied person-years in order to inform the CIs.
[b] The mean rates are estimated as weighted proportions of the separately presented rates for ARM categories 0 and 1, based on the distribution of patients in categories 0 and 1 at follow-up.

To inform CIs for the AMD incidence rate, the age-specific numbers of cases of AMD developing in persons previously in stages '0 + 1' and '2 + 3' are estimated from the combined incidence rates and the implied person-years at risk. The combined estimates of the number of AMD cases in each age group occurring in persons in categories '0 + 1' and '2 + 3' (see the section 'Visual acuity', p. 32, for a description of progression rates from early ARM) are compared with the observed aggregate numbers of cases of AMD occurring in each age group. The results of this comparison are presented in *Table 4*, which shows a reasonable degree of agreement. As these data only inform the CIs, the effect of the difference between the observed and predicted values is limited.

Table 5 presents the age-specific distribution of AMD between dry and wet AMD, which can be applied to the aggregate AMD rate to estimate the individuals rates for dry and wet AMD.

The Copenhagen study

The Copenhagen study was a population-based cohort study that included 946 residents (age range 60–80 years) of Copenhagen who were examined between 1986 and 1988 and 359 persons (97.3% of survivors) were re-examined between

TABLE 4 *Results of validation check for predicted number of AMD cases occurring from individuals with no ARM or early ARM*

Age (years)	Total observed	Predicted		
		Category 0 + 1	Category 2 + 3	Total
60–69	6	3.6	3.6	7.2
70–79	24	6.5	16.7	23.2
80+	17	3.0	11.7	14.8
Total	47	13.1	32.1	45.2

TABLE 5 *Distribution of dry and wet AMD in incident cases of AMD in persons without early ARM: the Rotterdam study*[2]

Age (years)	Cases of AMD		Proportion Wet AMD		
	Dry	Wet	Mean	95% CI	
				Lower	Upper
60–64	0	1	1	0.05	1
65–69	3	2	0.4	0.0527	0.8534
70–74	3	7	0.7	0.3475	0.9333
75–79	5	9	0.6429	0.3514	0.8724
80+	8	9	0.5294	0.2781	0.7702
Total	19	28	0.5957	0.4427	0.7363

2000 and 2002.[22] It is stated that "Because the correlations are high between eyes, the following analyses for lesions associated with ARM are presented for the right eye only". It is reported that aggregate incidence for late ARM was 14.8% for the right eye and 16.9% for either eye, and 31.5% and 37.8% for early ARM in the right or either eye, respectively.

It was not possible to estimate separate incidence rates for AMD for persons with and without early ARM at baseline, although we know that 254 eyes were at risk of early ARM and 297 were at risk of AMD, so presumably 43 (14.5%) had early ARM at baseline. *Table 6* presents the estimated incidence rates for early ARM and AMD. The Copenhagen study did not report person-years at risk, and CIs were estimated on the basis of persons at risk. Person-years may be estimated as the number of persons in each group multiplied by 14.

The Blue Mountains Eye Study

The Blue Mountains Eye Study (BMES) examined 3654 residents between 1992 and 1994 and re-examined 2335 (75.1% of survivors) between 1997 and 1999.[23] As in the Copenhagen study, incidence rates of AMD are not presented separately by initial stage, that is, the rates of late ARM include people with early ARM at baseline, which is 10% in 70–80-year-olds and 20% in 80+-year-olds. *Table 7* presents the incidence rates with CIs for early ARM and AMD, which were based on the reported cases and the stated number of persons at risk of each outcome.

The Beaver Dam study

The Beaver Dam (Wisconsin) study was a population-based cohort study that initially examined 4926 persons (age range 43–86 years) between 1988 and 1990;[24] 3684 participated in a 5-year follow-up examination and 2764 participated in a 10-year follow-up. As in the Copenhagen and Blue Mountains studies, incidence rates of AMD were not presented separately by initial stage, that is, the rates of AMD include people with early ARM at baseline, which is 17% in 55–64-year-olds and 41% in 75+-year-olds. *Table 8* presents the incidence rates with CIs for early ARM and AMD, which were based on the reported cases and the stated number of persons at risk of each outcome.

Separate incidence rates for dry and wet AMD were presented only for the right eye, as a function of drusen type and drusen size. These data were used to estimate the proportion of wet AMD cases, as presented in *Table 9*. The alternative approaches to estimating the proportion result in a similar estimate of around 60% choroidal neovascularisation (CNV) cases.

The Age-Related Eye Disease Study

The Age-Related Eye Disease Study (AREDS) was a randomised, double-blind, placebo-controlled evaluation of the AREDS formulation of high-dose antioxidants and zinc.[25] Eleven clinical centres enrolled 4757 participants (aged 55–80 years) between 1992 and 1998; 1117 patients in category 1 (no ARM) at baseline had few if any drusen.

TABLE 6 *Incidence rates in the right eye for early ARM and AMD in the Copenhagen study*[23]

Age (years)	At risk	14-year incidence			Annual incidence		
		Mean	95% CI		Mean	95% CI	
			Lower	Upper		Lower	Upper
Early ARM							
60–64	92.5	0.25	0.174	0.349	0.020	0.014	0.030
65–69	92.5	0.33	0.240	0.430	0.028	0.019	0.039
70–74	34.5	0.36	0.218	0.529	0.031	0.017	0.052
75–80	34.5	0.5	0.346	0.668	0.048	0.030	0.076
Dry AMD							
60–64	92.5	0.015	0.003	0.059	0.001	0.000	0.004
65–69	92.5	0.015	0.003	0.059	0.001	0.000	0.004
70–74	34.5	0.135	0.049	0.271	0.010	0.004	0.022
75–80	34.5	0.135	0.049	0.271	0.010	0.004	0.022
Wet AMD							
60–64	92.5	0.055	0.024	0.122	0.004	0.002	0.009
65–69	92.5	0.075	0.031	0.136	0.006	0.002	0.010
70–74	34.5	0.135	0.049	0.271	0.010	0.004	0.022
75–80	34.5	0.235	0.127	0.407	0.019	0.010	0.037

TABLE 7 *Incidence rates for early ARM and AMD in the Blue Mountains study*[23]

Age (years)	5-year incidence			Annual incidence		
	Mean	2.5th CI	97.5th CI	Mean	2.5th CI	97.5th CI
Early ARM						
<60	0.032	0.020	0.048	0.006	0.004	0.010
60–69	0.074	0.058	0.093	0.015	0.012	0.019
70–79	0.183	0.150	0.220	0.040	0.032	0.049
80+	0.148	0.081	0.239	0.032	0.017	0.053
Dry AMD						
<60	0.000	0.000	0.004	0.000	0.000	0.001
60–69	0.005	0.002	0.012	0.001	0.000	0.002
70–79	0.017	0.008	0.031	0.003	0.002	0.006
80+	0.036	0.010	0.090	0.007	0.002	0.019
Wet AMD						
<60	0.000	0.000	0.004	0.000	0.000	0.001
60–69	0.005	0.002	0.012	0.001	0.000	0.002
70–79	0.024	0.013	0.041	0.005	0.003	0.008
80+	0.036	0.010	0.090	0.007	0.002	0.019
AMD[a]						
<60	0.000	0.000	0.004	0.000	0.000	0.001
60–69	0.006	0.002	0.014	0.001	0.000	0.003
70–79	0.024	0.013	0.041	0.005	0.003	0.008
80+	0.054	0.020	0.114	0.011	0.004	0.024

[a] Late ARM includes geographic atrophy only if it involves the fovea.

TABLE 8 *Incidence rates for early and late ARM in the Beaver Dam study*[24]

Age (years)	At risk	Cases	10-year incidence			Annual incidence		
			Mean	2.5th CI	97.5th CI	Mean	2.5th CI	97.5th CI
Early ARM								
43–54	1136	47	0.041	0.031	0.055	0.004	0.003	0.006
55–64	856	92	0.107	0.088	0.130	0.011	0.009	0.014
65–74	654	154	0.236	0.203	0.270	0.027	0.022	0.031
75+	185	68	0.367	0.298	0.441	0.045	0.035	0.057
AMD								
43–54	1250	1	0.001	0.000	0.004	0.000	0.000	0.000
55–64	1032	10	0.010	0.005	0.018	0.001	0.000	0.002
65–74	899	40	0.044	0.032	0.060	0.004	0.003	0.006
75+	315	30	0.095	0.065	0.133	0.010	0.007	0.014

Upon contacting the AREDS team, we obtained unpublished data describing the detailed progression of persons in category 1 at baseline. *Table 10* presents the age-specific 5-year and annual incidence rates, with corresponding CIs, for early and late ARM.

The Melton Mowbray study

The Melton Mowbray study was undertaken between 1980 and 1990 in a small English town whose entire population was served by a single general practice.[26] Sparrow and colleagues specify three categories of AMD (none, minor and major). The main problems with these data are that the analysis is presented by eye and the ARM state of the fellow eye is not reported, and that the age distribution of the responders is not presented, as shown in *Table 11*.

Eye 1 incidence commentary

Estimates of the age-specific incidence of early ARM, dry AMD and wet AMD in the first eye are required for the model. It is currently accepted that the presence of drusen and early ARM is a

TABLE 9 *Estimation of the distribution of dry and wet AMD from the Beaver Dam study*[24]

Parameter	Dry AMD			Wet AMD			Proportion CNV
	At risk	10-year incidence	Estimated cases	At risk	10-year incidence	Estimated cases	
Max. drusen diameter (μm)							
0	381	0	0	355	0	0	
<63	2191	0	0	2158	0	0	
63–125	527	0.003	1.58	517	0.01	5.17	
125–250	229	0.044	10.08	229	0.045	10.31	
>250	59	0.117	6.90	64	0.244	15.62	
Total			18.56			31.09	0.63
Drusen type							
None or hard indistinct	378	0	0	362	0	0	
Hard distinct	2465	0	0	2447	0	0	
Soft distinct	246	0.012	2.95	239	0.02	4.78	
Soft indistinct	241	0.065	15.67	248	0.097	24.06	
Total			18.62			28.84	0.61

TABLE 10 *Incidence rates for early and late ARM for persons with no ARM in the placebo arm of the AREDS trial*[25]

	5-year risks					Annual risks		
	Cases	At risk	Mean	95% CI		Mean	95% CI	
				Lower	Upper		Lower	Upper
Age 55–59								
Categories 2 or 3	0	2	0.000	0.000	0.776	0.000	0.000	0.259
Category 4	0	2	0.000	0.000	0.776	0.000	0.000	0.259
Age 60–64								
Categories 2 or 3	30	151	0.199	0.138	0.271	0.043	0.029	0.061
Category 4	0	151	0.000	0.000	0.020	0.000	0.000	0.004
Age 65–69								
Categories 2 or 3	33	187	0.176	0.125	0.239	0.038	0.026	0.053
Category 4	1	187	0.005	0.0001	0.029	0.001	0.000	0.006
Age 70–74								
Categories 2 or 3	27	118	0.229	0.157	0.315	0.051	0.033	0.073
Category 4	1	118	0.008	0.0002	0.046	0.002	0.000	0.009
Age 75–80								
Categories 2 or 3	9	30	0.300	0.147	0.494	0.069	0.031	0.127
Category 4	0	30	0.000	0.000	0.095	0.000	0.000	0.020

TABLE 11 *Incidence rates for minor and major ARM for persons in the Melton Mowbray study*[26]

	Cases	At risk	7-year incidence	95% CI		Annual incidence	95% CI	
				Lower	Upper		Lower	Upper
Minor AMD	13	27	0.481	0.269	0.681	0.090	0.044	0.150
Major AMD	3	27	0.111	0.024	0.292	0.017	0.003	0.048

risk factor for AMD, but that persons may progress directly to AMD (dry or wet) without experiencing early ARM [information provided by one of the authors (UC)]. A problem with data describing the incidence of early ARM and AMD (from no ARM) in the first eye is that it is not possible to observe whether incident cases of AMD progressed through early ARM prior to developing AMD. The longer the period between follow-up points, the more likely it is that a proportion of incident AMD cases experienced prior early ARM. The assumption that all observed incident cases of AMD occur directly without prior early ARM provides the upper estimate for the number of direct cases of AMD.

A wide range of estimates of the incidence of ARM is presented in the literature. The Rotterdam study, based on follow-up at 2 years and 6.5 years, reports annual incidence rates of between 0.0014 (ages 55–59 years) and 0.051 (over 80 years) for early ARM. Annual incidence rates for AMD are between 0.00029 (60–69 years) and 0.0014 (over 80 years).

The 14-year period between baseline and follow-up in the Copenhagen study[11] is likely to lead to the greatest overestimate of the number of cases of directly incident AMD (and underestimate of incident early ARM). It is also not possible to distinguish the cases of AMD that occurred in patients with no ARM, and early ARM, at baseline. One can only estimate that around 14.5% of the population had early ARM at baseline. Age-specific incidence rates are presented for the right eye, which is not helpful as these incidence rates include cases in which the left eye developed ARM previously. In summary, the only useful data presented by the Copenhagen study are the aggregate annual incidence of early ARM and AMD in either eye, which are estimated to be 0.033 and 0.013, respectively. The combined annual incidence of early ARM in the Copenhagen study (0.033) is higher than the reported rate in the Rotterdam study in all age categories other than the oldest (over 80 years). The combined annual incidence of AMD is higher than the observed incidence in all age categories of the Rotterdam study.

The Australian BMES[23] incorporated one follow-up point 5 years after the baseline observation, and reported similar levels of follow-up to the Rotterdam study (75% of survivors attended follow-up). The estimated annual incidence rates of both early ARM and AMD are slightly higher in the younger age groups (e.g. 0.006 for early ARM in the under-60 years category compared with 0.0014 in the 55–59 years category of the Rotterdam study), but lower in the oldest age group (0.032 for early ARM compared with 0.051 in the over-80 years category). Part of the reason for the generally higher incidence rates for AMD is that, as in the Copenhagen study, the incidence rates for AMD include persons with early ARM at baseline, which is estimated to be around 5% in total (although up to 20% in the oldest age group).

The Beaver Dam study[24] included two follow-up points, at 5 and 10 years, and also reports age-specific incidence rates for early ARM that are higher than the Rotterdam study. The AMD incidence rates include cases in which early ARM was present at baseline (estimated to be around 19%), which, combined with the longer intervals between follow-up points, provide methodological reasons for the higher reported rates of AMD. However, van Leeuwen and colleagues[2] believe that the observed differences may be due to differences in the underlying risk of the respective populations.

The US-based prospective cohort study, AREDS, followed up participants at annual visits beginning at year 2, and had a median follow-up of 6.3 years.[27] The reported incidence rates of early ARM are higher than the above reported studies, although the CIs from AREDS are wide and overlap in most cases (although not with the Rotterdam study). Compared with the Rotterdam study, the definition of early ARM is broader; for example, it includes eyes with pigment abnormalities alone that are not included in the Rotterdam definition of early ARM.

Only two incident cases of AMD were observed in AREDS. Combined with AREDS having the shortest intervals between follow-up points and higher incidence rates of early ARM, this implies that a significant proportion of incident cases of AMD observed in the previous studies experienced early ARM prior to AMD.

The only UK study informing incidence rates is the Melton Mowbray study,[26] which reports 7-year incidence rates for minor and major AMD. Minor AMD includes all forms of drusen and pigment abnormalities, other than indistinct hard drusen. Major AMD includes more severe representations of drusen as well as geographic atrophy (GA) and CNV. In addition to the variable definitions, the sample is small and no age-specific data are presented.

The problems noted with the Melton Mowbray and other studies mean that the age-specific incidence rates presented by the Rotterdam study appear of most relevance to a UK study, given the similar environmental and demographic characteristics. However, the Rotterdam study reports the lowest incidence rates of all the identified studies, which is unlikely to be explained fully by differences in underlying risk. Buch and colleagues[22] recognised the higher observed rate in the Copenhagen study, and discussed potential explanatory factors. A key factor may be differences in participation rates as the Copenhagen study achieved a 97.3% follow-up rate, with 38.5% of incident late ARM cases being found through home examinations. The Rotterdam study, for example, achieved only 82% (range 57–87% across age groups) and 71% (range 29–79% across age groups) follow-up rates of living patients at the 2- and 6.5-year follow-up points, respectively. Differences in study design, sample variability, geographic location and methodology are also cited as possible sources of disparity among studies.

Buch and colleagues[22] also stated that incidence does not remain constant over time, especially for AMD, such that the longer follow-up in the Copenhagen study is likely to result in higher estimated annual rates. This issue is addressed by the estimation of age-specific incidence rates, which allows the model to increase the probability of incidence as patients with early ARM reach sequential age thresholds.

More generally, the competing risk of death may affect the accuracy of the reported incidence rates. Persons dying between follow-up points may be more likely to develop ARM prior to death, but such cases are not observed.

On the basis of the above comparison, the input parameter estimates for the incidence of first eye early ARM and AMD were based on the Rotterdam data, although adjustments were initially made to reflect the lower follow-up rates in this study. The incidence rates in the age categories 60–69, 70–79 and 80+ years were adjusted upwards by factors of 1.2, 1.4 and 1.6, respectively. The relative adjustments were based on the reported follow-up rates in the different age categories (the older age groups had poorer follow-up rates) and the aim of increasing the weighted mean incidence rate by 40% (slightly higher than the 38.5% of incident late ARM cases that were found through home examinations in the Copenhagen study as only 16% of follow-up was undertaken at home, i.e. some additional detection may be due to increased follow-up of persons attending the eye clinic).

To represent the uncertainty in the model's first eye incidence parameters, beta probability distributions were specified for each age category for early ARM incidence, and AMD incidence, based on the estimated number of cases and person-years at risk. The only exception is the incidence of AMD in the age category 55–59 years, in which no cases were observed in approximately 2179 person-years at risk. Based on the mean value of zero and the estimated upper 95% CI (0.0014), a standard deviation of 0.0007 is fitted to a normal distribution with mean zero so that the upper 95% CI equals 0.0014. The model can then sample a probability of progression such that if a value between 0 and 0.5 is sampled, the probability of incidence is zero, whereas values above 0.5 result in a positive probability of incidence.

Uncertainty around the likelihood of a case of AMD being dry or wet is also handled by beta distributions informed by the reported numbers of total cases of dry and wet AMD in each age category (i.e. including cases of AMD that progressed from early ARM). The only exception is for the age category 60–64 years, in which one case of wet AMD and no cases of dry AMD were observed. Lower and upper 95% CIs are estimated (0.05 and 1, respectively), which, combined with the mean probability that the AMD is wet, were used to define a triangular distribution.

Fellow eye incidence

Nine studies presenting data describing the incidence of ARM in the fellow eye were identified. The data extracted from these studies, and the re-analyses of these data, are presented in this section.

The Rotterdam study

The Rotterdam study describes outcomes for 56 patients with uniocular AMD at baseline, although only 25 participated at the first follow-up and seven at the second follow-up.[2] *Table 12* presents the estimated annual incidence rates and 95% CIs for the possible transitions, based on the number of cases in each category and the presented person-years at risk data.

The Blue Mountains Eye Study

The only data relating to second eye incidence identified in reports of the BMES state that the 5-year incidence rate for the development of AMD

TABLE 12 *Annual incidence rates of fellow eye AMD by initial and subsequent AMD: the Rotterdam study*[2]

Transition	Annual incidence	95% CI	
		Lower	Upper
1st eye dry AMD, fellow eye dry AMD	0.079	0.017	0.214
1st eye dry AMD, fellow eye wet AMD	0.026	0.001	0.138
1st eye wet AMD, fellow eye dry AMD	0.000	0.000	0.051
1st eye wet AMD, fellow eye wet AMD	0.088	0.029	0.193

(dry AMD defined as involving the fovea) in the second eye of participants with AMD in one eye at baseline was 28.6% (six of 21).[23]

The AREDS study

The AREDS study report no. 19[27] presents data describing the incidence of AMD (dry AMD involving the centre of the macula) in the second eye of patients with unilateral AMD over a mean follow-up time of 6.3 years. Data from patients in all four treatment groups (placebo, antioxidants, zinc, antioxidants + zinc) are combined, which requires consideration of the fact that zinc and antioxidants + zinc were shown to reduce significantly the incidence of wet AMD in the fellow eye of patients with unilateral AMD.

Data describing the number at risk and the number of cases of dry AMD and wet AMD are presented. In addition, odds ratios (ORs) for the development of wet or dry AMD in patients aged 65–69 versus <65 years and age >70 versus <65 years are presented. As the paper does not present the age-specific event rates, the number of cases of dry and wet AMD occurring in each age group are estimated by solving equations for the presented ORs simultaneously so that the total number of cases equals the observed cases. The outputs from these estimates are presented in *Table 13*.

TABLE 13 *Annual incidence rates of second eye AMD in patients with unilateral AMD: AREDS*[27]

Age (year)[a]	Mean	95% CI	
		Lower	Upper
Wet AMD			
<65	0.043	0.030	0.060
65–69	0.065	0.051	0.081
>70	0.074	0.064	0.085
Central dry AMD			
<65	0.012	0.006	0.023
65–69	0.015	0.010	0.024
>70	0.020	0.015	0.026

[a] Age-specific rates are estimated by solving equations for the presented ORs simultaneously so that the total number of cases equals the observed cases.

The Beaver Dam study

The Beaver Dam study[24] reports the incidence of either dry or wet AMD in the fellow eyes of eyes with dry or wet AMD at baseline. Dry AMD is defined as being in any subfield. *Table 14* presents the estimated annual incidence rates and their corresponding 95% CIs. Eight cases of dry AMD were observed, although two cases that were observed at the 5-year follow-up point developed wet AMD by the 10-year point. These persons are counted twice as the sequential observation of dry and then wet AMD represents the true incidence.

TABLE 14 *Incidence of dry and wet AMD in eyes with uniocular late ARM at baseline: the Beaver Dam study*[24]

	At risk	Cases	10-year incidence	95% CI		Annual incidence	95% CI	
				Lower	Upper		Lower	Upper
2nd eye dry AMD								
1st eye dry AMD	11	5	0.455	0.168	0.766	0.059	0.018	0.135
1st eye wet AMD	15	3	0.200	0.043	0.481	0.022	0.004	0.063
2nd eye wet AMD								
1st eye dry AMD	11	1	0.091	0.002	0.413	0.009	0.000	0.052
1st eye wet AMD	15	3	0.200	0.043	0.481	0.022	0.004	0.063

The CNV Prevention Trial

The CNV Prevention Trial (CNVPT)[28] was a randomised trial that compared laser photocoagulation with observation. The eligible population included eyes without AMD and VA >20/40, but with >10 large drusen (>63 μm diameter), whose fellow eyes had evidence of CNV or serious RPE detachment. Laser treatment was found to be ineffective and potentially harmful, so data from the observed group were analysed for use in the natural history model. Unlike the population prevalence studies, patients in the CNVPT presented clinically with the CNV in the first eye.

Data describing patients followed up at different time points and graphs of the proportion of patients developing dry AMD (within 1500 μm of the centre of the fovea) or wet AMD over time were used to estimate the respective annual incidence rates by year of follow-up. To inform CIs, the numbers of cases of AMD at each follow-up point were estimated by multiplying the overall incidence rate by the number of patients at risk. *Table 15* presents the estimated annual incidence rates and associated CIs. The most striking result is the difference in the estimated annual incidence rate based on the 1-year and the 2-, 3- or 4-year follow-up data, which shows that the incidence rate increases sharply after the first year, although the CIs do overlap.

The Macular Photocoagulation Study

The Macular Photocoagulation Study (MPS) group have published three papers that describe different data on the incidence of second eye wet AMD.[29–31] A 1996 paper presents 5-year follow-up data on fellow eyes of patients from two trials covering patients with unilateral EF and JF wet AMD.[30] Fellow eyes did not have wet AMD at baseline but could have had early ARM or dry AMD.

Separate results are presented for patients aged under 50 years, JF first eye lesions, EF first eye lesions, the laser treatment group and the observation group. The rates in the treatment and observation group are not significantly different ($p = 0.28$), although the mean rate of second eye involvement is lower in the observation group. The results are not presented by location and treatment group. *Table 16* presents the estimated annual incidence rates and associated CIs.

A 1997 paper by the MPS group published 5-year follow-up data for fellow eyes of patients from three clinical trials covering new JF wet AMD, new SF wet AMD and recurrent SF CNV secondary to AMD.[31] Again, fellow eyes did not have wet AMD at baseline but could have had early ARM or dry AMD. It is not explicit, but it appears that the reported JF trial is the same as that reported in the previous paper.[30] However, this study presents a range of useful data including incidence rates of wet AMD in all fellow eyes over time,[31] which allows an assessment of whether incidence rates are constant over time. *Table 17* presents these data, which show that the estimated annual incidence is almost identical based on the data at each of the 5 years of follow-up.

The 1997 paper also presents data describing the 5-year incidence of fellow eye wet AMD by the drusen characteristics of the central macula in the

TABLE 15 *Incidence of dry and wet AMD in fellow eyes with early ARM of first eyes with CNV: the CNVPT[28]*

Follow-up (years)	At risk	Cases	Cumulative incidence	95% CI		Annual incidence	95% CI	
				Lower	Upper		Lower	Upper
Wet AMD								
1	58	2.999	0.052	0.011	0.119	0.052	0.011	0.119
2	47	12.220[a]	0.260	0.156	0.404	0.140	0.081	0.228
3	38	11.780[a]	0.310	0.139	0.380	0.116	0.049	0.147
4	37	14.001	0.378	0.225	0.552	0.112	0.062	0.182
Dry AMD								
1	58	3.480	0.060	0.019	0.144	0.060	0.019	0.144
2	47	3.760	0.080	0.024	0.175	0.041	0.012	0.092
3	38	6.460	0.170	0.077	0.313	0.060	0.026	0.117
4	37	7.770	0.210	0.098	0.352	0.057	0.026	0.103

[a] The reduction in the number of cases between follow-up at 2 and 3 years is an anomaly. The data are not adjusted as the key parameter is the baseline incidence rate, which is not affected by the anomaly.

TABLE 16 *Incidence of wet AMD in the fellow eye of patients with first eye wet AMD*

	Cases	At risk	5-year incidence	95% CI		*p*-Value	Annual incidence	95% CI	
				Lower	Upper			Lower	Upper
All	35	394	0.089	0.063	0.121		0.018	0.013	0.026
>50 years old	6	115	0.052	0.019	0.110	0.28	0.011	0.004	0.023
1st eye EF	20	181	0.110	0.069	0.166		0.023	0.014	0.036
1st eye JF	15	213	0.070	0.040	0.114	0.18	0.014	0.008	0.024
Laser treatment	21	202	0.104	0.066	0.155		0.022	0.013	0.033
Observation	14	192	0.073	0.040	0.119	0.28	0.015	0.008	0.025

TABLE 17 *Incidence of wet AMD in the fellow eye of patients with unilateral JF or SF wet AMD: the MPS*[31]

Follow-up (years)	Cumulative incidence	Annual incidence
1	0.1	0.100
2	0.19	0.100
3	0.28	0.104
4	0.36	0.106
5	0.42	0.103

fellow eye.[31] These results are presented in *Table 18* and indicate that fellow eyes with early ARM (defined as drusen size >63 μm) have a significantly increased rate of developing wet AMD compared with fellow eyes with no ARM or small drusen. The data also indicate that eyes with dry AMD have similar wet AMD incidence rates to those with early ARM.

The third form of data describes age-specific incidence rates of wet AMD in fellow eyes, although these data are not presented by drusen characteristic. The data presented in *Table 19* show an upward trend in the rate of fellow eye wet AMD with increasing age.

The third study by the MPS group presents 5-year follow-up of fellow eyes of patients from a trial of argon laser photocoagulation for EF wet AMD.[29] The dates and patient numbers of the trials of argon laser photocoagulation for eyes with EF AMD reported in this study and in the above-mentioned study[30] are similar but not identical, implying that they are reporting results from

TABLE 18 *Incidence of wet AMD in the fellow eye of patients with unilateral JF or SF wet AMD by drusen characteristics: the MPS*[31]

	At risk	Cases	5-year incidence	95% CI		Annual incidence	95% CI	
				Lower	Upper		Lower	Upper
Largest druse (μm)								
None	23	5	0.230	0.075	0.437	0.051	0.015	0.109
<63	173	48	0.280	0.212	0.351	0.064	0.047	0.083
64–125	158	90	0.570	0.489	0.648	0.155	0.126	0.188
>125	85	45	0.530	0.418	0.639	0.140	0.103	0.184
Dry AMD								
None	464	204	0.440	0.394	0.486	0.109	0.095	0.125
Dry AMD	20	10	0.490	0.272	0.728	0.126	0.062	0.229

TABLE 19 *Incidence of wet AMD in the fellow eye of patients with unilateral JF or SF wet AMD by age: the MPS*[31]

Age (years)	At risk	Cases	5-year incidence	95% CI		Annual incidence	95% CI	
				Lower	Upper		Lower	Upper
50–69	237	83	0.350	0.290	0.415	0.083	0.066	0.102
70–74	168	76	0.450	0.376	0.531	0.113	0.090	0.140
>75	265	133	0.500	0.440	0.564	0.129	0.110	0.153

separate trials. Fellow eyes did not have wet AMD at baseline but could have had early ARM or dry AMD.

Table 20 presents data describing the incidence of dry or wet AMD in the fellow eye of patients with unilateral EF wet AMD by drusen characteristics, which show that the incidence of dry AMD is low. The data support the noted similarity of wet AMD progression in fellow eyes with early ARM or dry AMD (as observed in fellow eyes of eyes with JF or SF AMD). The reported zero incidence of wet AMD in fellow eyes with only small drusen or no ARM is surprising. Although the numbers are relatively small, the estimated upper 95% CI for the annual incidence rate is only 2.5%.

Baltimore studies

In the Baltimore studies, Bressler and colleagues[32] present data on fellow eyes of patients with first eyes with poorly defined angiographic leakage, which was assumed to represent wet AMD. All fellow eyes are defined as having drusen, although further details are not provided. *Table 21* presents the incidence rates, which are broadly in line with the data presented by the MPS group[29,30] (considering that a proportion of patients may have had small drusen in the current study).

In another Baltimore study, Sunness and colleagues[33] reports the incidence of second eye wet AMD in 46 patients with first eye wet AMD, and second eye dry AMD at baseline. The criteria for dry AMD were at least one area of discrete retinal pigment epithelial atrophy of at least 500 mm in diameter within one disc diameter of the fovea. *Table 22* presents the estimated annual incidence rates and CIs at years 1–4, which show very similar annual rates of progression across the years.

Munster study

Pauleikhoff and colleagues[34] in the Munster study present data on fellow eyes of patients with unilateral wet AMD, in which fellow eyes were required to have VA of 20/30 or better. It is implied that all fellow eyes had drusen. *Table 23* presents the estimated annual incidence rates by type of wet AMD in the first eye (classic and

TABLE 20 *Incidence of wet or dry AMD in the fellow eye of patients with unilateral EF wet AMD by drusen characteristics: the MPS[31]*

	At risk	Cases	5-year incidence	95% CI		Annual incidence	95% CI	
				Lower	Upper		Lower	Upper
Dry AMD								
1+ large drusen or focal hyperpigmentation	53	2	0.038	0.005	0.130	0.008	0.001	0.027
Small drusen	24	0	0	0	0.117	0	0	0.025
Other significant macular disease	11	0	0	0	0.238	0	0	0.053
None of the above	2	0	0	0	0.776	0	0	0.259
Wet AMD								
Dry AMD	11	5	0.455	0.168	0.766	0.114	0.036	0.252
1+ large drusen or focal hyperpigmentation	53	20	0.377	0.248	0.521	0.090	0.055	0.137
Small drusen	24	0	0	0	0.117	0	0	0.025
Other significant macular disease	11	2	0.182	0.023	0.518	0.039	0.005	0.136
None of the above	2	0	0	0	0.776	0	0	0.259

TABLE 21 *Incidence of wet AMD in the fellow eye of eyes with wet AMD: the Baltimore study[32]*

	At risk	Cases	28-month incidence	95% CI		Annual incidence	95% CI	
				Lower	Upper		Lower	Upper
Drusen	31	6	0.194	0.075	0.375	0.088	0.033	0.182

TABLE 22 *Progression from dry to wet AMD in fellow eyes of first eyes with wet AMD: the Baltimore study*[33]

Follow-up (years)	Cumulative incidence	95% CI		Annual incidence	95% CI	
		Lower	Upper		Lower	Upper
1	0.08	0	0.17	0.080	0.000	0.170
2	0.18	0.04	0.3	0.094	0.020	0.163
3	0.22	0.06	0.36	0.079	0.020	0.138
4	0.34	0.12	0.51	0.099	0.031	0.163

TABLE 23 *Incidence of CNV in the fellow eye of eyes with CNV by first eye CNV type: the Munster study*[34]

Year of follow-up	At risk	Cases	Cumulative incidence	95% CI		Annual incidence	95% CI	
				Lower	Upper		Lower	Upper
All patients								
1	187	6	0.032	0.012	0.069	0.032	0.012	0.069
2	178	27	0.152	0.102	0.213	0.079	0.053	0.113
3	142	37	0.261	0.191	0.341	0.096	0.068	0.130
4	123	50	0.407	0.319	0.499	0.122	0.092	0.159
1st eye classic wet AMD								
1	130	2	0.015	0.002	0.055	0.015	0.002	0.055
2	125	13	0.104	0.057	0.171	0.053	0.029	0.090
3	107	20	0.187	0.118	0.274	0.067	0.041	0.101
4	94	30	0.319	0.227	0.423	0.092	0.062	0.129
1st eye occult wet AMD								
1	57	4	0.070	0.020	0.170	0.070	0.020	0.170
2	53	14	0.264	0.153	0.403	0.142	0.079	0.228
3	35	17	0.486	0.314	0.660	0.199	0.118	0.302
4	29	20	0.690	0.492	0.847	0.254	0.156	0.375

occult), which indicates a higher incidence of wet AMD in the fellow eyes of first eyes with occult wet AMD. The CIs do overlap, but this may be due to the sample size, which is small.

These data also indicate a non-constant rate of second eye involvement, showing a steadily increasing annual incidence rate over the 4-year follow-up period. This result is at odds with the observed time sequence in the CNVPT,[28] which showed a decreased incidence rate in the first year followed by seemingly constant rates in subsequent years. It is also contrary to the results presented by the MPS group, who reported a constant incidence rate for fellow eye wet AMD over time.

Danish study

In a Danish study, Baun and colleagues[35] report data on 45 patients with wet AMD in one eye at baseline; results are presented by the state of the fellow eye at baseline. The small numbers produce wide CIs, but the data presented in *Table 24* indicate low rates of wet AMD in fellow eyes with no ARM. That the highest rate is in the small drusen group is surprising, although, as noted, the CIs are wide.

Fellow eye incidence commentary

Separate estimates of ARM incidence rates in the second eye are required for different eye 1 ARM states, that is, eye 2 incidence given early ARM, GA or CNV, in the first eye. The following sections describe the respectively defined input parameter values.

Fellow eye incidence given early ARM in the first eye

No data were identified describing the incidence of ARM in the fellow eye of eyes with early ARM. Though it may tend to overestimate incidence, similar fellow eye incidence rates to those estimated for fellow eyes of eyes with dry AMD were assumed.

Fellow eye incidence given dry AMD in the first eye

The Rotterdam study presents aggregate data based on 38 person-years at risk, which can be

TABLE 24 *Incidence of wet AMD in the fellow eye of eyes with wet AMD by fellow eye characteristics: the Danish hospital study* [35]

Fellow eyes at baseline	At risk	Cases	4-year incidence	95% CI		Annual incidence	95% CI	
				Lower	Upper		Lower	Upper
No changes	5	0	0	0	0.451	0	0	0.139
Cluster(s) of small drusen	8	5	0.625	0.245	0.915	0.217	0.068	0.460
Medium-sized drusen	17	4	0.235	0.068	0.499	0.065	0.017	0.159
Large confluent drusen	10	3	0.300	0.067	0.653	0.085	0.017	0.232
Dry AMD	5	2	0.400	0.053	0.853	0.120	0.013	0.381
Total	45	14	0.311	0.182	0.467	0.089	0.049	0.145

used to estimate annual incidence rates of dry AMD (0.079) and wet AMD (0.026) in the second eye given dry AMD in the first eye. The Beaver Dam study allows the estimation of annual incidence rates of 0.059 and 0.009 for second eye dry AMD and wet AMD, respectively, given dry AMD in the first eye.

These rates are similar, and as first eye incidence was informed by the Rotterdam study, which is also deemed to have the most similar demographics to a UK population, the Rotterdam study informs the aggregate incidence rate for fellow eyes given dry AMD in the first eye.

Age-specific incidence rates for central dry AMD and wet AMD in patients with uniocular AMD were estimated using data presented by AREDS.[27] Only 74 of 788 (9.4%) patients had first eye dry AMD, although these data remain the most relevant age-specific data, and the ratios of incidence rates in the different age groups were used to disaggregate the aggregate Rotterdam study incidence rates.

To represent the uncertainty in the parameter estimates, the above parameters were specified as beta distributions; the sampled values from each were combined to estimate age-specific fellow eye incidence rates.

Fellow eye incidence given wet AMD in the first eye

Three studies presented data describing fellow eye incidence given first eye wet AMD and no ARM (where no ARM includes small drusen) at baseline in the fellow eye, two of which were published by the MPS group. An aggregate annual incidence rate of 0.061 for the development of fellow eye wet AMD in second eyes with no or small drusen is estimated.[19] The rates were similar in the no drusen (0.051) and the <63-μm drusen (0.064) categories. Age-specific rates of fellow eye wet AMD are also presented, although not by drusen characteristics.[30]

Data presented by the Beaver Dam study[24] allow the estimation of annual incidence rates of 0.022 for both fellow eye dry and wet AMD given wet AMD in the first eye. No cases of dry or wet AMD were observed in the fellow eye given no or small drusen at baseline, although an upper 95% CI of 0.11 is estimated from the data presented for both outcomes. Baun and colleagues[35] observed no cases of CNV in fellow eyes with no changes (based on five observations), but five out of eight cases in eyes with small clusters of drusen. The CIs do overlap.

Data from the Rotterdam study estimate annual rates of 8.8% and 0% for fellow eye wet and dry AMD, respectively, given first eye wet AMD.[2] These data inform beta probability distributions describing the incidence of fellow eye dry or wet AMD, given first eye wet AMD. As above, the age-specific incidence rates of central dry AMD and wet AMD in patients with uniocular advanced AMD presented by AREDS are used to define age-specific incidence rates.

Natural history

The natural history of ARM refers to the progression of disease between different stages of the disease.

Progression from early ARM and dry AMD

Six studies are identified that present data describing the progression of early ARM or dry AMD to wet AMD. The data extracted from these studies and the re-analyses of these data are presented in this section.

The Rotterdam study presents age-specific 5-year incidence of dry and wet AMD in eyes with early ARM at baseline.[2] The estimation of the age-specific probabilities of AMD required some re-analysis of the presented data as separate mean

TABLE 25 *Annual incidence of AMD in persons with early ARM: the Rotterdam study*[2]

Age (years)	Person-years	Cases[a]	Mean[b]	95% CI	
				Lower	Upper
60–69	359	3.6	0.0101	0.003	0.0242
70–79	724	16.7	0.0230	0.0137	0.0356
80+	335	11.7	0.0350	0.0186	0.058

[a] The numbers of cases are estimated from the reported mean rate and implied person-years in order to inform the CIs.
[b] The mean rates are estimated as weighted proportions of the separately presented rates for ARM categories 2 and 3, based on the distribution of patients in categories 2 and 3 at follow-up.

TABLE 26 *Incidence of AMD in persons with alternative forms of early AMD at baseline: the Copenhagen study*[22]

	At risk	Cases[a]	14-year incidence			Annual incidence		
			Mean	95% CI		Mean	95% CI	
				Lower	Upper		Lower	Upper
Early ARM								
Wet AMD	37	18	0.486	0.319	0.631	0.046	0.027	0.069
Dry AMD	37	12	0.324	0.180	0.470	0.028	0.014	0.044
Hard distinct drusen								
Wet AMD	105	3	0.029	0.0059	0.0812	0.002	0.000	0.006
Dry AMD	105	0	0	0	0.0281	0.000	0.000	0.002
Soft distinct drusen								
Wet AMD	47	9	0.192	0.0915	0.3326	0.015	0.007	0.028
Dry AMD	47	4	0.083	0.0237	0.2038	0.006	0.002	0.016
Soft indistinct drusen								
Wet AMD	32	17	0.531	0.3474	0.7091	0.053	0.030	0.084
Dry AMD	32	11	0.344	0.1857	0.5319	0.030	0.015	0.053

[a] Early AMD is defined as the absence of signs of advanced AMD and the presence of (1) soft, indistinct or reticular drusen or (2) hard, distinct or soft, distinct drusen with pigmentary abnormalities (RPE depigmentation or increased retinal pigment).

rates are presented for stage 2 and stage 3 ARM (the component parts of early ARM). A combined AMD incidence rate is estimated as a weighted proportion of the separately presented rates for ARM categories 2 and 3, based on the mean distribution of patients between categories 2 and 3 at follow-up (the distribution of ARM stages at baseline is not presented).

CIs for AMD incidence in persons with early ARM were informed by estimating the age-specific numbers of cases of AMD developing in persons previously in ARM stages '0 + 1' and '2 + 3' from the combined incidence rates and the implied person-years at risk. The same age-specific distribution of dry and wet AMD, as described for incident cases of AMD in persons without early ARM (see the section 'First eye incidence', p. 12) is applied to the aggregate AMD rate to estimate the individual rates for dry and wet AMD. The resulting estimates are presented in *Table 25*.

The Copenhagen study[22] describes 14-year incidence of dry AMD and wet AMD by drusen category and presence of early ARM at baseline, although not by age. *Table 26* presents 14-year and annual incidence rates of dry and wet AMD for different subgroups of early ARM at baseline.

AREDS report no. 19[27] describes AMD incidence in patients with "early or intermediate AMD at baseline", which is defined as including AMD categories 2 and 3a. Category 2 participants had mild or borderline age-related macular lesions [multiple small drusen, non-extensive (<20), intermediate drusen (63–124 μm in diameter), pigment abnormalities or any combination of these] in their most advanced eye and VA of 20/32

or better in both eyes. In category 3a, both eyes had at least one large druse (≥125 μm in diameter), extensive (as measured by drusen area) intermediate drusen, dry AMD that did not involve the centre of the macula or any combination of these. The mean follow-up time was 6.3 years and the data presented combine patients in all four treatment groups (placebo, antioxidants, zinc, antioxidants + zinc), although the only significant effects of treatment were for zinc and antioxidants + zinc for the prevention of CNV in patients with unilateral AMD.

Data describing the number at risk and the number of cases of dry AMD (involving the centre of the macula) and wet AMD are presented. In addition, ORs for the development of dry or wet AMD for a range of variables compared with the base case are presented, including age 65–69 versus <65 years and age >70 versus <65 years. As the paper does not present the age-specific event rates, the number of cases of dry and wet AMD occurring in each age group are estimated by solving equations for the presented ORs simultaneously so that the total number of cases equals the observed cases. The outputs from these estimates are presented in *Table 27*.

Data from the Beaver Dam study[24] describe the 10-year incidence of dry AMD (central and non-central) and wet AMD in the right eye of patients with different categories of early ARM or no ARM in their right eye at baseline. The estimated annual incidence rates and CIs for dry and wet AMD are presented in *Tables 28* and *29*, respectively.

TABLE 27 *Annual incidence rates of central dry AMD and wet AMD from early and intermediate AMD: AREDS[27]*

	Mean[a]	95% CI	
		Lower	Upper
Wet AMD			
<65	0.010	0.007	0.013
65–69	0.016	0.013	0.019
>70	0.022	0.018	0.026
Dry AMD			
<65	0.005	0.003	0.008
65–69	0.009	0.007	0.012
>70	0.011	0.009	0.014

[a] Age-specific rates are estimated by solving equations for the presented ORs simultaneously so that the total number of cases equals the observed cases.

Wang and colleagues[36] describe the 5-year risk of AMD in eyes with macular drusen and hyperpigmentation from the BMES, using a similar categorisation to that used by AREDS. However, the study presents separate results for right and left eyes, does not report any age-specific progression rates and does not separate out eyes with and without fellow eyes with AMD. These data are of limited relevance given other data sources.

Holz and colleagues[37] report data from a prospective study undertaken in the UK at Moorfields Eye Hospital on 126 patients with bilateral macular drusen (BMD). Patients

TABLE 28 *Incidence of dry AMD in the right eye of patients by maximum drusen diameter and drusen type: the Beaver Dam study[24]*

	At risk	Cases	10-year incidence	95% CI		Annual incidence	95% CI	
				Lower	Upper		Lower	Upper
Maximum drusen diameter (μm)								
0	381	0	0	0	0.008	0.000	0.000	0.001
<63	2191	0	0	0	0.001	0.000	0.000	0.000
63–125	527	2	0.003	0.001	0.014	0.000	0.000	0.001
125–250	229	10	0.044	0.021	0.079	0.004	0.002	0.008
>250	59	7	0.117	0.049	0.229	0.013	0.005	0.026
>125	288	17	0.059	0.035	0.093	0.006	0.004	0.010
>63	815	19	0.023	0.014	0.036	0.002	0.001	0.004
Drusen type								
None or hard indistinct	378	0	0	0	0.008	0.000	0.000	0.001
Hard distinct	2465	0	0	0	0.001	0.000	0.000	0.000
Soft distinct	246	3	0.012	0.003	0.035	0.001	0.000	0.004
Soft indistinct	241	16	0.065	0.038	0.106	0.007	0.004	0.011
Soft distinct or indistinct	487	19	0.039	0.024	0.060	0.004	0.002	0.006
Pigmentary irregularities								
Any	224	18	0.082	0.0483	0.124	0.009	0.005	0.013

TABLE 29 *Incidence of wet AMD in the right eye of patients by maximum drusen diameter and drusen type: the Beaver Dam study*[24]

	At risk	Cases	10-year incidence	95% CI		Annual incidence	95% CI	
				Lower	Upper		Lower	Upper
Maximum drusen diameter (μm)								
0	355	0	0	0	0.008	0.000	0.000	0.001
<63	2158	0	0	0	0.001	0.000	0.000	0.000
63–125	517	5	0.010	0.003	0.022	0.001	0.000	0.002
125–250	229	10	0.045	0.021	0.079	0.005	0.002	0.008
>250	64	16	0.244	0.150	0.374	0.028	0.016	0.046
>125	293	26	0.089	0.059	0.127	0.009	0.006	0.014
>63	810	31	0.038	0.026	0.054	0.004	0.003	0.006
Drusen type								
None or hard indistinct	362	0	0	0	0.008	0.000	0.000	0.001
Hard distinct	2447	0	0	0	0.001	0.000	0.000	0.000
Soft distinct	239	5	0.020	0.007	0.048	0.002	0.001	0.005
Soft indistinct	248	24	0.097	0.063	0.141	0.010	0.006	0.015
Soft distinct or indistinct	487	29	0.060	0.040	0.084	0.006	0.004	0.009
Pigmentary irregularities								
Any	236	15	0.065	0.036	0.1027	0.007	0.004	0.011

meeting the defined eligibility criteria were recruited over a 3-year period. The study reports separate 1-year incidence rates (with 95% CIs) for dry and wet AMD for all patients with BMD, where dry AMD is defined as involving the fovea (*Table 30*).

Combined incidence rates for AMD are presented by drusen characteristics in the worst affected eye (*Table 31*).

Sunness and colleagues[33] aimed to report the rate of developing wet AMD in eyes with dry AMD and the characteristics of the wet AMD in these eyes. They report separate rates of developing wet AMD in 91 patients with bilateral dry AMD and 13 patients with dry AMD in the study eye and drusen and/or pigmentary abnormalities of the RPE without evidence of dry or wet AMD in the fellow eye. The criteria for dry AMD included at least one area of discrete RPE atrophy of at least 500 mm in diameter within one disc diameter of the fovea.

TABLE 30 *Incidence of dry and wet AMD in patients with bilateral drusen: the Moorfields study*[37]

Age (years)	No. cases	1-year incidence	95% CI	
			Lower	Upper
Wet AMD				
>65	12	0.064	0.0335	0.1088
All ages	13	0.047	0.025	0.0782
Dry AMD				
>65	5	0.026	0.0086	0.0602
All ages	5	0.018	0.0058	0.0407

None of the 13 patients with drusen in the fellow eye developed wet AMD over the follow-up period, though the numbers at risk in each year allow the estimation of upper CIs. Wet AMD incidence rates for persons with bilateral dry AMD, with accompanying CIs, are presented directly. Both sets of data are presented in *Table 32*.

Sunness and colleagues[33] hypothesise that higher rates of wet AMD may be expected in eyes with smaller areas of dry AMD where there is still some intact macular choriocapillaris to support the growth of wet AMD. Their study found that central atrophy less than two disk areas was a risk factor for developing wet AMD in eyes with dry AMD in the fellow eye CNV group. The AMD natural history model does not categorise dry AMD, so the implicit assumption is that the size distribution of dry AMD in the model is equal to that in the studies reporting rates of wet AMD progression from dry AMD.

Two other studies from the late 1980s report the development of wet AMD in eyes with dry AMD, although neither explicitly describes the status of the fellow eyes at either baseline, or within the population who developed wet AMD at follow-up.[38,39] As the presence of wet AMD in the fellow eye is known to be a risk factor for the development of wet AMD, the data presented by these studies are of limited use in the context of the AMD natural history model.

TABLE 31 *Combined incidence rates for AMD by drusen characteristics in the worst affected eye: the Moorfields study*[37]

Age (years)	Cases	Person-years at risk[a]	1-year incidence	95% CI	
				Lower	Upper
Drusen no. central					
<10	0	27	0	0	0.105
10 to 20	1	13	0.0769	0.0019	0.3603
>20	15	138	0.1087	0.0621	0.1729
Drusen no. peripheral					
<10	1	38	0.0263	0.0007	0.1381
10 to 20	5	37	0.1351	0.454	0.2877
>20	10	103	0.0971	0.0475	0.1713
Drusen size (μm) central					
<50	0	13	0	0	0.2058
50 to 500	14	143	0.0979	0.0546	0.1588
>500	2	22	0.0909	0.0112	0.2916
Drusen size (μm) peripheral					
<50	0	21	0	0	0.1329
50 to 500	16	157	0.1019	0.0594	0.1602
Focal hyperpigmentation central					
Absent	5	118	0.0424	0.0139	0.0961
Present	11	60	0.1833	0.0952	0.3044
Non-foveal dry AMD					
Absent	11	154	0.0714	0.0362	0.1242
Present	5	24	0.2083	0.0713	0.4215

TABLE 32 *Incidence of wet AMD in patients with dry AMD: the Baltimore study*[33]

Follow-up (years)	Incidence	95% CI		Annual incidence	95% CI	
		Lower	Upper		Lower	Upper
Bilateral dry AMD						
1	0	0	0.032	0	0	0.032
2	0.020	0	0.050	0.010	0	0.025
3	0.040	0	0.090	0.014	0	0.031
4	0.110	0	0.210	0.029	0	0.057
Fellow eye drusen						
1	0	0	0.238	0	0	0.238
2	0	0	0.283	0	0	0.153
3	0	0	0.369	0	0	0.142
4	0	0	0.527	0	0	0.171

Commentary on progression from early ARM and dry AMD

Eye one progression from early ARM given no ARM in the fellow eye

A problem with many of the data presented in the literature is that papers do not explicitly describe the status of the fellow eye of eyes with early ARM. It is assumed that unless a population is stated to have bilateral ARM, only one eye is affected.

There is a marked difference between the alternative studies, even after considering differences in definitions. Based on follow-up at 2 and 6.5 years, the Rotterdam study[2] reports aggregate annual progression rates to dry and wet AMD from early ARM of between 0.01 (60–69 years) and 0.035 (80+ years). The Copenhagen study[22] estimates an aggregate annual progression rate of 0.074 for right eyes across all ages, where over 80% of people with early ARM at baseline had progressed to either dry or wet AMD at the 14-year follow-up.

The Beaver Dam study[24] presents 10-year incidence data from which annual incidence rates of progression to AMD are estimated as 0.007 for

right eyes with soft indistinct drusen, and 0.016 for right eyes with any pigmentary irregularities. AREDS[27] presents aggregate progression rates from early and intermediate ARM to AMD of between 0.015 (<65 years) and 0.033 (>70 years).

The Beaver Dam study[24] progression rates appear slightly lower than those is the other studies, although comparison is hindered by the fact that progression rates relating to drusen size, drusen type and pigmentary irregularities are all presented separately, and not as a singly defined early ARM category. The highest rate in the Beaver Dam study is observed for the pigmentary irregularities category, although eyes with pigmentary irregularities alone are not defined as early ARM in the Rotterdam scale. Hence one may expect an equivalent 'early ARM' progression rate (if available) to be in line with the Rotterdam and AREDS rates. The age-specific rates estimated from the Rotterdam study and AREDS are in close agreement.

The obvious outlier is the Copenhagen study, from which a much higher annual progression rate is estimated, although the CIs overlap with all of the other studies.[22] As noted above, the higher follow-up rate achieved in the Copenhagen study may be a significant factor in these observed results. As in the previous section, the effect of the lower follow-up rate in the Rotterdam study is a concern, particularly as 38.5% of incident AMD cases were found through home examinations in the Copenhagen study, which may be assumed to be the cases most likely to be missed by the other studies.

A similar approach to that used to specify first eye incidence rates was used to define input parameter estimates for the progression of first eye early ARM, in the absence of ARM in the fellow eye (*Table 33*). The values were based on the Rotterdam data, with the same age-specific uprate factors applied to the low follow-up rates.

Progression from early ARM given early ARM in both eyes

AREDS report no. 19[27] states that the paper presents AMD incidence in patients with bilateral AMD, although the detailed description of the AREDS categories included in the paper implies that unilateral drusen were also included. As such, these data were included in the previous section that described unilateral early ARM progression.

The only other identified paper that usefully describes bilateral drusen progression was based at Moorfields Eye Hospital in England.[37] Data from this study were used to estimate the incidence of the first case of AMD in patients with BMD. The aggregate over 65 years progression probability is disaggregated into three probabilities representing progression in persons aged 60–69, 70–79 and over 80 years based on the age-specific progression probabilities observed for the progression from early ARM given no ARM in the fellow eye. It is assumed that the observed aggregate probability of progression from early ARM given BMD for persons aged over 65 years applies to persons aged over 60 years. Age-specific progression probabilities were estimated to fit the aggregate progression probability and the observed ratios of the probabilities between the three age groups. The type of incident AMD (dry or wet AMD) in patients aged over and under 65 years is based on the aggregate split between dry and wet AMD in patients aged over and under 65 years, respectively.

Progression from early ARM given dry AMD in the fellow eye

No data were identified describing progression from early ARM given dry AMD in the fellow eye. It was assumed that progression rates are similar to those estimated for progression from early ARM given early ARM in the fellow eye.

Progression from early ARM given wet AMD in the fellow eye

The CNVPT group presented data that allowed the estimation of annual progression rates to dry

TABLE 33 *Estimation of uprate factors for first eye progression rates given no ARM in the fellow eye*

Age (years)	Mean proportion population at follow-up	Mean late ARM rate	Uprate factor	Revised progression rate
60–69	0.46	0.010	1.20	0.012
70–79	0.38	0.023	1.40	0.032
80+	0.16	0.035	1.60	0.056
Weighted mean (all ages)		0.019		0.027
Weighted mean increase			1.41	

AMD and wet AMD for eyes with early ARM whose fellow eyes have wet AMD.[32] Separate data are presented for years 1–4, although only an aggregate rate is derived as the differences between years were not significant. The estimated aggregate annual rates of 0.057 and 0.112 for dry and wet AMD, respectively, were combined with the distribution of second eye wet AMD observed across three age groups of patients experiencing second eye wet AMD given first eye wet AMD (second eyes could have no ARM, early ARM or dry AMD) reported by the MPS group.[31]

Progression from dry AMD given no ARM in the fellow eye

No data were identified describing progression rates for dry to wet AMD in patients with no evidence of ARM in the fellow eye. As the observed data for dry AMD where the fellow eye has drusen show a zero progression rate (as described in the next section), it is assumed that the probability of progression of dry AMD given no ARM in the fellow eye is the same as that observed for the progression of dry AMD given early ARM in the fellow eye.

Progression from dry AMD given early ARM in the fellow eye

Only one study was identified that reported progression rates to wet AMD for patients with dry AMD. Sunness and colleagues[33] report that none of 13 patients with dry AMD and fellow eye drusen developed wet AMD over the 4-year follow-up period. The aggregate number of person-years at risk is estimated by multiplying the estimated follow-up percentages at years 1, 2, 3 and 4 by the numbers of patients dropping out after each follow-up point. The follow-up percentages at years 1, 2, 3 and 4 are based on the reported follow-up percentages at years 2 and 4 and assuming a constant rate of decrease between baseline, year 2 and year 4.

Assuming a binomial distribution, the aggregate upper 95% CI is 0.206. The positive relationship between the probability of progression of dry AMD and age is the same as that observed for the progression of early ARM given no ARM in the fellow eye. Age-specific upper CIs for the dry AMD progression parameter were estimated to fit the aggregate upper 95% CI and the observed ratios of the probabilities between the three age groups for the early ARM (no ARM in the fellow eye) progression parameter. The median age of all participants at baseline (including 91 patients with bilateral dry AMD and 46 with dry AMD in one eye and fellow eye CNV) was 78 years, with a range of 63–94 years. As the specific age distribution of the 13 persons is not reported, the population is assumed to be equally distributed between the three age categories (60–69, 70–79 and over 80 years).

Based on the mean value of zero and the estimated upper 95% CIs for each age category, standard deviations informing normal distributions with mean zero are fitted so that the upper 95% CIs equal the estimated intervals for each of the three age categories. The model can then sample a probability of progression such that if a value between 0 and 0.5 is sampled, the probability of progression is zero, whereas values above 0.5 result in a positive probability of progression.

Progression from dry AMD given bilateral dry AMD

Sunness and colleagues[33] observed progression to wet AMD in four of 91 patients with bilateral dry AMD over a 4-year follow-up period (the follow-up rate at 4 years was 32%). Progression rates, with 95% CIs, are presented for each year of follow-up, from which equivalent annual rates are estimated.

As above, it is assumed that progression probabilities increase with age, and age-specific mean values for the dry AMD progression parameter were estimated to fit the aggregate progression probability (0.029) and the observed ratios of the probabilities between the three age groups for the early ARM (no ARM in the fellow eye) progression parameter. The ages of the four patients at the time of progression are presented (74, 76, 80 and 87 years), although it is only stated that the median age of all participants at baseline was 78 years, with a range of 63–94 years. As the baseline age distribution is not reported, the population is assumed to be equally distributed between the three age categories (60–69, 70–79 and over 80 years).

Given the estimated mean values describing the probability of progressing, and the assumed equal distribution of patients between the three age categories, separate beta distributions are estimated for each age category.

Progression from dry AMD given wet AMD in the fellow eye

Three studies report numbers of cases of progression from dry AMD to wet AMD, given wet AMD in the fellow eye, together with person-years at risk.[29,31,33] These data are combined to inform mean annual rate of progression of 11.2%

(24 cases in 214.4 person-years), and also a beta distribution for the aggregate rate of progression.

Age-specific rates of progression were estimated based on the ratio of events reported in an MPS study of progression to wet AMD in the fellow eye of eyes with wet AMD.[31]

Progression to subfoveal wet AMD

Eyes with EF wet AMD may progress to JF or SF wet AMD, and eyes with JF wet AMD may progress to SF wet AMD. Occult lesions may progress to MC or PC lesions, and MC lesions may progress to PC lesions.

Patient-level data from patients diagnosed with wet AMD from the study reported by Ali and colleagues were analysed to inform rates of progression.[40] The dataset contained morphometric analyses of 98 sets of angiograms separated by an interval of at least 3 weeks, with no treatment delivered in the intervening period between angiograms. Fully corrected distance VA measured on logMAR Early Treatment of Diabetic Retinopathy Study charts was available at baseline and at a subsequent visit in 78 subjects.

Initial analyses of combined progression of lesion by type and location were undertaken, but the results show insignificant associations between type and location. It was assumed, therefore, that movement between locations and types of lesion are independent. Separate survival regression analyses were undertaken to inform progression rates from:

- EF to JF
- EF to SF
- JF to SF
- occult to MC
- occult to PC
- MC to PC lesions.

Progression rates were found to be time dependent, and a Weibull survival curve was found to be the best fit to the available data. *Figures 4* and *5* show the estimated mean survival curves for progression between lesion type and location, respectively. The estimated standard errors around each of the survival analysis parameters were used to inform probability distributions around the survival curves that were sampled from multivariate normal distributions.

Given incidence of a non-end state wet AMD lesion type (i.e. occult or MC) and/or lesion location (i.e. EF or JF), the model randomly samples a value between 0 and 1 for sequential months following incidence. If the sampled value is below the sampled probability of progression for the given lesion type and/or location within that month, the lesion is described as progressing. This process of sampling progression of wet AMD continued until either:

- the next sampled event occurred after the individual reached the age of 100 years, or
- the lesion location progressed to SF.

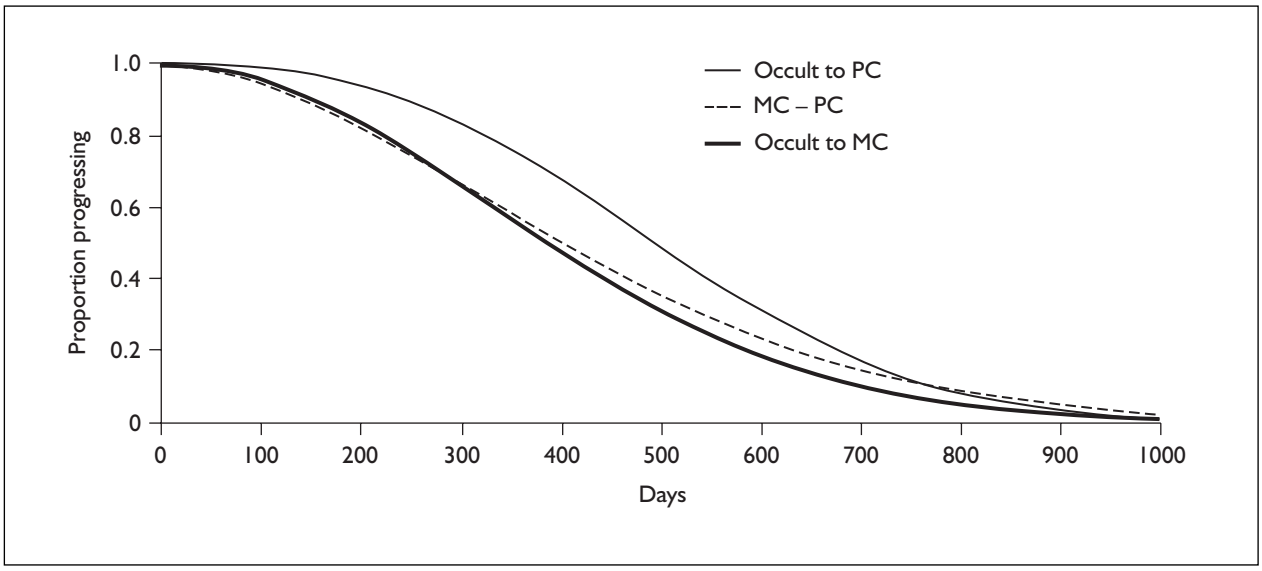

FIGURE 4 *Rate of progression between lesion types for occult and MC lesions*

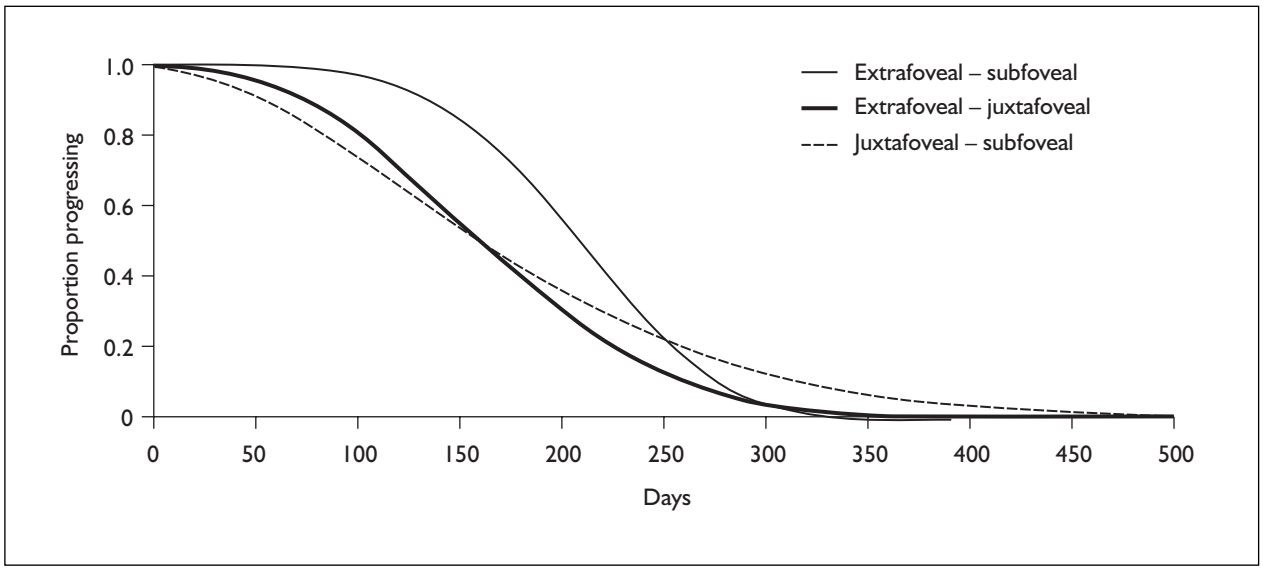

FIGURE 5 *Rate of progression between lesion locations for extrafoveal and juxtafoveal lesions*

Visual acuity

As described in Chapter 2, the AMD screening model estimates QALYs by assigning utility values to the VA level in each individual's best seeing eye in each year of life. The following sections describe the data, assumptions and analyses undertaken to inform the following VA parameters:

- progression of VA in eyes with dry AMD
- progression of VA in eyes with wet AMD.

Visual acuity in dry AMD

Dry AMD does not usually lead to an abrupt loss of vision – a complaint of abrupt vision loss leads one to suspect wet AMD; however, dry AMD can be associated with a loss in VA.[41] Sunness and colleagues report data describing the loss of VA in 139 eyes with dry AMD (defined here as GA), which did not develop wet AMD over the follow-up period.[42] The rate of losing three or more lines of VA due to worsening of dry AMD alone in the fellow eye wet AMD group was 31% (95% CI 8 to 47%) at 2 years and 45% (95% CI 15 to 65%) at 4 years. The corresponding rates of a three-line or greater loss in patients with bilateral dry AMD was 29% (95% CI 16 to 39%) at 2 years and 47% (95% CI 29 to 60%) at 4 years. As the rates of decline were not statistically significantly different between the two groups, these data were combined to estimate rates of VA progression due to dry AMD. *Table 34* presents the mean parameter values and the 95% CIs that were used to inform uniform probability distributions representing the uncertainty in these parameters.

TABLE 34 *Input parameter values describing progression from dry AMD*

Year since incidence	Cumulative proportion losing ≥3 lines vision		
		95% CI	
	Mean	Lower	Upper
1	0.15	0.06	0.23
2	0.41	0.27	0.52
3	0.60	0.44	0.72
4	0.70	0.49	0.83

Rates of loss of six lines or greater for all study eyes were 13% (95% CI 6 to 18%) by 2 years and 29% (95% CI 17 to 39%) by 4 years. Although these data included an additional 13 patients whose dry AMD progressed to wet AMD, they are used to inform the magnitude of VA loss. These data inform the estimate that two-thirds of patients experiencing a loss of at least three lines of vision lose three lines, whereas one-third lose six lines of vision.

Visual acuity in wet AMD

At the point of incidence with wet AMD, lesions are assigned a type (occult, MC or PC) and location (EF, JF or SF). Given a lesion type and location, a VA score at incidence of wet AMD is sampled. The probability distributions of VA scores at incidence were based on subjectively defined ranges of VA that were informed by discussion with clinical expert members of the research team and reflect the assumption that lesions further away from the fovea have fewer

TABLE 35 *Estimated ranges of visual acuity (in logMAR units) at incidence of alternative forms of AMD*

AMD type	Min	Max
Occult EF	0	0.5
Occult JF	0.1	0.7
Occult SF	0.3	1.2
MC EF	0	0.5
MC JF	0.1	0.7
MC SF	0.3	1.2
PC EF	0	0.5
PC JF	0.1	0.7
PC SF	0.3	1.2
Dry AMD	0	0.3

negative effects on VA. The specified ranges of VA at AMD incidence are described in *Table 35*.

Upon progression, a new VA score is sampled from additional regression analyses of the data from Ali and colleagues' study[40] (see the section 'Progression to subfoveal wet AMD', p. 31). VA progression was modelled as a function of previous VA, the time in previous vision state and the current lesion type. Other covariates were tested, including current and previous lesion location, but such covariates were found to be highly insignificant. The results of the final regression analysis informing VA progression up to the incidence of SF wet AMD are presented in *Table 36*.

From the point at which a lesion progresses to an SF location, a separate model function describes VA progression over the remainder of individuals' lifetimes. Patient-level data from the placebo arms of the TAP and the VIP trials of PDT (which were restricted to SF lesions) were combined with patient-level data from the SubFoveal Radiotherapy Study (SFRADS).[43]

The SFRADS compared 12 Gy of external beam radiation therapy (EBRT) delivered as 6×2 Gy fractions to the macula of an affected eye versus observation. Patients were UK-based and had SF CNV and a VA equal to or better than 6/60 (logMAR 1.0). The trial found that there were no statistically significant differences between treatment and control subjects in any measures of VA. Hence the data from both the control and treatment groups are combined to describe VA progression in non-treated SF wet AMD on the advice of a clinical member of the research team (UC).

The maximum duration of follow-up for placebo patients in the TAP and VIP trials was 2 years (placebo patients in the TAP trial crossed over to PDT at 2 years), whereas the maximum follow-up in the SFRADS was 2.67 years.

The combined dataset was adapted to describe the time to failure for each included eye, where failure was defined as a drop in VA of at least five letters (equivalent to a 0.1 drop on the logMAR scale), or the time to censoring if VA did not decline by five letters over the follow-up period. After a VA level drop, any subsequent follow-up data were used to create a new observation, that is, the baseline VA for the new observation is the VA level to which the index eye dropped at the last drop.

The combined and adapted dataset contained 1238 observations. Survival analyses on the combined dataset were undertaken to describe the survival curves for individuals maintaining VA at initial levels. Alternative survival models were tested, but the implemented model was a Weibull model containing the following covariates: age at incidence of SF wet AMD, VA at incidence of SF wet AMD and dummy variables for presence of occult and MC lesions. *Figure 6* describes the mean survival curves for individuals maintaining their initial VA by lesion type. The estimated standard errors around each of the survival analysis parameters were used to inform probability distributions around the survival curves that were sampled from multivariate normal distributions.

The curves show that the profiles do not differ greatly by lesion type, although further analysis suggested that the magnitude of the decrease for

TABLE 36 *Results of the regression analysis predicting VA progression in lesions up to progression to subfoveal wet AMD*

Variable	Regression coefficient	Standard error	t	$p > \|t\|$	95% CI
Baseline VA	0.919	0.067	13.657	0.000	0.786 to 1.052
Log(days)	0.048	0.038	1.258	0.211	–0.027 to 0.123
Lesion type[a]	–0.049	0.030	–1.630	0.106	–0.109 to 0.011
Constant	0.070	0.188	0.373	0.710	–0.303 to 0.443

[a] Lesion type was modelled as an ordered categorical variable, increasing severity from occult to MC to PC.

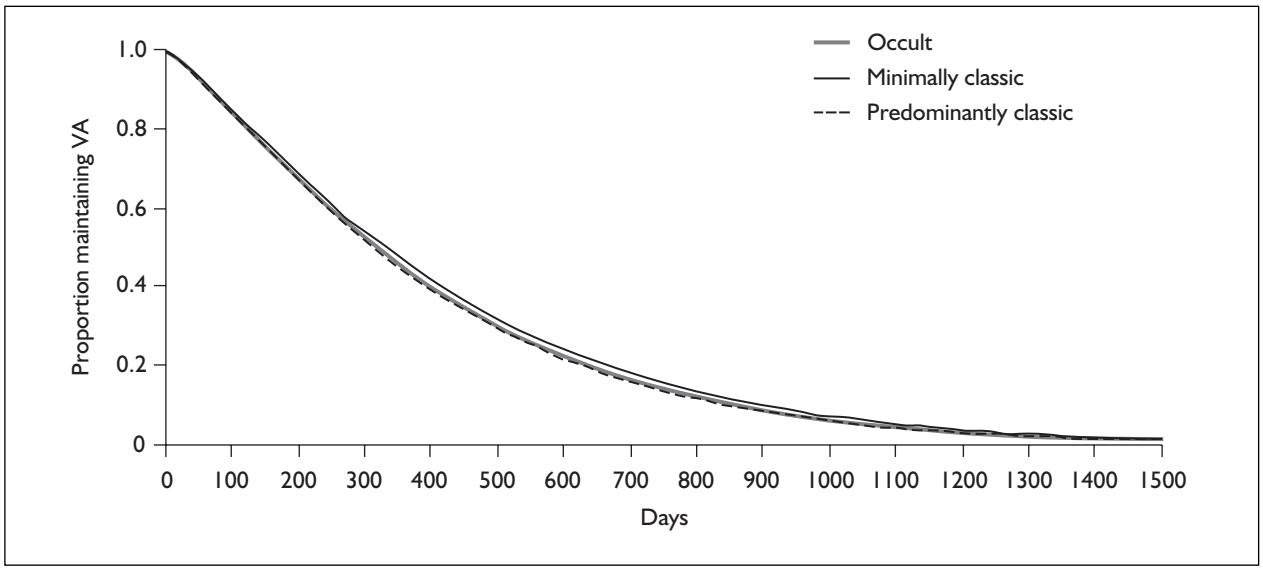

FIGURE 6 *Rate of loss of VA in individuals with subfoveal wet AMD by lesion type, for a 71-year-old with 0.3 logMAR VA at incidence*

those losing VA does differ more significantly between the lesion types. Additional regression analyses were undertaken to inform the extent of the drop in VA (i.e. number of letters lost) at each drop point. This was a multi-logit regression analysis that described the probabilities that the number of letters lost at each drop point was either 5, 10, 15 or 20. The best fitting model included the following covariates: age at SF incidence or last drop, time since SF incidence or last drop, VA score at SF incidence or last drop and dummy variables for presence of occult and MC lesions.

The results of this regression analysis are presented in *Table 37*. Given a set of input parameters (i.e. age, follow-up time, etc.) the regression coefficients are used to estimate probabilities describing the likelihood that a drop in VA is of 5, 10, 15 or 20 letters. *Table 38* provides an example of the conversion process.

As noted above, there is a more noticeable difference in the magnitude of visual loss across the lesion types than was observed for individuals losing any VA (as shown in *Figure 6*). PC lesions are more likely to be associated with larger drops

TABLE 37 *Results of a multi-logit regression analysis to predict the magnitude of decrease of VA in subfoveal lesions*

Letters lost	Parameter	Regression coefficient	Standard error	z	p > |z|	95% CI
10	Age (years)	0.007	0.013	0.534	0.593	–0.019 to 0.033
	Follow-up time	–0.001	0.001	–1.478	0.139	–0.002 to 0.000
	Baseline VA	0.013	0.007	1.985	0.047	0.000 to 0.027
	Occult	0.201	0.203	0.989	0.323	–0.197 to 0.598
	MC	–0.454	0.217	–2.094	0.036	–0.880 to –0.029
	Constant	–1.655	1.075	–1.539	0.124	–3.762 to 0.453
15	Age	–0.024	0.015	–1.599	0.110	–0.053 to 0.005
	Follow-up time	0.000	0.001	–0.561	0.575	–0.002 to 0.001
	Baseline VA	0.006	0.008	0.774	0.439	–0.009 to 0.021
	Occult	–0.137	0.233	–0.587	0.557	–0.595 to 0.321
	MC	–0.522	0.241	–2.170	0.030	–0.993 to –0.051
	Constant	0.716	1.190	0.602	0.547	–1.617 to 3.048
20	Age	0.002	0.014	0.123	0.902	–0.026 to 0.029
	Follow-up time	–0.001	0.001	–1.506	0.132	–0.002 to 0.000
	Baseline VA	0.050	0.007	6.824	0.000	0.036 to 0.065
	Occult	–0.673	0.219	–3.071	0.002	–1.103 to –0.244
	MC	–0.958	0.229	–4.176	0.000	–1.407 to –0.508
	Constant	–2.832	1.150	–2.463	0.014	–5.087 to –0.578

TABLE 38 *An example of the estimation of the probability distribution describing the magnitude of drop in VA for patients with subfoveal wet AMD*

Regression coefficient values			Probabilities			
2 levels	**3 levels**	**4 levels**	**1 level**	**2 levels**	**3 levels**	**4 levels**
−1.4495	−1.5769	−1.9291	0.6302	0.1479	0.1302	0.0917

in VA. The estimated standard errors around each of the survival analysis parameters were used to inform probability distributions around the survival curves that were sampled from multivariate normal distributions.

This process of sampling progression of VA in subfoveal lesions continues until either:

- the next sampled VA drop occurred after the individual reached the age of 100 years, or
- VA decreased to under 20 letters.

Further survival regression analyses describing the progression of lesion type in SF wet AMD were undertaken, which used data from the Ali and colleagues' dataset[40] to describe the annual probability that occult or MC lesions progress. Due to the small number of observations (two occult lesions and three MC lesions were observed to progress), the analyses were not linked to VA progression.

Chapter 4

Screening and treatment parameters

This chapter presents the available evidence regarding the effectiveness of screening tools for detecting AMD and on interventions for treating different stages of AMD. The screening model parameters to be informed include the probability of individuals detecting an abnormality and presenting at their opticians, to be defined by severity of disease, that is, early ARM, dry AMD and wet AMD. The screening process also includes the probabilities that opticians would refer on patients with the different severities of disease to the hospital eye service.

An effective screening programme must be able to offer an appropriate treatment for the condition in the cases detected. At clinical presentation, it was also necessary to define the treatment options available for individuals with different severities of disease. The ARM screening model facilitates two broad forms of intervention for ARM. First, interventions may be specified that reduce the risk of disease progression, for example, of early ARM progressing to dry or wet AMD or dry AMD progressing to wet AMD, or that reduce the risk of the incidence of ARM in the fellow eye of the first affected eye. Second, interventions may be implemented that reduce the loss of vision in eyes due to either dry AMD or different forms of wet AMD.

The first sections of this chapter describe the limited evidence on the screening parameters, which led to the implementation of an expert elicitation exercise to inform these parameters further. Subsequent sections describe the data and assumptions informing the impact of interventions on the natural history of ARM.

Screening parameters

There was little evidence to suggest that widespread use of the Amsler grid would prove to be a valuable screening tool.[44] *Table 39* shows the studies which have undertaken work looking at screening tools, and illustrates the problem that the present study had in identifying a simple and effective tool which would be used in the community. It became apparent that this would be a major area that would need to be referred to our panel of experts.

Screening parameter expert elicitation

Once the searches were completed, we were able to see where the literature lacked data. We began the process of contacting experts in the field of this branch of ophthalmology. A short presentation describing the aims and objectives of the study was delivered at a number of key scientific meetings in the UK. The presentation explained about the study, why we needed the input of a number of experts and what kinds of information, including any unpublished data in which the team were interested. This was followed up by written and telephone communications to a number of individuals who had expressed an interest in collaborating with the team.

A number of visits were undertaken by team members to meet with the experts on an individual basis. We convened a panel of six experts (UC, AB, IC, YCY, SH, CB). Members of the core study team met with these individuals to develop the elicitation study.

A questionnaire was developed out of these meetings which addressed a number of issues, including screening tests, referrals from optometrists, treatments and future possibilities. We posted this out to the panel members with a letter explaining that they could complete a paper version or an electronic version or talk directly to a member of the study team (see Appendix 3). The experts were contacted again if any clarification was required.

In addition, as part of the collaborative process of this work, a number of the clinicians made available existing datasets and additional unpublished data from previous studies. We were able to reanalyse these and incorporate them in the model.

We also undertook a small survey of ophthalmologists (n = 30) who referred patients to either the Sheffield or Liverpool PDT clinics in order to inform estimates of the number of patients presenting with AMD, and the distribution of AMD states at presentation. These data inform the model calibration process and are described in more detail in Chapter 8. This survey document is presented in Appendix 4.

TABLE 39 *Summary of screening studies*

Study	Study design	Inclusion/exclusion	Numbers	AMD type	Statistical results	Comments
AREDSRG (2001) USA[25]	Standardised photographs Cumulative sample	Not described	1230 eyes	Advanced AMD	Agreement 96% (kappa = 0.88) Satisfactory reliability for detecting onset of advanced AMD	Suitable for longitudinal multi-centre studies
Barthes (2001) France[45]	Computerised image processing Compared with results of 3 specialists' counts of drusen	Not described	58 retinal images	Drusen only	Manual counting inter-observer correlation coefficients lie in the range 0.71–0.78 A correlation coefficient of 0.89 is obtained when the average of the three expert countings is compared with the drusen number given by the computerised method	Analysis is quicker but manual validation is still required
Fine (1986) USA[46]	Case series of 103 patients with neovascular maculopathy and relatively recent vision loss	Consecutive patients – interview (first visual symptom) asked about Amsler grid use	103 patients, 68 with AMD	AMD	Of 89 who previously had the Amsler grid, only 49 were actually using it to monitor their central vision on a regular basis. Although all but one of these 49 patients had a demonstrable grid defect, only five stated that the first visual symptom was noticed while observing the Amsler grid	Targeted use of the grid does not seem to be effective
van Leeuwen (2003) Europe[71]	EUREYE study data Comparison of stereo digital images with stereo 35 mm transparencies	Validation study in Belfast and Rotterdam, 65+-year-olds invited for eye examination	137 eyes (91 subjects)	ARM according to International Classification System	Our study showed there were no important differences between both photographic techniques in the grading results in an epidemiologic setting	Practical advantage of digital imaging
Schmitt (2003) USA[47]	Evaluation trial	92 patients with vision 20/80 or better aged 50+ years	92 eyes tested	AMD, 30 people	We found EMS RT distribution did not differ between AMD, cataract, diabetic retinopathy and glaucoma groups	Not a sensitive screening tool
Woods (1998) Australia[88]	Retrospective analysis of clinical cross-sectional survey	Randomly selected residents aged over 50 years from an Australian health district	3283 subjects, diagnosis confirmed in 2522	AMD and other pathologies	A person older than 50 years of age with reduced contrast sensitivity, as determined by Arden plate 7, requires extra care in subsequent examinations because that person is likely to have an ophthalmic disease	Arden 7 had a PPV of 0.96 and an NPV of 0.97 in the population studied

EMS, Eger macular stressometer; NPV, negative predictive value; PPV; positive predictive value; RT, recovery time.

The survey included both qualitative and quantitative responses. The qualitative responses are summarised, highlighting areas of general agreement and any specific detail that was relevant to the model. The quantitative responses are presented as ranges that were used to inform the relevant model parameters.

Regarding the choice of screening tools and their fitness for purpose, the panel indicated that there was some use for the Amsler chart in clinical practice. The experts were clear that the Amsler grid was of some use with patients, but that it was not an appropriate test to be used by optometrists to screen patients and refer on to an ophthalmologist. The problem highlighted with any test was that they cannot detect recent onset or progression.

It was generally agreed that it was appropriate to give patients instructions to check for visual distortion by covering one eye and observing an object with fixed horizontal lines, for example door or window frames. Patients would be asked to repeat this for the second eye. The abnormality would be described as disturbances, blurring or distortion of the central vision.

Quantitatively, the experts were asked to identify the proportion of people using the cover test who would notice an abnormality when self-testing. *Table 40* shows the results as the range of the percentages of people who the experts predicted would detect AMD using the self-completing cover test.

It was questioned whether macular haemorrhage was an appropriate indicator of wet AMD and, if not, what other indicators could be used by optometrists to identify suspected wet AMD. It was agreed that macular haemorrhage was easily detected if present, but other indicators such as subretinal fluid, exudate and hyperpigmentation were also important and these could be found by optometrists using a slit lamp. It was felt that there was a high referral rate with any signs of wet AMD, but that some indicators could be overlooked by optometrists even if patients had early symptoms described as photo stress or dazzle.

The second quantitative question concerned the proportion of patients presenting at opticians who would be referred on to a hospital eye service, by disease severity. *Table 41* shows the ranges of percentages estimated by the expert panel of ophthalmologists, accounting for the use of macular haemorrhage as a marker for wet AMD, and for other indicators of wet AMD.

Specific questions were asked about the stage of disease at which NHS consultants would expect patients to be referred to the hospital eye service. Although there was some small variation in the comments, there was generally more agreement that suspected wet AMD should be the main referral criterion. There was more willingness to see other patients in the academic unit, which perhaps reflects individual research interests.

Model screening parameters

The above responses informed the definition of screening process in the AMD screening model that was based on self-testing within the eligible population, driven by a reminder letter at specified intervals. Self-defined positive screens are advised to present at an optometrist's for examination and possible referral on to a hospital eye service.

The screening parameters included in the model describe the likelihood that individuals who receive a reminder to self-test for AMD actually undertake the advised self-test, and also the likelihood that individuals with different forms of ARM in one or both eyes present at an

TABLE 40 *Percentage of people detecting visual distortion with cover test by AMD type*

AMD type	Proportion noticing visual distortion after self-completing a cover test (%)
No AMD	<1–5
Drusen	2–5
Dry AMD	5–8
EF CNV	10–30%
JF CNV	30–80
SF CNV	60–100

TABLE 41 *Proportion referred to consultant ophthalmologist by optometrists by AMD type*

AMD type	Macular haemorrhage	Other indicator of CNV
No AMD		1–5
Drusen		5–15
Dry AMD		3–25
EF CNV	10–100	30–70
JF CNV	30–100	30–75
SF CNV	25–100	50–75

optometrist following a self-test. No data were available to inform the probability that individuals who receive a reminder to self-test for AMD undertake the advised self-test. Such parameters are not specific to the disease process and so were not able to be estimated as part of the expert elicitation study. Therefore, the rate of uptake of screening was described as a uniform distribution ranging from 0.3 to 0.7. *Table 42* presents the applied ranges for the probability of screen detection according to the ARM state of the worst affected eye, which were represented by uniform distributions in the model.

As described in Chapter 2, the costs and benefits of individuals without ARM presenting at an optometrist as a result of an AMD screening programme are assumed to be neutral, that is, the benefits of the interventions received equal the costs. Therefore, the AMD model does not incorporate a false positive rate.

Treatment parameters

The systematic review did not include individual trial papers on treatments for AMD, although high-quality reviews of treatment options were assessed. However, treatment options for AMD are currently in a state of flux, with multiple intervention options at various stages of the evaluation and regulatory process. The first stage of the analysis incorporated expert elicitation to inform the appropriateness of current treatment options, and also to inform a process of horizon scanning to identify future possible treatments. The second stage involved the analysis of any available data to populate the model's treatment parameters.

Treatment parameter expert elicitation

The survey used to inform the screening parameters also included questions relating to treatment options for AMD. We wanted to obtain a spread of opinion about the treatment options for various subgroups of patients. We asked first about treatment options other than PDT that would be considered for subfoveal lesions. All agreed that pegaptanib would be a choice of treatment. In addition, one suggested that intravitreal steroid injections (IVSI), argon laser, transpapillary thermo-therapy (TTT) and inhibitors of vascular endothelial-derived growth factor (anti-VEGFs) could all be considered.

For JF lesions, pegaptanib, PDT and steroid use were also considered along with argon laser. They were asked about treatments for EF lesions and whether they agreed that laser photocoagulation was the only treatment. The experts were divided in that two agreed that laser would be the first line of treatment, whereas another concurred but only for classic lesions, as the evidence did not support any intervention for occult EF lesions. The other two experts agreed that there was some scope for clinical judgement and that PDT may be useful along with IVSI or anti-VEGFs.

To inform sensitivity analyses of the model that assessed the potential impact of future interventions for AMD, the experts were asked to engage in some horizon scanning in the area of treatments for dry AMD. They were not hopeful; only one suggested RPE cell transplantation as a possible option. The same exercise was set for prevention of progression to wet AMD and how many cases could be prevented. The experts were more divided, as three did not think that there would be major changes in prevention interventions and did not give any numbers for cases prevented. Two thought that between 5 and 8% of cases may be prevented. Lifestyle changes, mainly stopping smoking, were considered useful generally.

The experts were also asked about what advice, if any, patients could expect to receive if they were not going to be seen in hospital. Lifestyle advice about stopping smoking would be the main advice offered. There was less agreement about diet, although most thought it reasonable, but vitamin supplements were more controversial. Those patients with visual loss due to dry AMD were likely to be referred to the low vision service, but this seems to be dependent on provision within the hospital. Any further monitoring was variable as some did not wish to monitor and others recommended reporting any changes in fellow eyes.

Current treatment model parameters

The base case analysis of the model follows current guidelines in the UK NHS, which do not

TABLE 42 *Screening parameters given the stage of AMD in the worst eye*

ARM state	Minimum	Maximum
Probability of presentation at optometrist		
Early ARM	0.02	0.08
Dry AMD	0.02	0.1
Probability presentation and referral to hospital eye service		
EF wet AMD	0.1	0.3
JF wet AMD	0.5	0.8
SF wet AMD	0.6	0.95

include the use of interventions aimed at reducing progression from early ARM or dry AMD, or second eye ARM incidence. The main purpose of detecting individuals with early ARM is to inform them about the increased likelihood of developing AMD and so encourage more frequent self-testing. In the screening model, it is assumed that individuals with detected early ARM present, and receive appropriate intervention, at the point at which wet AMD develops. This is recognised to be an optimistic assumption, which would be a key aspect to be assessed in any pilot study of a screening programme for AMD.

PDT with verteporfin is the principal current treatment option for wet AMD in the UK, although the likelihood of treatment is dependent on the type and location of the lesion. *Table 43* describes the assumed treatment options for wet AMD by type and location. Once an eye has been treated with either PDT or triamcinolone, it is assumed that the same eye cannot receive additional intervention if and when the lesion progresses; for example, if an eye with an occult lesion is treated with PDT, and later progresses to PC, the eye does not receive a new course of PDT.

The effectiveness parameters for PDT were defined to describe the additional proportion of patients receiving PDT who maintained their VA at their initial level compared with patients receiving placebo. To estimate effectiveness parameters for PDT, we had access to the patient-level data from the TAP and VIP trials. Analyses of the TAP and VIP data require weak assumptions about the long-term effects of treatment, as only 2-year follow-up data are available. In line with the above conservative assumptions regarding clinical presentation with AMD, optimistic estimates of the effectiveness of PDT treatment are defined. The main assumption is that patients in the TAP and VIP trials who lost fewer than 15 letters at the 2-year follow-up point maintain the same level of VA for the remainder of their lifetime. The data were analysed to estimate the absolute risk reduction (ARR) in the proportion of patients losing 15 letters or more, which was then defined in the screening model as the probability that patients receiving PDT maintain their vision from the point of treatment.

Table 44 presents the results of the analysis of the TAP and VIP trial data, by wet AMD lesion type. Analyses of MC lesions, and for 15 letters lost and also 10 letters lost, are presented for comparative purposes. The data show that the baseline VAs between the PDT and placebo groups of each lesion type were very similar, so the ARR is simply estimated as the difference in the proportions of patients losing the defined number of letters at 24 months. PDT is shown to have the greatest effect on patients with PC lesions, with the ARR for occult lesions being approximately half that for PC lesions. The ARR for MC lesions is significantly lower, as expected, as PDT is not a current treatment option for these types of lesion. The proportions losing >10 letters at 24 months are described as beta distributions in the model, with the ARRs for PC and occult lesions being estimated for each iteration of the model based on the sampled values from the relevant distributions.

Estimates of the effectiveness of laser photocoagulation for the treatment of EF lesions are based on the reported results of a trial that randomised 119 patients to argon blue–green laser treatment and 117 to no treatment (*Table 45*). Inclusion criteria included EF lesions with VA of 20/100 or better. The trial had a 5-year follow-up period.[49] Results are only presented for the proportion of eyes with >30 letters lost at 5 years. To inform estimates of effectiveness, it was optimistically assumed that the additional proportion of eyes in the treatment group without >30 letters lost at 5 years maintained their vision at their initial VA over the remainder of their lifetime. Beta distributions were used to describe the uncertainty in the proportions.

TABLE 43 *Treatment options for wet AMD with VA better than 6/60*[a]

Lesion location	Lesion type		
	Occult	**MC**	**PC**
EF	Laser photocoagulation	Laser photocoagulation	Laser photocoagulation
JF/SF	Not treated	Not treated	Photodynamic therapy

[a] Eyes with VA worse than or equal to 6/60 do not receive treatment intervention, but are referred to the low vision service.

TABLE 44 *Effectiveness data from the TAP and VIP trials for PDT*

Variable	N	Mean
Proportion with >15 letters lost at 24 months		
PC on PDT	129	0.38
PC on placebo	73	0.67
MC on PDT	172	0.53
MC on placebo	84	0.55
Occult on PDT	174	0.51
Occult on placebo	93	0.69
Absolute risk reduction		
PC on PDT		0.29
MC on PDT		0.02
Occult on PDT		0.18
Proportion with >10 letters lost at 24 months		
PC on PDT	129	0.54
PC on placebo	73	0.79
MC on PDT	172	0.60
MC on placebo	84	0.65
Occult on PDT	174	0.61
Occult on placebo	93	0.74
Absolute risk reduction		
PC on PDT		0.25
MC on PDT		0.05
Occult on PDT		0.13

Potential treatment model parameters

A range of potential treatment options for ARM are described in the following sections. Estimates of the potential effectiveness of alternative interventions for different stages of the disease are specified and tested in sensitivity analyses of the AMD screening model.

Interventions aimed at preventing progression from early ARM or second eye ARM incidence

The potential impacts of preventative interventions are explored in additional analyses. Two systematic reviews of antioxidant vitamin and mineral supplements for ARM were identified,[10,50] including a total of eight trials, six of which were common to both studies. Excluding the ABTA study of β-carotene and vitamin A,[51] as it did not include a baseline measurement, the AREDS study comprised over 88% of the total numbers of individuals randomised.[50] As a meta-analysis was not deemed possible by the authors of the reviews (due to the trials using different formulations), and given the dominance of the AREDS study, the estimates of the potential effectiveness of preventative measures were based on the results of the AREDS study.

TABLE 45 *Proportion of EF lesions with >30 letters lost at 5 years: MPS group Senile Macular Degeneration Study (SMDS)*

Treatment group	N	Proportion
Laser photocoagulation	119	0.48
No treatment	117	0.62

Unpublished data describing progression of individuals with drusen up to size 63 μm, or a maximum diameter of 125 μm (about 5–15 small drusen) and no pigment abnormalities, from the AREDS trial were kindly made available to the current study. One out of 451 individuals at risk and three out of 490 at risk in the antioxidant and placebo arms, respectively, experienced AMD (dry or wet) over a 5-year follow-up period. These data inform an estimated relative risk (RR) of AMD in individuals receiving antioxidant supplements of 0.36 (with very wide CIs). These data were considered too unstable for use in the model.

Published data include ORs describing the likelihood of individuals with bilateral drusen (early ARM) or unilateral AMD (dry or wet) experiencing AMD in eyes without AMD at baseline. Based on these data, in the sensitivity analyses it was assumed that individuals presenting with early ARM or unilateral AMD receive zinc supplements that reduce their risk of developing wet AMD and dry AMD by 15 and 20% in individuals with early ARM, respectively, and by 47 and 24% in individuals with unilateral AMD, respectively. Log-normal distributions were estimated for each of the four defined RRs based on the reported CIs, as presented in *Table 46*.

Interventions aimed at treating dry AMD

At present, ophthalmologists do not intervene for patients presenting with dry AMD, and the reference case analysis assumes that individuals with detected dry AMD present, and receive appropriate intervention, at the point at which wet AMD develops.

TABLE 46 *Relative risks associated with zinc supplements: AREDS*

	Mean	95% CI	
		Lower	Upper
Early ARM to			
Dry AMD	0.8	0.49	1.34
Wet AMD	0.85	0.57	1.28
2nd eye incidence of			
Dry AMD	0.53	0.35	0.81
Wet AMD	0.76	0.35	1.65

A clinical trial evaluating the safety and effectiveness of treatment with the investigational drug anecortave acetate to a sham procedure with the aim of preventing progression of dry AMD to wet AMD is currently ongoing. Eligible patients must currently have (or have previously had) wet AMD in one eye and dry AMD in the other eye, and be at risk of having their dry AMD progress to wet AMD.[52] Although no effectiveness data are available, this is a potentially important area of development of treatment. Due to the absolute uncertainty around the potential effectiveness of this intervention, a uniform probability distribution of RRs of between 0.25 and 0.75 is specified.

Another intervention, RHEOVision Treatment, is currently being evaluated as part of a small clinical trial for the prevention of vision loss in patients with dry AMD. This intervention is a specialised form of blood cleansing technique that aims to remove excess levels of substances known to thicken the blood, decrease blood flow and cause damage to capillary vessels. A recently published paper of interim results from the trial for the first 43 treated patients showed that at 12 months, 28% of the rheopheresis-treated eyes versus 18% of the placebo-treated eyes showed an increase of at least two lines of best corrected visual acuity (BCVA), and 12 versus 0%, respectively, showed an increase of at least three lines.[53] Pulido[54] also present data showing that, in all patients, 8% of the rheopheresis-treated eyes versus 18.2% of placebo-treated eyes showed at least a two-line loss in BCVA to 12 months. These effectiveness data informed estimates of the additional proportion of treated eyes that gain three lines of VA (0.12), and the additional proportion who did not lose vision (0.102). Log-normal distributions were used to describe the uncertainty in the 'difference in proportion' estimates, based on the standard errors presented in *Table 47*.

A surgical option for the treatment of dry AMD involves the transplantation of sheets of fetal neural retina together with its adjacent retinal pigment epithelium into the space under the fovea. The most recent report on this technique describes its effect on only one patient with dry AMD (and four with retinitis pigmentosa). The dry AMD patient had a pre-surgery VA of 20/640, which improved to 20/240 at 6 months post-operation, but declined to 20/400 at 12 months. Based on such preliminary data, the model does not assess the potential impact of this surgical procedure for dry AMD.

TABLE 47 *Effectiveness estimates for RHEOvision*

	Improve VA by 3 lines	Maintain VA
RHEOvision probability	0.12	0.92
No. at risk	43	43
No treatment probability	0	0.82
No. at risk	43	43
Mean ARR	0.12	0.102
Standard error	0.05	0.07

Interventions aimed at treating wet AMD

In addition to the currently used interventions for treating wet AMD, two additional analyses explored the potential impact of other intervention options that have recently been discussed in the literature. These options are summarised in *Table 48* and discussed below.

In the USA, the debate at the time of writing appears to be around the use of combination therapy (PDT + triamcinolone) for all lesions, that is, PDT is provided to patients with MC wet AMD. A poll taken among attendees of the annual meeting of the American Society of Retina Specialists in 2004 showed that 80% were using combination therapy.[55] Little evidence of the effectiveness of intravitreal injection of triamcinolone acetonide was available, and some of the data identified indicate that triamcinolone is least effective in eyes with MC wet AMD. Jonas and colleagues reported a mean loss in VA for 18 eyes with MC wet AMD, while reporting mean

TABLE 48 *Alternative treatment option sets for wet AMD*[a]

Treatment option set	Lesion location	Lesion type		
		Occult	MC	PC
1	JF/SF	PDT + triamcinolone	PDT + triamcinolone	PDT + triamcinolone
2	JF/SF	Anti-VEGF therapy	Anti-VEGF therapy	PDT + Anti-VEGF therapy

[a] Eyes with VA worse than or equal to 6/60 do not receive treatment intervention, but are referred to the low vision service.

gains for eyes with occult or 100% classic wet AMD.[56]

Bhavsar[57] reported a retrospective review of 26 eyes of 23 patients with MC SF wet AMD, who were treated with PDT and 4 mg of triamcinolone. At a median follow-up of 6 months, 13 eyes experienced an increase in VA; 23 eyes (88%) gained acuity or lost less than three lines.

The largest case series to date has recently been published, which provided combination PDT + triamcinolone to 184 patients with wet AMD and a mean baseline VA of 20/125.[58] Aggregate results are presented, which show that the average increase in VA was between 1.22 and 1.43 lines, although no data on the proportions maintaining and improving vision are reported. The paper does state that there was no difference in response regarding lesion type.

The data reported by Bhavsar[57] were used to inform the potential effectiveness of the PDT + triamcinolone combination. An ARR of 0.15 is estimated by comparing the 6-month rates of visual loss reported by Bhavsar and the MC patients receiving placebo in the TAP trial (0.12 vs 0.27). After adjusting for differences in the ARRs for >15 letters and >10 letters lost for PDT (as reported in *Table 44*), a final ARR for PDT + triamcinolone of 0.11 was assumed. It is recognised that the assumptions informing the potential effectiveness of triamcinolone for MC CNV lesions are weak and based on questionable indirect comparisons, but they are in line with the optimistic assumptions made about the effectiveness of PDT.

The other potential intervention that is tested in the sensitivity analysis is a generically specified form of anti-VEGF endothelial growth factor therapy. Vascular endothelial growth factor (VEGF) is a chemical that is critical in causing abnormal blood vessels to grow under the retina. Recently reporting clinical trials have reported promising results around the use of anti-VEGF therapies that can block VEGF and hence reduce the growth of abnormal blood vessels, slow their leakage and help to slow vision loss.[59]

Pegaptanib sodium (pegaptanib) blocks VEGF, which is thought to be one of the underlying mechanisms promoting the occurrence of wet AMD. The VEGF Inhibition Study in Ocular Neovascularisation (VISION) found that at 2 years 59 and 45% of patients receiving pegaptanib 0.3 mg and the sham intervention, respectively, had lost less than 15 letters, whereas 27 and 10% had gained at least two lines of vision, respectively. The proposed advantage of pegaptanib over PDT is that it is equally effective for all types of wet AMD, that is, pegaptanib could be preferred in MC and occult lesions. In the VISION, in all the treatment groups, an average of 8.5 injections were administered per patient out of a possible total of nine injections.[60]

The other principal potential intervention that has been evaluated as part of a randomised clinical trial is ranubizimab, which binds to and inactivates VEGF. The MARINA trial compared ranubizimab with a sham injection in eyes with MC or occult wet AMD. The 1-year MARINA data showed that 95% of ranubizimab patients had lost fewer than 15 letters compared with 62% in the control group, and between 25 and 34% (depending on dose) gained 15 or more letters compared with 5% in the control group, with 40% of ranubizimab patients achieving VA of 20/40.[61] The ANCHOR trial compared ranubizimab with PDT in PC lesions. The 1-year ANCHOR data showed that 95% of ranubizimab patients had lost fewer than 15 letters compared with 64% in the PDT group, and between 36 and 40% (depending on dose) gained 15 or more letters compared with 6% in the PDT group.[61]

A Phase I/II trial, FOCUS, compared ranubizimab in combination with PDT with PDT alone in eyes with SF wet AMD. At 1 year, 90% of the ranubizimab + PDT group had stable or improved VA compared with 68% of the PDT alone group. Ranubizimab is provided in four weekly cycles, although no data are presented on the number of ranubizimab treatments received by patients. A new trial, the Safety Assessment Intravitreal Ranubizimab for AMD (SAILOR) trial, that evaluates safety, states that ranubizimab will be administered once per month for 3 months and thereafter as needed based on retreatment criteria (which are unstated).

An interesting development in the treatment of wet AMD is the increasing usage of off-label bevacizumab (which Genentech developed for cancer treatment) as treatment for MC and occult forms of wet AMD. In the USA, off-label use of bevacizumab is quickly replacing pegaptanib, due to its more impressive success rate and lower cost.[62] At the 2005 American Academy of Ophthalmology annual meeting, Genentech presented a range of concerns about the drug's potentially adverse effects when used intravitreally for wet AMD. However, Dr Rosenfeld (who is leading the study of bevacizumab for retinal

treatment at the Bascom Palmer Eye Institute in Miami) stated that his laboratory has had no safety issues so far, and that the majority of concerns raised by Genentech are theoretical and have not been identified in actual practice.

Gragoudas and colleagues[60] identify other anti-VEGF interventions that are being developed, including VEGF-Trap that "competitively binds" VEGF, and which is in early phase trials. Studies of RNA molecules that target specific aspects in the VEGF receptor mRNA are also ongoing.

The impact of a generic anti-VEGF therapy is tested in the sensitivity analysis, where the most optimistic estimates of the potential effectiveness of such an intervention are specified, based on the observed results reported by clinical trials to date. The main eligibility criterion for these treatments appears to be that an eye's RPE remains intact, which provides the potential for visual improvement with such biological interventions. RPE status can be approximated as a function of lesion size with lesions smaller than 7 mm^2 usually having an intact RPE, whereas in lesions of size 10 mm^2 or greater the RPE is usually removed [information provided by one of the authors (AB)]. However, as only aggregate results have been published, and as the screening model does not describe lesion status by RPE status or lesion size, the effectiveness of anti-VEGF monotherapy is assumed to be equal across all MC or occult JF and SF wet AMD. Assumed rates of VA maintenance and improvement in patients with MC or occult CNV are as follows:

- 30% improved their VA by three lines compared with 5% in the control group.
- 75% of treated patients maintained their vision at the same level as at diagnosis compared with 29% in the control group.

In patients with PC JF and SF wet AMD receiving PDT + anti-VEGF therapy:

- 38% improved their VA by three lines compared with 6% in the control group.
- 96% of treated patients lost fewer than 15 letters compared with 64% in the control group.

Uncertainty is represented by normal distributions describing the uncertainty in the difference in proportions between each of the outcomes in the two treatment groups, as presented in *Table 49*.

Other potential treatment options include submacular surgery, which has been tested in patients with new and recurrent SF CNV. Thomas and Ibanez[63] report, however, that no difference in the proportion of patients losing two or more lines was observed between a surgery and observation group in a total of 454 eyes, and that surgery is not recommended for any subgroup. An alternative form of surgery for AMD patients with SF CNV involves the translocation of a retinal choroidal patch. van Meurs and van den Biesen[64] report a case series of 41 patients (29 MC, nine occult, three classic) with baseline VA ranging from 20/400 to 20/80. At 12 months' follow-up, 67% of patients had lost two lines or less, and eight patients had VA of 20/80 or better (only one had 20/80 vision at baseline). Submacular surgery is not included in the additional analyses of potential interventions. Retinal choroidal patch grafting appears to be more promising, especially as the procedure is described as being relatively simple (involving a one-step, 1.5 hour process) that is applicable to a wide range of neovascular membranes (e.g. MC, very large). Moreover, the authors imply that more effective procedures based on "more sophisticated upgraded cultivated RPE cells on a suitable artificial substratum" may soon be available. The clinical impact of such interventions may be that CNV becomes a curable disease such that intervention can be delayed until vision declines beyond an acceptable level (e.g. 20/100), which may reduce the need for screening as all clinically presenting lesions will be treatable.

TABLE 49 *Estimated effectiveness of anti-VEGF therapy for juxtafoveal and subfoveal wet AMD*

	Occult or MC		PC	
	Improve VA by 3 lines	**Maintain**	**Improve VA by 3 lines**	**Maintain**
Probability (anti-VEGF)	0.30	0.75	0.38	0.96
No. at risk	480	480	282	141
Probability (no anti-VEGF)	0.05	0.29	0.06	0.64
No. at risk	240	240	282	141
Mean ARR	0.25	0.46	0.32	0.32
Standard error	0.03	0.04	0.03	0.04

Chapter 5

Costs and utility parameters

The screening model incorporates three broad categories of costs: screening, diagnosis and surveillance costs, treatment costs and costs associated with blindness and rapidly deteriorating vision. The broad set of assumptions for the base case analysis and the additional sensitivity analyses are presented in *Table 50*. The following sections describe the data and assumptions informing the estimated cost values used in the screening model in more detail.

Screening, diagnosis and surveillance costs

The actual process of screening is assumed to be a costless activity, as it is assumed to comprise a simple self-test; for example, individuals are advised to cover each eye in turn and look at the window frame, and if the window frame appears not to be straight the individuals are advised to attend an optometrist's. Costs are incurred in the organisation of the screening programme, which is assumed to involve the distribution of personalised reminders to all individuals aged over 50 years on a 3-yearly cycle.

Other economic studies of mass screening programmes have estimated the cost of administering screening invitations, although no empirical evidence of the administration costs of screening were identified. A pilot evaluation of liquid-based cytology for screening for cervical cancer stated that there will be economies of scale benefits in having letter administration coordinated in larger centres, and assumed that the cost of administration of letters to the women was £3 per smear.[65] Roderick and colleagues[66] describe the costs of inviting and administering the general population sample of around 4000 to attend a screening for infection with *Helicobacter pylori* to be £2, although it is not clear if this is the cost per attendee or per invitation.

TABLE 50 *Costing assumptions for the base case and additional sensitivity analyses*

Base case analysis	Additional sensitivity analyses
Individuals present at an optometrist with identified early ARM, dry AMD or wet AMD	
The costs and benefits of individuals presenting at an optometrist without ARM, as a result of a screening programme for AMD, are neutral from the perspective of the NHS and are not included in the AMD screening model	
Individuals with early ARM are managed in the community and told to re-attend at the optometrist's upon vision deterioration	
Individuals with dry AMD or wet AMD are referred on to the hospital eye service for diagnosis	
Individuals with JF or SF PC wet AMD receive PDT. Individuals with EF wet AMD receive laser photocoagulation (PDT)	Individuals with early ARM receive treatment advice from an optometrist. A range of treatment options is specified for different forms of AMD
Individuals with early ARM, dry AMD, EF wet AMD, JF or SF occult or MC wet AMD are advised to self-test their vision at regular intervals and to re-attend if and when their vision deteriorates	Individuals with early ARM, dry AMD or EF wet AMD are advised to self-test their vision at regular intervals and to re-attend if and when their vision deteriorates
Individuals re-attend upon vision deterioration, a maximum of once per year until they develop either JF or SF PC wet AMD	Individuals re-attend upon vision deterioration, a maximum of once per year until they develop either JF or SF wet AMD
Patients treated for EF wet AMD may receive subsequent PDT. No further treatment costs are assumed for individuals with JF or SF PC wet AMD	Patients treated for early ARM, dry AMD or EF wet AMD may receive subsequent treatments. No further treatment costs are assumed for individuals with JF or SF wet AMD
Individuals whose vision deteriorates to 6/60 or worse incur estimated costs associated with blindness and rapidly deteriorating vision	

It was assumed that an AMD screening programme would be administered at a national level as there is no need to coordinate screening invitations and screening test resources (as the test is a self-test). Drawing on the economies of scale argument, the cost of administration of a screen reminder was assumed to be between £0.50 and £2 per invitation sent.

Regardless of whether a case is screen detected, all individuals who seek medical care owing to a defect in vision that is due to either early ARM, dry AMD or wet AMD are assumed to present initially at an optometrist's. The Royal College of Ophthalmologists' guidelines recommend that mild, early AMD requires no special management and can be managed in the community.[67] Optometrists are assumed to continue to carry out routine examinations and refraction in this group of patients upon vision deterioration until dry AMD or wet AMD is suspected.

All individuals with dry AMD or wet AMD are referred on to a hospital eye service to confirm diagnosis via a fluorescein angiography and an outpatient appointment with an ophthalmologist. It is recognised that some individuals may present via their GP, but the cost impact of the different pathways to the hospital eye service is likely to be small and so a single pathway is described.

The unit costs informing the diagnosis and surveillance of ARM are presented in *Table 51*. The cost of the initial presentation at an optometrist's is estimated from the perspective of the NHS, and is informed by the published value of vouchers available to help with the costs of optical care. The proportion of individuals who are eligible for such help is unknown, and so it is assumed that 50% of the individuals presenting with vision defects due to ARM will be eligible. The costs of a first outpatient visit plus an angiography are applied at the point of diagnosis, whereas the costs of a follow-up outpatient visit plus angiography are applied at subsequent points of surveillance.

Individuals with bilateral ARM follow the pathway described for the eye with the most intensive intervention (e.g. a pathway leading to treatment). Individuals with no lesion(s) eligible for treatment are assumed to receive no further care until vision in the affected eye(s) worsens, which may or may not be due to the lesion type or location varying. It is recognised that vision may worsen without the lesion type or location varying. At the point at which vision declines, the individual is assumed to attend the hospital eye service and receive a further fluorescein angiography to identify the current lesion type and location.

Individuals are assumed to continue to attend the hospital eye service for surveillance upon worsening VA until either treatment for JF or SF wet AMD is instigated or the individual's better eye VA declines to 6/60, at which point treatment is assumed to be ineffective and costs associated with blindness and rapidly deteriorating vision are applied to individuals (see the section 'Costs associated with blindness and rapidly deteriorating vision', p. 50). In the absence of treatment initiation, it is assumed that individuals present only once per annum at a hospital eye service.

Treatment costs

Costs for treatments included in the base case analysis of the model are described in the subsequent section, followed by a section describing cost estimates for the potential interventions that are included in the sensitivity analyses of the AMD screening model.

Current treatment options

In the base case model analysis, only two treatment options are included: laser photocoagulation and PDT. The estimated costs of

TABLE 51 *Diagnosis and surveillance costs*

Resource	Mean cost (£)	Interquartile range (£)	Data source
Optometrist visit	18.39		Department of Health[a]
Angiography	142.64	82.12–166.91	2002 Reference Costs[b]
First outpatient visit	92.11	71.39–108.85	2004 Reference Costs[b]
Follow-up outpatient visit	56.92	46.10–63.77	2004 Reference Costs[a]

[a] HC12 Charges and optical voucher values, 1 April 2005: sight tests and NHS vouchers for glasses and contact lenses. 50% of attendees are assumed to be eligible for help with health costs.
[b] All NHS reference cost sources are uprated to January 2006 values using the NHS Pay and Prices Index.

PDT are based on the reported frequency of therapy observed in the pivotal trials of PDT: the TAP and VIP trials. A mean cost per patient on PDT of £8052 (discounted at 3.5%) is estimated based on the data reported in *Tables 52* and *53*, which describe the proportion of patients receiving alternative numbers of PDT sessions. For each PDT session, the costs comprise the costs of verteporfin, laser treatment of the retina, an angiography and a follow-up outpatient visit. Each patient is assumed to attend for one additional angiography and outpatient visit after finishing PDT. The aggregate cost is applied at the point at which PDT commences and is assumed to cover all subsequent healthcare received by an individual with respect to the treated eye until best eye VA declines to 6/60. Individuals may receive subsequent treatment for the fellow eye.

Unit costs for resources associated with laser photocoagulation included the costs of angiography, outpatient visits and laser treatment of the retina. The frequency of intervention was informed by two studies. Busbee and colleagues estimated the cost–utility of laser photocoagulation for EF wet AMD.[68] They describe the process of undertaking additional angiographies 2–4 and 4–6 weeks after initial treatment, in addition to assuming that 25% of patients require re-treatment, incorporating three additional angiographies and outpatient visits (in addition to the extra laser treatment). Bonastre and colleagues present a burden of illness analysis for AMD in France, and present observed data on 105 patients, 76 of whom received laser photocoagulation.[69] The mean number of sessions for treated patients is stated to be 2.2. The data from these two studies are combined to estimate an aggregate mean cost of laser photocoagulation of £1536, as presented in *Table 54*.

Potential treatment options

A range of potential treatment options were included in the sensitivity analyses of the screening model. Treatment costs for interventions included in the additional model analyses are listed in *Table 55*. The data and assumptions informing the cost estimates are described in this section. For early ARM, vitamin supplements are assumed to be bought by individuals upon advice from the optometrist and do not impose a cost on the NHS.

The cost of anecortave acetate (Retaane depot) is unknown, although Sharma and colleagues[70] analysed the same intervention in the context of a new treatment for wet AMD in order to determine the cost at which this treatment might offer economic value to society, using incremental cost-effectiveness ratios (ICERs). They found that an

TABLE 52 *PDT treatment frequency and costs*

No. of treatments within 2 years	Proportion	Cost (£)	Discounted (£)
1	0.045	1349	1349
2	0.072	2497	2497
3	0.102	3646	3646
4	0.085	4795	4795
5	0.144	5944	5743
6	0.127	7093	6853
7	0.137	8242	7963
8	0.288	9391	9074
Mean no. of treatments beyond 2 years	1.52	1746	1630
Total cost			8052

TABLE 54 *Costs of laser photocoagulation*

Costs per session	Cost (£)
3 × angiography	428
3 × follow-up outpatient visit	171
1 × laser treatment	99
Total	698
Mean number of sessions	2.2
Total cost per patient	1536

[a] It is assumed all treatment sessions occur within 1 year of initial treatment.

TABLE 53 *Unit costs associated with the provision of PDT*

Resource	Mean cost (£)	Interquartile range (£)	Data source
Verteporfin	850.00		BNF 50
Laser treatment of retina	99.39	73.06–130.65	2002 Reference Costs[a]
Angiography (fluorescein or indocyanine)	142.64	82.12–166.91	2002 Reference Costs[a]
Follow-up outpatient visit	56.92	46.10–63.77	2004 Reference Costs[a]

[a] All NHS reference cost sources are uprated to January 2006 values using the NHS Pay and Prices Index.

TABLE 55 *Medication costs for potential interventions for AMD evaluated in the additional sensitivity analyses*

Treatment	Aggregate treatment cost (£)[a]	Data source
Vitamin supplements for early ARM	0	Individuals' self-supply
Retaane depot (for dry AMD)	5,100	Threshold analysis (Sharma *et al.*[70])
RHEOVision treatment (for dry AMD)	5,100	Assumed to be same as Retaane depot
PDT + triamcinolone	1,579	Augustin and Schmidt-Erfurth[58]
Generic anti-VEGF therapy	10,148	Pegaptanib US cost
Bevacizumab anti-VEGF therapy	1,358	Pollack[72]

ICER of US$100,000 per QALY would be associated with an anecortave cost of US$3022 per vial, and an ICER of US$50,000 per QALY with an anecortave cost of US$2986 per vial. A cost of US$3000 (£1700) per 15 mg is assumed in the screening model.[70] No costs for RHEOVision treatment are presented, so a similar cost profile to that estimated for anecortave acetate is used (£1700 per 6 months). No data were identified that could inform the likely number of treatment sessions, so a range of 2–4 sessions was assumed for both treatment options for dry AMD (with a mean of three sessions).

Triamcinolone is given in 4-mg doses as injections (aqueous suspension) for which the medication cost is £1.02 (Adcortyl, triamcinolone acetonide 10 mg/ml; net price of a 1-ml ampoule = £1.02). The cost per session of providing PDT + triamcinolone is estimated as the cost of a PDT session, as described above, plus the cost of the additional medication. In a case series of 199 patients treated with verteporfin PDT combined with intravitreal triamcinolone for CNV, patients required a mean of 1.25 treatments to achieve persistent inactivation of the neovascular membrane.[71] All treated patients are also assumed to receive an additional angiography and outpatient visit following their last treatment session.

Regarding the costs of anti-VEGF therapies, no costs for the provision of ranubizimab have been published; whereas some have predicted a cost of US$4000 per dose,[73] others suggest that the cost will be similar to that of pegaptanib, which costs around US$1000 per dose (but is given every 6 weeks, rather than every 4 weeks for ranubizimab).[72] The cost of a generic anti-VEGF therapy, based on the reported costs of pegaptanib, assumes a drug cost of £600 per injection, plus the cost of a follow-up outpatient visit per 6-weekly treatment application.

Only very limited information describing the number of ranubizimab injections that patients may receive is included in the criteria for the SAILOR trial, which state that ranubizimab will be administered once per month for 3 months and thereafter as needed based on re-treatment criteria (which are unstated). Therefore, treatment frequency was also based on data from the pegaptanib studies, which reported that a mean number of treatments for the 2 years for all patients re-randomised to continue pegaptanib therapy was 16 out of 17 possible treatments.[60,74]

Given the reported use of bevacizumab, and ongoing clinical studies evaluating bevacizumab as a potentially cheaper form of anti-VEGF therapy, which may have similar levels of effectiveness and frequency of intervention (although some doctors think that bevacizumab will require less frequent injections), but provided at a much lower cost, bevacizumab is not an inexpensive drug, costing US$4400 per month when used as an intervention for colorectal cancer, but these doses are being divided into tiny portions to be injected into the eye. The amount needed for each injection costs only about US$30–100.[72]

Costs associated with blindness and rapidly deteriorating vision

Costs to the NHS and local and central government associated with blindness and rapidly deteriorating vision were informed by the estimates presented in an HTA of PDT.[75] Uprating the presented aggregate costs to January 2006 using the NHS Pay and Prices Index, the estimated initial costs associated with blindness range from £52 to £295, and the annual costs range from £1325 to £16,804 (*Table 56*).

Utility values

The QoL literature review presented identified two separate groups that had assessed utility related to diminished vision. Colleagues at ScHARR undertook a study to obtain general

TABLE 56 *Costs associated with blindness and rapidly deteriorating vision*[75]

	Base case (£)		Low range (£)		High range (£)	
	Proportion	**Annual**	**Proportion**	**Annual**	**Proportion**	**Annual**
Blind registration	0.945	97	0.5	40	0.945	170
Low vision aids	0.33	136	0.33	56	0.74	136
Low vision rehabilitation	0.11	205	0.11	125	0.11	309
Housing/council tax benefit	0.45	2,714	0.21	2,413	0.73	3,588
Social security	0.63	1,924	0.17	0	0.63	2,876
Tax allowance	0.05	319	0.05	145	0.18	319
Depression	0.386	392	0.06	392	0.5	392
Hip replacement	0.05	3,669	0.005	1,177	0.247	3,933
Community care	0.06	2,849	0.06	1,138	0.4	4,759
Residential care[a]	0.3	11,133	0.13	5,490	0.56	16,509
Initial cost[b]	160 (170)		52 (56)		295 (315)	
Annual cost[b]	6,295 (6,719)		1,325 (1415)		16,804 (17,937)	

[a] It is assumed that 30% of individuals requiring residential care fund themselves and do not contribute costs from the perspective of the government.
[b] Figures in parentheses are uprated to January 2006.

population utility values for VA and contrast sensitivity (CS) states.[76] A total of 209 patients with unilateral or bilateral AMD were recruited and interviewed. The study involved the completion of a number of visual tests to measure near and distant VA and CS. To estimate utility values, the respondents completed three preference-based measures, the Health Utility Index 3 (HUI-3), EuroQol 5 Dimensions (EQ-5D) and Short Form 6 Dimensions (SF-6D), in addition to estimating utility values via a time trade-off (TTO) process.

This study actually showed that CS had a slightly better relationship and explained more variation in health status than VA. However, the other data used in the model did not measure CS, hence it was not possible to develop a model based on CS progression and so the model is restricted to using VA-related utility data. *Table 57* presents the summary data describing utility values as a function of alternative levels of VA for each of the valuation approaches.

In the Sheffield study, a marked correlation with age was identified, which led to the estimation of an algorithm to predict utility values as a function of both age and VA. The algorithm was based on the HUI-3 results as general population values were considered most relevant [in line with recommendations by the National Institute for Health and Clinical Excellence (NICE)]. Regression analyses of the 209 patient responses tested a range of alternative models. Restricting the observations to the range 0–1.6 logMAR units (as used in the model), a linear model had the highest R^2 and produced the best predictions. The algorithm parameters are presented in *Table 58*.

TABLE 57 *Mean (standard deviation) scores of preference-based measures by VA in the best seeing eye: Sheffield study*[76]

Distant logMAR	***N***	**TTO**	**HUI-3**	**SF-6D**	**EQ-5D**
>2.00	16	0.47 (0.31)	0.10 (0.18)	0.63 (0.10)	0.63 (0.22)
1.31–2.00	60	0.60 (0.33)	0.27 (0.24)	0.65 (0.11)	0.71 (0.21)
0.61–1.30	59	0.64 (0.30)	0.36 (0.25)	0.66 (0.14)	0.75 (0.20)
0.31–0.60	41	0.67 (0.31)	0.38 (0.25)	0.67 (0.14)	0.70 (0.20)
≤0.30	33	0.73 (0.30)	0.50 (0.35)	0.70 (0.18)	0.75 (0.27)
η^2		0.04[b]	0.13[a,b]	0.02	0.02

η^2: variability in health status score explained by VA, and calculated as the sum of squares between groups divided by the total sum of squares from the analysis of variance results.
[a] $p < 0.05$ between groups.
[b] $p < 0.05$ linear trend.

TABLE 58 *Sheffield linear visual acuity utility algorithm*

Parameter	Coefficient
Age	–0.00792
LogMAR units (0–1.6)	–0.10872
Constant	1.078315

An example estimate of utility is presented below for an 85-year-old with a better eye logMAR score of 0.2:

$$\text{utility value} = 1.0783 - (0.0079 \times 85) - (0.2 \times 0.10872) = 0.384$$

Brown and colleagues have published a range of AMD utility studies.[77,78] The most relevant study that was identified used the TTO approach to elicit utility values for AMD patients' current health state.[77] The results are presented in *Table 59*.

Although the Brown study used a slightly different grouping for VA compared with that used by the Sheffield group, the Brown estimates indicate a slightly stronger relationship between VA levels and utility than the Sheffield study, that is, the difference between the best and worst VA categories is greater. However, the differences between the two sets of TTO results are unlikely to be statistically significant, even though there were differences in the applied TTO methodology. Brown and colleagues used an open-ended variant of TTO where respondents are asked how long they are expected to live and then asked how much of the remaining time of life they would be willing to trade for a treatment that would restore vision. The Sheffield study used the interactive variant developed at York University, and which was subsequently used to value the EQ-5D.[76]

TABLE 59 *Non-age-specific AMD utility values by VA*[78]

Vision	Mean utility	95% CI
6/6–6/7.5	0.89	0.82 to 0.96
6/10–6/15	0.81	0.73 to 0.89
6/20–6/30	0.57	0.47 to 0.67
6/60–3/60	0.52	0.38 to 0.66
Count fingers to light perception	0.4	0.29 to 0.5

The model was analysed using two separate sets of utility values. The first set was based on the reported Sheffield algorithm, which adjusted the aggregate utility values for co-morbidities and other effects related to ageing. This utility algorithm assigns a relatively small utility effect to changes in VA; for example, a person with a better eye logMAR score of 0 (equivalent to 6/6 vision) has only 0.109 better utility than a person with a logMAR score of 1 (equivalent to 6/60 vision, and able to register as blind). The equivalent utility difference in the Brown study is around 0.3 utility points.

The model was also analysed using a set of utility values that were not adjusted for age effects, and so the inputted utility values are constant across all age groups. To provide the greatest contrast with the age-specific utility values, the values presented by Brown and colleagues are used. These values have also previously been used to inform the NICE appraisal of PDT for AMD.[79]

Chapter 6

Model implementation and analysis

The evaluative framework for the evaluation of screening programmes for AMD is a hybrid individual sampling/cohort Markov decision model, which is designed to reduce the number of iterations that would be required if the model was built as a pure individual sampling model. Given the complexity of the pathways described, implementation of a pure cohort model was infeasible. Individual sampling models analyse multiple first-order iterations of the model to estimate mean values for each of the model's outputs for a given set of input parameters. Each first-order iteration of the model describes the progression of disease in an individual person from age 50 to 100 years. For every model iteration, and every defined natural history, the model also describes the progression of disease assuming that individuals are clinically diagnosed in each year subsequent to the age at which ARM is the first incident; for example, if an individual first develops early ARM at age 70 years, the model describes separate 32 lifetime profiles for that individual to represent the effects of that individual being diagnosed with ARM at ages 70, 71, 72, …, 98, 99, 100 years, or ARM never being diagnosed. The costs and effects estimated for each of the separate lifetime profiles are multiplied by the probability that an individual presents at each of the ages (or that the individual never presents). The probabilities of clinical diagnosis are dependent on the lesion(s) state(s), whether one or both eyes are affected and whether a screening programme is in place.

Multiple second-order analyses of the model are required to estimate the mean cost-effectiveness of alternative screening programmes for AMD, and also to represent the uncertainty around the mean cost-effectiveness estimates. Mean values for the model's input parameters were not specified because there was great uncertainty around the value of many of the parameters, and especially concerning the correlation between alternative input parameters. It is particularly important to minimise the likelihood of sampling infeasible combinations of values for alternative input parameters. The impact of infeasible correlations is likely to be greater in screening models than treatment models, because the range of input parameters is greater. An example involves the sampling of high values for both disease incidence and disease progression, which can lead to extremely unlikely model outputs. Therefore, the second-order analysis of the model was informed by a process of calibration, which is described in the following section.

Calibration methods

Almost all natural history-based screening models include unobservable parameters, such as the probability of clinical presentation from a given stage in the natural history of a disease. Many screening models use calibration methods to populate baseline (mean) values for unobservable parameters, although very few use calibration to represent parameter uncertainty. The AMD screening model is calibrated to inform sets of correlated input parameters that are used to estimate mean cost-effectiveness values, in addition to informing probabilistic sensitivity analyses that represent the sum of the uncertainty in the model.

The general calibration process involves analysing the model for a large number of second-order iterations, from which the model predicts a set of outputs for alternative sets of input parameter values. The outputs include parameters that can be compared with data that have been empirically observed, such that the accuracy of each set of input parameter values in predicting alternative model outputs can be assessed quantitatively. The accuracy of each iteration's predictions for the defined outputs is represented as a weight. If multiple outputs are predicted, the sum of the weights across all the outputs is used to describe the likelihood that each input parameter set is the most accurate set of input parameters. For each iteration of the second-order analysis of the model, a set of input parameters is sampled according to the weights attached to each input parameter set as part of the calibration process.

Calibration outputs

Three types of observed data were used to calibrate the AMD screening model:

- age- and state-specific clinical diagnosis rates of ARM
- VA at presentation by ARM state
- age-specific rates of bilateral 6/60 vision or worse due to ARM.

Age- and state-specific clinical diagnosis rates of ARM

Age- and state-specific clinical diagnosis rates of ARM incorporate the incidence and the natural history of ARM, in addition to clinical presentation rates. No routine data or published studies of clinical diagnosis rates of ARM were identified, so it was necessary to pursue new primary sources. To inform the current analysis, data were made available from the ophthalmology department at the Sheffield Teaching Hospitals NHS Foundation Trust that described the number of patients receiving treatment for wet AMD with PDT in the years 2002–5, by age.

The analysis of the treated patients was restricted to patients living at postcodes defined as being within the city of Sheffield, so excluding patients who were referred to the Sheffield PDT clinic from surrounding towns and cities, including Doncaster, Barnsley and Chesterfield. The analysis was so restricted in order to be able to define accurately the size of the relevant age-specific population from which the patents were drawn, but also because one of the authors (CB) advised that the referred patients from the Sheffield area were more likely to represent the full set of referred patients (e.g. patients from Chesterfield may be referred elsewhere).

The estimation of the total number of patients presenting clinically with ARM and the distribution of ARM states (in both eyes) at presentation required back-extrapolation of the PDT data. The first stage involved estimating the total number of patients who presented at the PDT clinic, because the data only described those patients who received PDT. The consultant ophthalmologist author (CB) was the sole clinician seeing attending patients at the Sheffield PDT clinic, and so his estimate of the percentage of presenting patients who received treatment was used to extrapolate to the total number of presenting patients. He estimated that between 33 and 40% of referred patients were treated, so a mean estimate of 36.5% was used to estimate the total number of presenting patients at the PDT clinic.

The data from 2004 and 2005 were used, as these were the most current estimates, and the number of treated patients increased year on year. The 2005 figures are uprated by 12/11 as the data describe numbers treated to November 2005.

The second step in the back-extrapolation required estimation of the proportions of patients presenting with ARM at general hospital eye services who were referred on to the Sheffield PDT clinic. This stage of the analysis was informed by a survey of all ophthalmologists who referred into the Sheffield PDT clinic. The ophthalmologists were asked the following questions:

- Of 100 patients receiving their first diagnosis of AMD or ARM, please estimate in your opinion how many are in each of the following AMD categories.
- Of 100 patients that you diagnose in the different categories of ARM, how many do you refer on to a PDT clinic? (Appendix 4).

Nine responses were received (a response rate of 31%), although three ophthalmologists stated that they could not provide responses without collecting data. The six sets of quantitative responses are presented in *Table 60*, which shows a very large range in the answers to both parts of the survey. As question 2 informs the total number of presented cases, it was decided to use the non-extreme responses to question 2 (respondents 2, 5 and 6) to inform the predicted number of individuals clinically presenting with ARM, as the extreme responses (both high and low) were unlikely to be representative of the full set of referring ophthalmologists. As the distribution of ARM states is likely to be correlated with the proportion of cases referred on to the PDT clinic, and a range of distributions were described by respondents 2, 5 and 6, the combined responses to questions 1 and 2 from these ophthalmologists were used to back-extrapolate the total number of presenting ARM patients and the corresponding distribution of lesion types.

The data presented in *Table 60* in answer to question 2 (for respondents 2, 5 and 6) were combined with the estimated numbers of patients presenting at the PDT clinic (*Table 61*) to estimate the age-specific numbers of patients presenting with some form of ARM in Sheffield. *Table 61* presents the resulting numbers showing that the largest group of patients is expected in the 75–84 years age group.

The responses to question 1 in *Table 60* were used to estimate ranges for the proportion of individuals within different age categories that

TABLE 60 *Survey of ophthalmologists: responses to questions about patients referred on to PDT clinic in Sheffield*

Question		Respondent					
		1	2	3	4	5	6
1	**Of 100 patients receiving their *first* diagnosis of AMD or ARM, please estimate in your opinion how many are in each of the following categories:**						
	Unilateral ARM	30	10	10	5	2	25
	Unilateral dry AMD	27	20	9	10	2	12
	Unilateral EF AMD	4	5	4	1	0	2
	Unilateral JF AMD	6	10	5	1	1	5
	Unilateral SF AMD	3	20	10	10	1	5
	Bilateral ARM	70	10	90	50	98	75
	Bilateral ARM/AMD, worst eye has dry AMD	50	10	10	5	82	40
	Bilateral ARM/AMD, worst eye has EF AMD	10	5	10	5	2	1
	Bilateral ARM/AMD, worst eye has JF AMD	5	5	70	1	4	5
	Bilateral ARM/AMD, worst eye has SF AMD	5	5	85	2	94	30
2	**Of 100 patients that you diagnose in the following categories, how many do you refer on to a PDT clinic?:**						
	Unilateral JF AMD	3	25	100	1	50	50
	Unilateral SF AMD	3	25	100	2	80	50
	Bilateral ARM/AMD, worst eye has JF AMD	5	30	100	2	60	50
	Bilateral ARM/AMD, worst eye has SF AMD	5	20	100	5	80	25

TABLE 61 *Estimated age-specific clinical incidence of ARM in Sheffield*

Age category (years)	Population at risk	Estimated cases presenting at PDT clinic	Cases presenting at general hospital eye service	
			Minimum	Maximum
50–59	120,553	11	19	133
60–64	50,362	12	20	142
65–74	85,868	42	72	515
75–84	60,966	138	235	1,684
85–89	14,412	32	54	388
90+	6,866	18	30	215
Total	339,027	253	429	3,077

present with different combinations of ARM states in both eyes (including no ARM in one eye). The resulting range of presenting patients for each age and state combination are presented in *Table 62*.

Visual acuity at presentation by ARM state

The second output parameter used to calibrate the AMD screening model describes the VA of presenting eyes at the point of clinical presentation. A dataset containing the morphometric status of eyes and the corresponding VA of 99 eyes with wet AMD at the time of initial presentation was made available. The dataset and the methods used to examine the eyes are described in detail by Ali and colleagues.[40] *Table 63* describes the frequencies of the alternative lesion types and locations.

Three separate regression analyses were undertaken to predict VA scores at presentation by lesion location. Covariates for occult and MC lesions were tested, although they were not statistically significant in any of the analyses. Based on the simple analysis, *Table 64* presents the 95% CIs for three lesion locations that were used in the calibration analysis.

Age-specific rates of bilateral 6/60 vision or worse due to ARM

The final output parameters against which the AMD screening model was calibrated describe the age-specific rates of visual impairment due to AMD in the UK. Evans and Wormald in 1996[80] looked at the incidence of those registered blind or partially sighted due to AMD over a period of 50 years. Over 15,000 people are registered

TABLE 62 *Estimated numbers of individuals presenting with AMD by bilateral ARM status in Sheffield*

ARM state	Age category (years)					
	50–59	60–64	65–74	75–84	85–89	90+
Unilateral ARM	0–11	0–12	0–42	0–139	0–32	0–18
Unilateral dry AMD	0.4–22	0.4–23	1.6–85	5.2–277	1.2–64	0.7–35
Unilateral EF AMD	0–5.5	0–6	0–22	0–69	0–16	0–9
Unilateral JF AMD	0.2–11	0.2–12	0.8–42	2.6–139	0.6–32	0.3–18
Unilateral SF AMD	0.2–22	0.2–23	0.8–85	2.6–277	0.6–64	0.3–35
Bilateral ARM	0–11	0–12	0–42	0–139	0–32	0–18
Bilateral ARM/AMD, worst eye has dry AMD	11–20	12–21	42–75	139–246	32–57	19–31
Bilateral ARM/AMD, worst eye has EF AMD	0.4–5.5	0.5–6	1.7–21	5.5–69	1.3–16	0.7–9
Bilateral ARM/AMD, worst eye has JF AMD	0.9–5.5	0.9–6	3.4–21	11.1–69	2.6–16	1.4–9
Bilateral ARM/AMD, worst eye has SF AMD	5.5–21	6–22	21–80	69–261	16–60	9–33
Population at risk	120,553	50,362	85,868	60,966	14,412	6,866

TABLE 63 *Summary of ARM lesions by type and location in Ali and colleagues' dataset*[40]

Location	Occult	Type		Total
		MC	PC	
EF	2	2	4	8
JF	5	7	17	29
SF	14	13	35	62
Total	21	22	56	99

TABLE 64 *95% CIs for wet AMD lesions at presentation (logMAR units)*

Lesion	95% CI	
	Lower	Upper
EF	0.27	0.79
JF	0.36	0.61
SF	0.58	0.76

annually due to this condition.[80] Owen and colleagues[4] undertook a systematic review of AMD prevalence and visual loss caused by AMD, and noted that there was a dearth of population-based prevalence studies in the UK and that the numbers were too small to provide accurate estimates. Based on a meta-analysis of six studies (including one UK-based study), three outcome measures were estimated: partial sightedness due to AMD, prevalence of dry AMD and prevalence of wet AMD.

The model is used to predict age-specific rates of partial sightedness, defined as 6/60 vision or worse, which is assumed to be equivalent to the rates of 6/60 vision as presented by Owen and colleagues.[4] *Table 65* presents the summary data from Owen and colleagues[4] regarding the percentage prevalence of individuals with best VA of between 6/60 and 3/60 and worse than 3/60. The reported data are combined to estimate rates of bilateral vision of 6/60 or worse in the age ranges specified in the AMD screening model.

Calibration analyses

To calibrate the AMD screening model, 2500 sets of the model's input parameters were randomly sampled from the probability distributions described for each input parameter. For each input parameter set, values for each of the calibration outputs described in the previous section were predicted, based on 200 first-order iterations of the model for each input parameter set. The number of first-order iterations describes the number of individuals flowing through the model for each second-order iteration, although the scale is multiplied up by the hybrid nature of the model, which incorporates multiple points of clinical presentation and subsequent treatment effect (as described in Chapter 2).

The predicted values of the calibration parameters were used to attach probabilities to each input parameter set, to reflect the probability that each set was the optimal set for predicting the calibration outputs. This process involved the following steps:

1. For each input parameter set, compare the predicted aggregate rate of clinical presentation with ARM with the (estimated) observed rate of clinical presentation. If the predicted value lies outside the observed range, the input parameter set is excluded from the main analysis. Otherwise, progress to step 2.

TABLE 65 *Percentage of population with alternative levels of partial sight/blindness with 95% CIs in parentheses*[4]

Age range (years)	*N*	Reported		Age range (years)	Estimated <6/60
		6/60–3/60	<3/60		
50–54	1823	0 (0 to 0.2)	0 (0 to 0.2)	50–59	0.02 (0 to 0.12)
55–59	2943	0 (0 to 0.13)	0.03 (0 to 0.19)	60–64	0.03 (0 to 0.19)
60–64	3528	0 (0 to 0.1)	0 (0 to 0.1)	65–74	0.06 (0.02 to 0.14)
65–69	3787	0 (0 to 0.1)	0 (0 to 0.1)	75–84	0.38 (0.21 to 0.63)
70–74	3288	0.06 (0.01 to 0.22)	0.06 (0.01 to 0.22)	85–89	4.21 (2.72 to 6.2)
75–79	2527	0.24 (0.09 to 0.52)	0.36 (0.16 to 0.68)	90+	8.67 (5.13 to 13.52)
80–84	1422	0.84 (0.44 to 1.47)	0.84 (0.44 to 1.47)		
85–89	570	0.88 (0.29 to 2.04)	3.33 (2.02 to 5.16)		
90+	196	2.55 (0.83 to 5.85)	6.12 (3.2 to 10.45)		

2. For each input parameter set, compare the predicted proportions of individuals presenting with ARM by age and bilateral ARM status to the observed ranges for each of the 60 output parameters described in *Table 62*. For each of the 60 age and state combinations, estimate the difference between the predicted value and the nearest boundary of the observed range. If the predicted value is within the range a difference of zero is estimated; if the predicted value is above the range, the difference is the predicted value minus the upper limit of the range; and if the predicted value is below the range, the difference is the lower limit of the range minus the predicted value. Sum the value of the differences across the 60 output parameters.
3. For each input parameter set, compare the predicted VA scores at presentation with the observed ranges for each of the three defined wet AMD states. For each parameter, estimate the difference between the predicted value and the nearest boundary of the observed range. Sum the value of the differences across the three output parameters.
4. For each input parameter set, compare the rates of bilateral visual acuity of 6/60 or worse with the observed ranges for each of the six defined age ranges reported in *Table 65*. For each parameter, estimate the difference between the predicted value and the nearest boundary of the observed range. Sum the value of the differences across the six output parameters.
5. For each input parameter set, calculate a separate weight for each of the three categories of calibration output parameters. The weights are estimated as the reciprocal of the sum of the differences for each of the three calibration outputs. For clinical incidence, if the sum of the differences across all parameters describing age- and state-specific clinical presentation rates is 0.025, a weight of 40 is estimated. If the sum of the differences is zero, a subjective weight of 1000 is applied.
6. For each of the three categories of calibration output parameters, sum the weights across all included input parameter sets.
7. For each input parameter set, calculate the probability that each set is the optimal set by dividing the weight for each input parameter set by the sum of the weights for each of the three output parameter categories.
8. For each input parameter set, calculate a weighted aggregate probability that each set is the optimal set across all calibration output parameters by combining the estimated probabilities according to the following weights:
   (a) age- and state-specific clinical diagnosis rates of ARM: 0.6
   (b) VA at presentation by ARM state: 0.15
   (c) age-specific rates of bilateral 6/60 vision or worse due to ARM: 0.25.

   The weights applied to the three output parameter categories are subjectively defined, and reflect the relative importance of model predictions of clinical presentation rates.
9. Order the input parameter sets and estimate the cumulative probability that the sets prior to and including each set are the optimal sets. In the main analysis of the model, input parameter sets are selected by randomly sampling a value between 0 and 1 and selecting the input parameter set with the cumulative probability that is nearest to the sampled value.

Calibration results

The results of the calibration analysis showed that of the 2500 second-order iterations, 716 iterations estimated aggregate incidence rates outside the observed range: these parameter sets were excluded from further analyses. The following paragraphs and figures provide an indication of

the success of the calibration process in predicting the observed data.

Of the remaining 1784 iterations, *Figure 7* displays the distribution of the sum of the differences between the predicted and observed logMAR scores for three locations of wet AMD: EF, JF and SF lesions. The distribution is more skewed than that for the sum of differences of incidence rates, with over 40% of iterations reporting a maximum of sum of differences of 0.2 logMAR unit. Over 90% of iterations reported a sum of differences across the three lesion locations of less than 0.6 logMAR unit.

The other calibration parameter describes the sum of the age-specific incidence rates of individuals whose best eye VA decreases to at least 6/60 (equivalent to a logMAR score of 1). These data also show a skewed distribution. The differences appear fairly large, although it is noted that *Figure 8* presents sums of the differences across six independent age categories, and the aggregate difference is smaller than the sum. The data still show that over 90% of the iterations result in a sum of differences of less than 0.06.

Model analysis

Two main sets of analyses of the AMD screening model were undertaken, each of which included 2000 second-order iterations, which were informed by 200 first-order iterations. For each set of analyses, 400,000 individuals passed through the model. For each second-order iteration, a set of input parameters was sampled based on the weights estimated as part of the calibration. Separately sampled input parameter values for the screening, cost and utility values were also included. Based on the mean values for each of the 200 first-order iterations, the following model outputs were collected for each second-order iteration:

- treatment costs
- costs associated with blindness
- aggregate costs
- QALYs
- cases of blindness.

Sixteen screening options (including no screening) were evaluated, with the outputs collected for the following range of screening options:

- no screening
- screening every 1, 2, 3, 4 and 5 years
- initiating screening at ages 50, 60 and 70 years.

The outputs from these analyses inform mean estimates of costs, QALYs and numbers of cases of legal blindness for each of the defined treatment options, which were used to estimate relevant ICERs for both outcomes. The estimated ratios identified dominated and extendedly dominated screening options, which were excluded and the

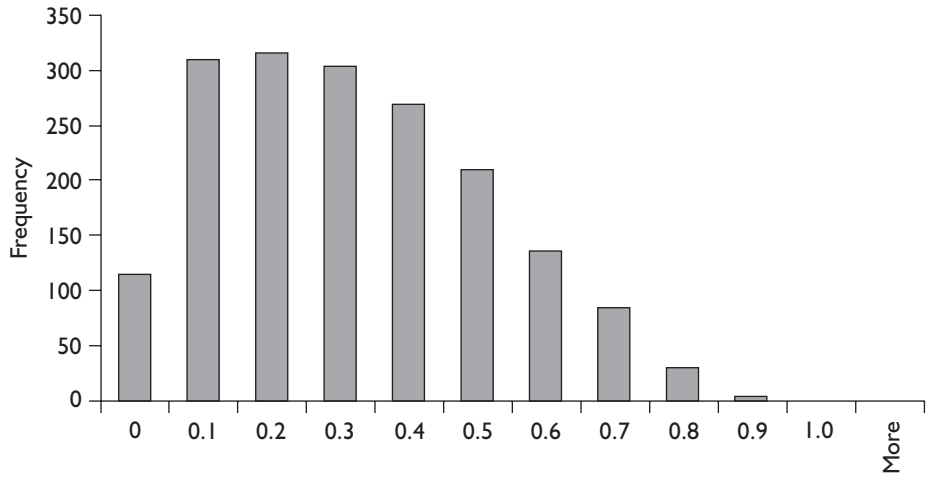

FIGURE 7 *Distribution of the sum of differences between the predicted and observed ranges for logMAR VA scores at clinical presentation*

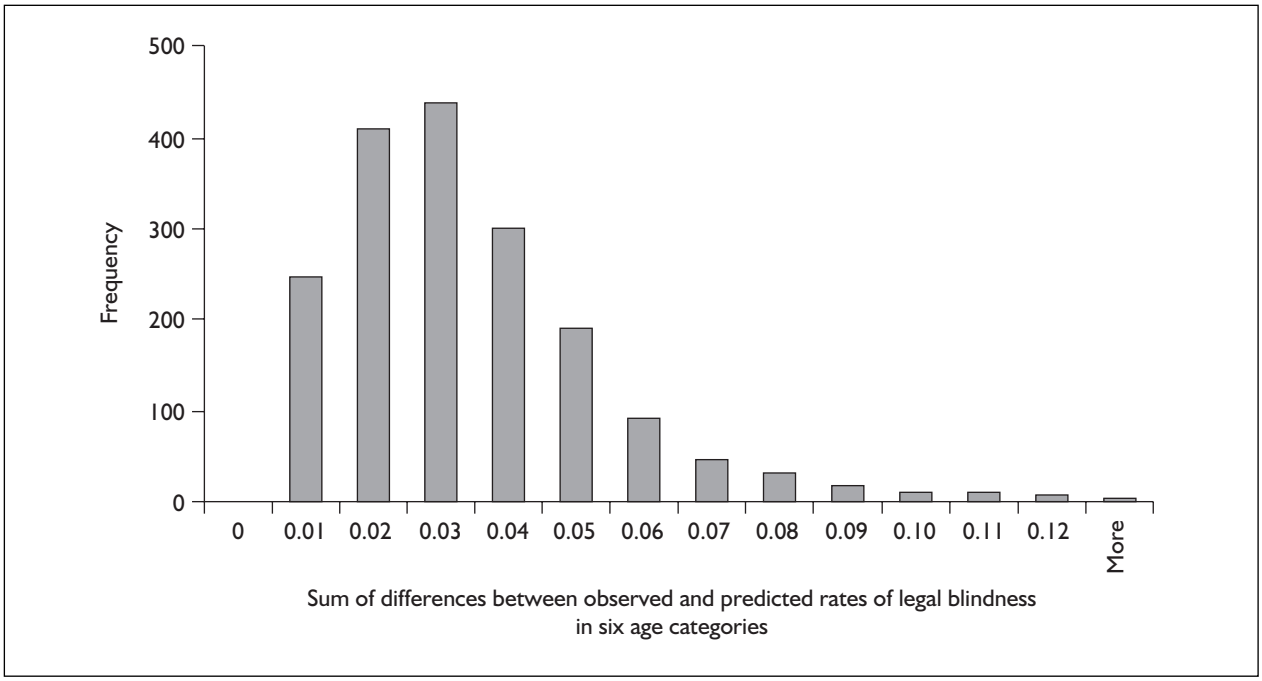

FIGURE 8 *Distribution of the sum of differences between the predicted and observed ranges for age-specific rates of legal blindness*

ratios re-estimated to provide an accurate assessment of the cost-effectiveness of screening.

Probabilistic sensitivity analyses were based on the observed costs and effects associated with each of the 2000 second-order iterations for each of the two analyses. The net benefits of each screening option in each iteration (including no screening), for a range of monetary values for the principal outcome measure (the QALY), are estimated to inform cost-effectiveness acceptability curves (CEACs). The CEACs inform the probability that each screening option is the most cost-effective at different monetary values of a QALY.

Future treatment options sensitivity analyses

Additional analyses of the 16 screening options were also undertaken for two additional treatment option scenarios. The chosen treatment option scenarios were based on the interventions described in Chapter 4. The first potential treatment option tested the impact of vitamin supplements that reduce the progression of early ARM to AMD, in addition to reducing the incidence of AMD in the fellow eye. This scenario also included the use of anecortave (Retaane) to reduce progression from dry AMD to wet AMD. The second potential treatment option tested the impact of the new anti-VEGF therapy for all JF and SF wet AMD lesions (plus PDT for predominantly classic lesions).

The hypothesis was that the availability of more preventative interventions would improve the cost-effectiveness of screening (treatment option 1), whereas more effective interventions available at the latter stages of disease would reduce the cost-effectiveness of screening.

Similar sets of analyses to those described for the main analyses were undertaken for the future treatment options, including 2000 second-order iterations, each of which was also informed by 200 first-order iterations. The same model outputs were collected and analysed to estimate mean costs and effects, in addition to a probabilistic sensitivity analysis.

Chapter 7
Results

As described in Chapter 6, the analysis of the model comprises two broad sets of analysis. The reference case analysis is based on current treatment options offered to AMD patients in the NHS, which were informed by expert consultation with ophthalmologists. Two sets of utility values were analysed in conjunction with the reference case clinical and cost parameter values. The first reference case analysis used the non-age-specific values that have been presented by Brown and colleagues,[77] which have informed most previous economic evaluations of interventions for AMD. The second set of utility values was based on an algorithm estimated by the Sheffield AMD patient utility study,[76] based on responses to the Health Utilities Index (version 3). The regression analyses found age to be an important predictor of utility, and so the algorithm estimates utility as a function of age and VA.

A series of alternative analyses, based on a range of potential treatment option combinations, were also undertaken. The first section below describes the range of results derived from the reference case analyses. The subsequent section describes the results from the horizon scanning analyses that illustrate how the cost-effectiveness of screening for AMD may change with the advent of new treatment options.

Reference case results

The reference case analysis comprised 2000 iterations of the AMD screening model, each informed by a separate set of input parameter values. Two outcome measures were defined: QALYs and cases of blindness. The model outputs were analysed to estimate the incremental cost per QALY and per case of blindness prevented between alternative screening options arranged in increasing order of effectiveness, after excluding dominated (more costly and less effective) options and extendedly dominated options (the subsequent screening option has a lower incremental cost-effectiveness).[81]

The results of the reference case analysis using the non-age-specific utility values are presented in *Tables 66–69*. Only the screening options that were non-dominated based on the mean estimates of cost-effectiveness are shown. Separate results are presented for the outcome measures, QALYs gained and cases of blindness prevented, and also for alternative costs of sending screening reminders to the eligible population at the relevant screening intervals, of £2 and of £3 per reminder.

The results presented in *Tables 66* and *67* show that the assumed cost of the screening programme has little impact on the incremental cost per QALY gained. The set of non-dominated screening options is similar, and based on the mean results an annual screening programme beginning at age 60 years is clearly the most cost-effective option based on recognised thresholds for QALY gains.[82]

Analyses based on the outcome 'number of cases of blindness prevented' do not vary greatly according to the cost of screening, although an additional non-dominated screening option (annual screening from age 70 years) is added to the core group of five non-dominated screening options when the cost per screen is £3. Based solely on the mean results, there is an obvious step up in the cost-effectiveness ratios when annual screening from age 60 years is compared with annual screening from age 50 years, where the ICERs increase by an order of magnitude to around £1 million per additional case of blindness avoided.

The QALY results from the reference case analyses in which the age-specific utility values were used are presented in *Tables 70* and *71*. These show that screening is predicted to be less cost-effective. The cost-effectiveness of the least effective (non-dominated) screening option compared to no screening is between £14,878 and £19,606 depending on the assumed cost of screening. Using a threshold of £20,000 per QALY, screening from age 60 years with a 5-year interval is the most cost-effective option (based on the mean results).

In the probabilistic sensitivity analysis, ideally, credible intervals would be estimated for every possible screening option. However, alternative

screening options may be dominated within different iterations of the model, and the ordering of the screening options may change by iteration. There were also comparisons that included some iterations in which costs and effects were higher for one screening programme, and other iterations in which costs and effects were higher for the other screening option (observations in the north-east and north-west quadrants). These factors make the analysis of results massively complex, if not infeasible. Therefore, 95% credible intervals describing the uncertainty around the mean cost-effectiveness results were estimated for each of the non-dominated screening options for which iterations were not observed in both the north-east and north-west quadrants.

The results for the non-age specific utility analyses, presented in *Tables 66–69*, show large levels of uncertainty across all analyses and all comparisons. The majority of comparisons demonstrate ranges of uncertainty that start with the more effective screening options (based on the mean results) dominating the less effective option, and end with the less effective option dominating the more effective option. Of the non-dominated upper intervals, the screening option with the lowest ratio is 4-yearly screening from age 60 years compared with no screening, although the incremental cost per QALY is still above £300,000.

Similar results are derived from the analyses informed by the age-specific utility values presented in *Tables 70* and *71*. The majority of comparisons are accompanied by 95% credible intervals that stretch from the less effective option dominating to the more effective option dominating. The only option that is unlikely to be cost-effective is annual screening from age 50 years, for which the lower interval is at least £195,000.

The next stage in the uncertainty analysis involved the estimation of cost-effectiveness acceptability frontiers. Cost-effectiveness acceptability frontiers are derivatives of the more usually presented CEACs. Frontiers are required in cases in which the distribution of net benefits is skewed and the median and mean net benefits diverge. The frontier describes the probability that the screening option with the highest mean net benefits (for a given value of output, e.g. a QALY) is the most cost-effective option based on the proportion of iterations of the model in which that option displayed the highest net benefits.

Figures 9–12 present the cost-effectiveness acceptability frontiers for the four QALY-based analyses (at screening costs of £2 and £3, for the age- and non-age-specific utility analyses). The frontiers do not vary greatly, and show that the no screening option has the highest net benefits at very low values of a QALY, and also has a high probability of being the most cost-effective screening option at these values. As the value attached to a QALY increases, and alternative screening options report the highest mean net benefits, the probability of the option with the highest mean net benefits being the most cost-effective option decreases dramatically. In *Figure 9*, for example, at a value of £10,000 per QALY gained, 2-yearly screening from age 60 years is the option reporting the highest net benefits, but this option has the highest net benefits in only 2% of the 2000 model iterations. As the value of a QALY increases further, the probability of the screening option with the highest net benefits – annual screening from age 60 years – being the most cost-effective option increases to 32% at a value of a QALY of £100,000.

These results illustrate the high level of uncertainty around the mean estimates of cost-effectiveness. The results also represent the fact that the differences in the number of QALYs gained and cases of blindness prevented between the screening options is very small, such that a relatively few iterations in which larger differences are observed have very significant effects on the mean cost-effectiveness. This effect is most noticeable with respect to the no screening option, which maintains the highest probability of being the most cost-effective option to a value of a QALY of £24,000, yet it only has the highest mean net benefits to a value of £2000.

The frontiers based on the age-specific utility values show that the no screening option produces the highest net benefits to a QALY value of between £15,000 and £19,000, depending on the cost of screening. There is also a relatively high probability that no screening is the most cost-effective option. Subsequently, up to a QALY value of between £70,000 and £90,000, the probability of the screening option with the highest net benefits being cost-effective is very low. After these thresholds, annual screening from age 60 years produces the highest net benefits. However, the no screening option remains the option with the highest probability of being cost-effective over all values of a QALY. At a value of £20,000, the probability of no screening being the most cost-effective option is over 50%.

TABLE 66 *Incremental cost per QALY results of screening for AMD, assuming a cost per screen of £2 (non-age-specific utility values)*

Age at first screen (years)	Screening interval	Screening costs (£)	Treatment costs (£)	Blind costs (£)	Aggregate costs (£)	QALYs	Differences		Incremental cost per QALY (£)		
							Costs (£)	QALYs	Mean	2.5th percentile	97.5th percentile
No screening		0.00	70	710	780	16.49096					
60	5-yearly	4.55	124	656	784	16.49300	4.0	0.0020	1,970	Dominates	303,539
60	3-yearly	6.20	145	637	788	16.49369	3.7	0.0007	5,349	Dominates	Dominated
60	2-yearly	9.64	165	619	794	16.49428	5.7	0.0006	9,710	Dominates	Dominated
60	Annual	19.96	198	591	809	16.49530	15.5	0.0010	15,169	Dominates	757,786
50	Annual	36.84	199	590	826	16.49535	16.3	0.0000	345,252	68,700	Dominated

TABLE 67 *Incremental cost per QALY results of screening for AMD, assuming a cost per screen of £3 (non-age-specific utility values)*

Age at first screen (years)	Screening interval	Screening costs (£)	Treatment costs (£)	Blind costs (£)	Aggregate costs (£)	QALYs	Differences		Incremental cost per QALY (£)		
							Costs (£)	QALYs	Mean	2.5th percentile	97.5th percentile
No screening		0.00	70	710	780	16.49096					
60	5-yearly	6.83	124	656	787	16.49300	6.3	0.0020	3,085	Dominates	317,837
60	4-yearly	7.22	133	648	788	16.49330	1.4	0.0003	4,807	Dominates	Dominated
60	3-yearly	9.30	145	637	791	16.49369	3.1	0.0004	7,861	Dominates	Dominated
60	2-yearly	14.46	165	619	799	16.49428	7.4	0.0006	12,641	Dominates	Dominated
60	Annual	29.94	198	591	819	16.49530	20.6	0.0010	20,227	Dominates	836,724
50	Annual	55.26	199	590	844	16.49535	24.7	0.0000	524,511	115,326	Dominated

TABLE 68 *Incremental cost per case of blindness prevented, assuming a cost per screen of £2 (non-age-specific utility values)*

Age at first screen (years)	Screening interval	Screening costs (£)	Treatment costs (£)	Blind costs (£)	Aggregate costs (£)	Blind	Differences		Incremental cost per case of blindness prevented (£)		
							Costs (£)	Blind	Mean	2.5th percentile	97.5th percentile
No screening		0.00	70	710	780	0.04523					
60	5-yearly	4.55	124	656	784	0.04175	4.0	0.0035	1,155	844	Dominated
60	4-yearly	4.81	133	648	786	0.04122	1.3	0.0005	2,489	Includes less costly and less effective iterations[a]	
60	3-yearly	6.20	145	637	788	0.04049	2.4	0.0007	3,272		
60	2-yearly	9.64	165	619	794	0.03942	5.7	0.0011	5,322		
60	Annual	19.96	198	591	809	0.03767	15.5	0.0018	8,827		
50	Annual	36.84	199	590	826	0.03765	16.3	0.0000	819,112	Dominates	Dominated

[a] The presence of such observations renders the estimation of credible intervals infeasible.

TABLE 69 *Incremental cost per case of blindness prevented, assuming a cost per screen of £3 (non-age-specific utility values)*

Age at first screen (years)	Screening interval	Screening costs (£)	Treatment costs (£)	Blind costs (£)	Aggregate costs (£)	Blind	Differences		Incremental cost per case of blindness prevented (£)		
							Costs (£)	Blind	Mean	2.5th percentile	97.5th percentile
No screening		0.00	70	710	780	0.04523					
60	5-yearly	6.83	124	656	787	0.04175	6.3	0.0035	1,809	1,011	Dominated
60	4-yearly	7.22	133	648	788	0.04122	1.4	0.0005	2,735	Includes less costly and less effective iterations[a]	
60	3-yearly	9.30	145	637	791	0.04049	3.1	0.0007	4,223		
60	2-yearly	14.46	165	619	799	0.03942	7.4	0.0011	6,928		
70	Annual	13.42	189	608	810	0.03812	11.8	0.0013	9,069		
60	Annual	29.94	198	591	819	0.03767	8.9	0.0005	19,437		
50	Annual	55.26	199	590	844	0.03765	24.7	0.0000	1,244,407	Dominates	Dominated

[a] The presence of such observations renders the estimation of credible intervals infeasible.

TABLE 70 *Incremental cost per QALY results of screening for AMD, assuming a cost per screen of £2 (age-specific utility values)*

Age at first screen (years)	Screening interval	Screening costs (£)	Treatment costs (£)	Blind costs (£)	Aggregate costs (£)	QALYs	Differences		Incremental cost per QALY (£)		
							Costs (£)	QALYs	Mean	2.5th percentile	97.5th percentile
No screening		0.00	73	698	771	10.21505					
60	5-yearly	4.55	129	644	778	10.21553	7.2	0.0005	14,878	Dominates	1,484,478
60	3-yearly	6.20	151	625	782	10.21569	4.1	0.0002	25,116	Dominates	Dominated
60	2-yearly	9.64	171	608	789	10.21583	7.0	0.0001	48,883	Dominates	Dominated
60	Annual	19.96	204	582	805	10.21607	16.5	0.0002	68,854	Dominates	2,898,130
50	Annual	36.84	204	580	821	10.21609	16.1	0.0000	1,260,676	195,119	Dominated

TABLE 71 *Incremental cost per QALY results of screening for AMD, assuming a cost per screen of £3 (age-specific utility values)*

Age at first screen (years)	Screening interval	Screening costs (£)	Treatment costs (£)	Blind costs (£)	Aggregate costs (£)	QALYs	Differences		Incremental cost per QALY (£)		
							Costs (£)	QALYs	Mean	2.5th percentile	97.5th percentile
No screening		0.00	73	698	771	10.21505					
60	5-yearly	6.83	129	644	780	10.21553	9.4	0.0005	19,606	Dominates	1,551,097
60	3-yearly	9.30	151	625	785	10.21569	4.9	0.0002	30,212	Dominates	Dominated
60	2-yearly	14.46	171	608	794	10.21583	8.7	0.0001	60,914	Dominates	Dominated
60	Annual	29.94	204	582	815	10.21607	21.6	0.0002	90,439	Dominates	3,440,834
50	Annual	55.26	204	580	840	10.21609	24.5	0.0000	1,922,621	285,602	Dominated

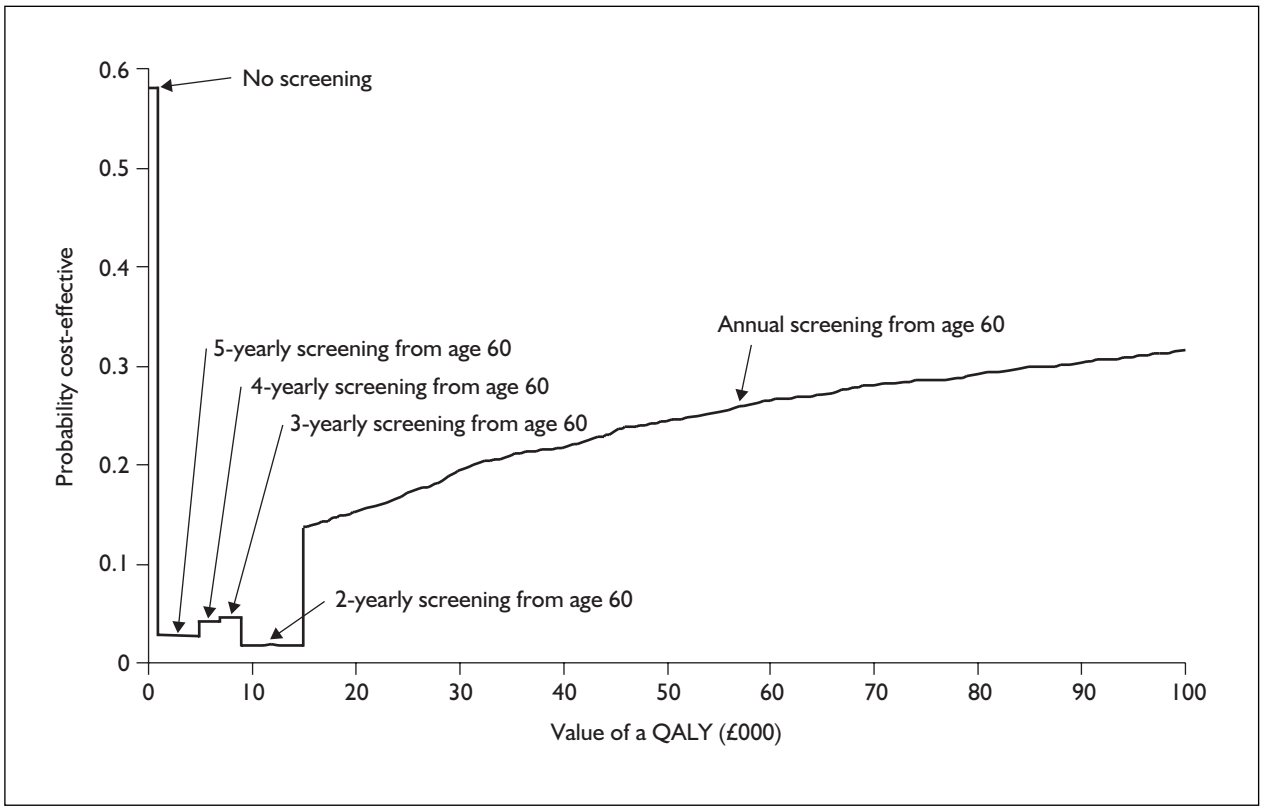

FIGURE 9 *Cost-effectiveness acceptability frontier for the cost per QALY of screening for AMD, assuming a cost per screen of £2 (non-age-specific utility values)*

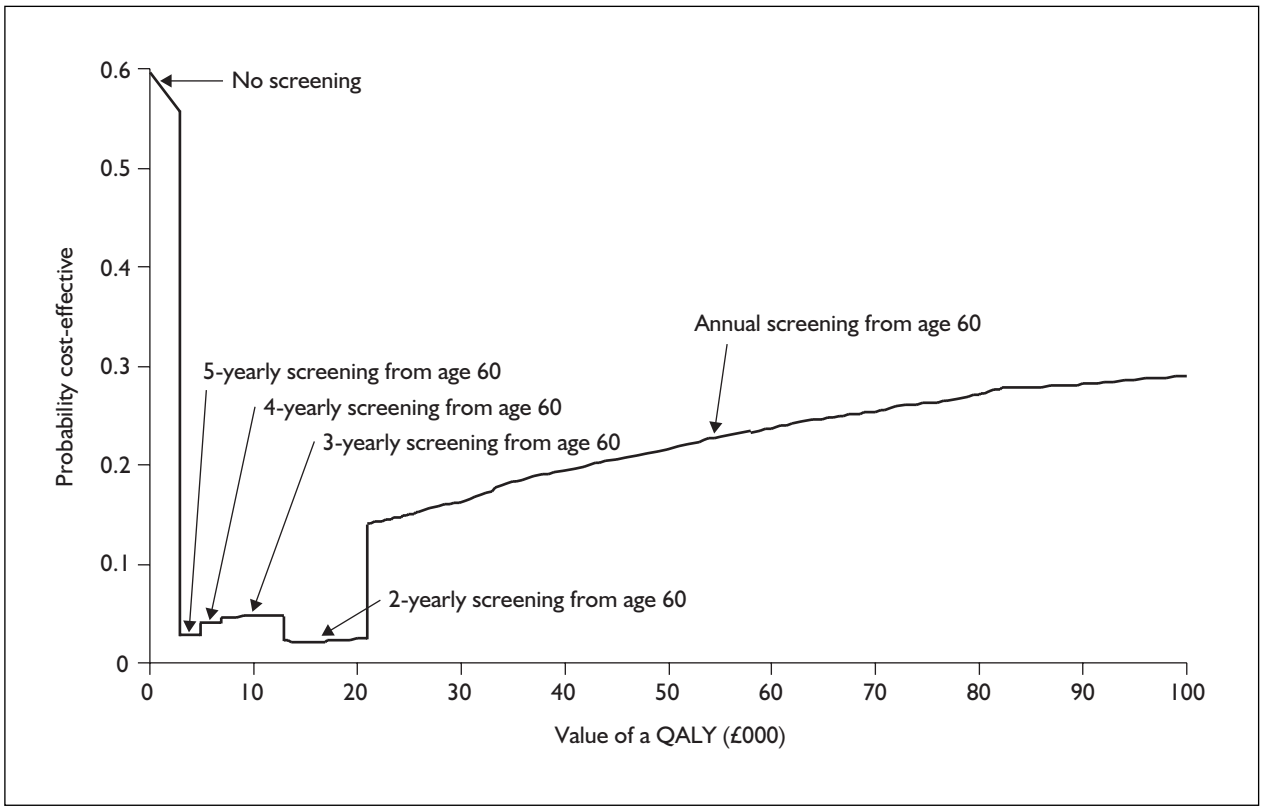

FIGURE 10 *Cost-effectiveness acceptability frontier for the cost per QALY of screening for AMD, assuming a cost per screen of £3 (non-age-specific utility values)*

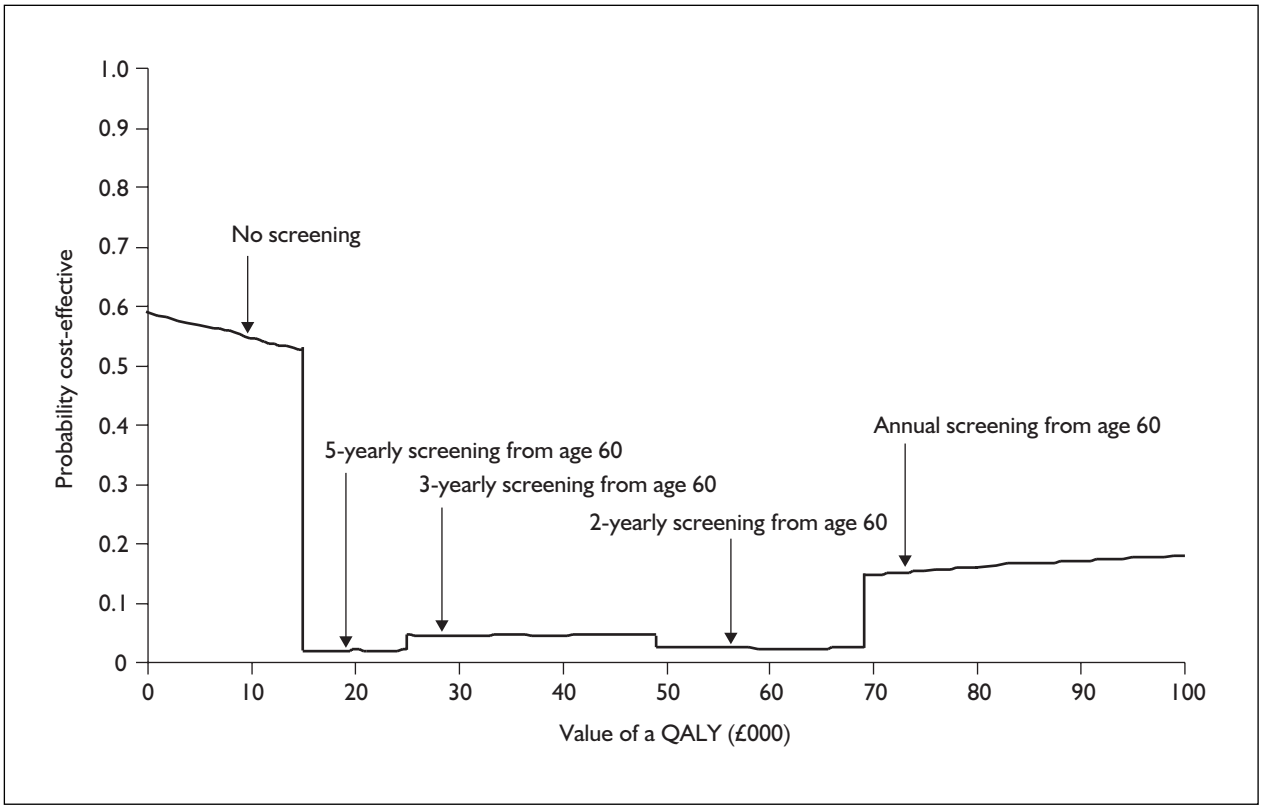

FIGURE 11 *Cost-effectiveness acceptability frontier for the cost per QALY of screening for AMD, assuming a cost per screen of £2 (age-specific utility values)*

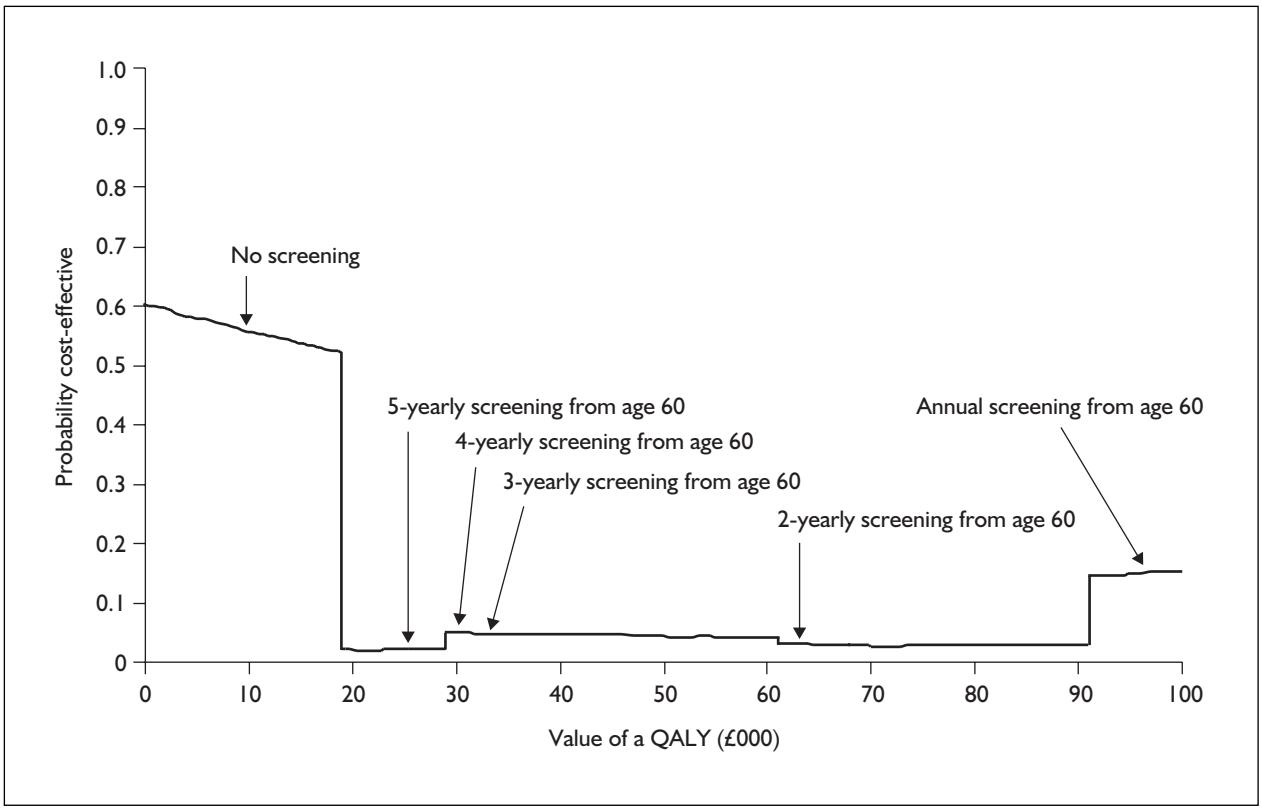

FIGURE 12 *Cost-effectiveness acceptability frontier for the cost per QALY of screening for AMD, assuming a cost per screen of £3 (age-specific utility values)*

Sensitivity analyses results

Two separate analyses of the AMD screening model were undertaken to estimate the impact of potential future interventions for different stages of ARM:

- Vitamin supplements that reduce the progression of early ARM to AMD, in addition to reducing the incidence of AMD in the fellow eye. This scenario also included the use of anecortare (Retaane) to reduce progression from dry AMD to wet AMD.
- The new anti-VEGF therapy for all JF and SF wet AMD lesions (plus PDT for PC lesions).

The following sections describe the incremental cost per QALY results for the two sensitivity analyses. The analyses incorporate only one set of utility values due to the running time requirements for the model. These analyses are largely illustrative, so the non-age specific utility values were chosen owing to the larger differences between the VA states, which in turn allows for more noticeable differences between the screening options.

Vitamin supplements for patients without dual eye wet AMD and anecortare (Retaane) for dry AMD

The sensitivity analysis of the AMD screening options assuming effective preventive interventions that reduce progression to set AMD shows that these interventions do increase the cost-effectiveness of screening. *Tables 72* and *73* present the results. Comparing these results with the reference case results presented in *Tables 68* and *69*, the set of non-dominated screening options is similar. The magnitude of the decrease in the ICERs is moderate. Assuming a screening cost of £2 per test, the cost-effectiveness of screening compared with no screening is £344 per QALY; in the reference case it was £1970. The ICER for annual screening from age 60 years, compared with 2-yearly screening from age 60 years, decreases from £15,169 in the reference case to £11,479.

The credible intervals for each comparison remain large, although the upper intervals for screening versus no screening approaches the £100,000 level for a screening cost of £2. Across the other comparisons, most stretch from dominates to dominated, although it appears unlikely that annual screening from age 50 years is a cost-effective option.

The cost-effectiveness acceptability frontiers, presented in *Figures 13* and *14*, show similar patterns. No screening has the highest expected net benefits at QALY values approaching zero; 2-and 3-yearly screening from age 60 years is

TABLE 72 *Incremental cost per QALY results of screening for AMD for the sensitivity analysis of preventative interventions, assuming a cost per screen of £2*

Age at first screen (years)	Screen interval	Aggregate costs (£)	QALYs	Differences		Incremental cost per QALY (£)		
				Costs (£)	QALYs	Mean	2.5th CI	97.5th CI
No screen		741.5	16.52080					
60	4-yearly	742.3	16.52321	0.8	0.0024	344	Dominates	122,584
60	3-yearly	745.2	16.52367	2.9	0.0005	6,384	Dominates	Dominated
60	2-yearly	750.8	16.52441	5.5	0.0007	7,471	Dominates	Dominated
60	Annual	764.6	16.52561	13.8	0.0012	11,479	Dominates	417,478
50	Annual	780.9	16.52562	16.4	0.0000	1,289,380	495,081	Dominated

TABLE 73 *Incremental cost per QALY results of screening for AMD for the sensitivity analysis of preventative interventions, assuming a cost per screen of £3*

Age at first screen (years)	Screen interval	Aggregate costs (£)	QALYs	Differences		Incremental cost per QALY (£)		
				Costs (£)	QALYs	Mean	2.5th CI	97.5th CI
No screen		742	16.52080					
60	4-yearly	745	16.52321	3.2	0.0024	1,342	Dominates	130,905
60	3-yearly	748	16.52367	3.6	0.0005	7,910	Dominates	Dominated
60	2-yearly	756	16.52441	7.2	0.0007	9,797	Dominates	Dominated
60	Annual	775	16.52561	19.0	0.0012	15,775	Dominates	565,479
50	Annual	799	16.52562	24.8	0.0000	1,953,219	752,016	Dominated

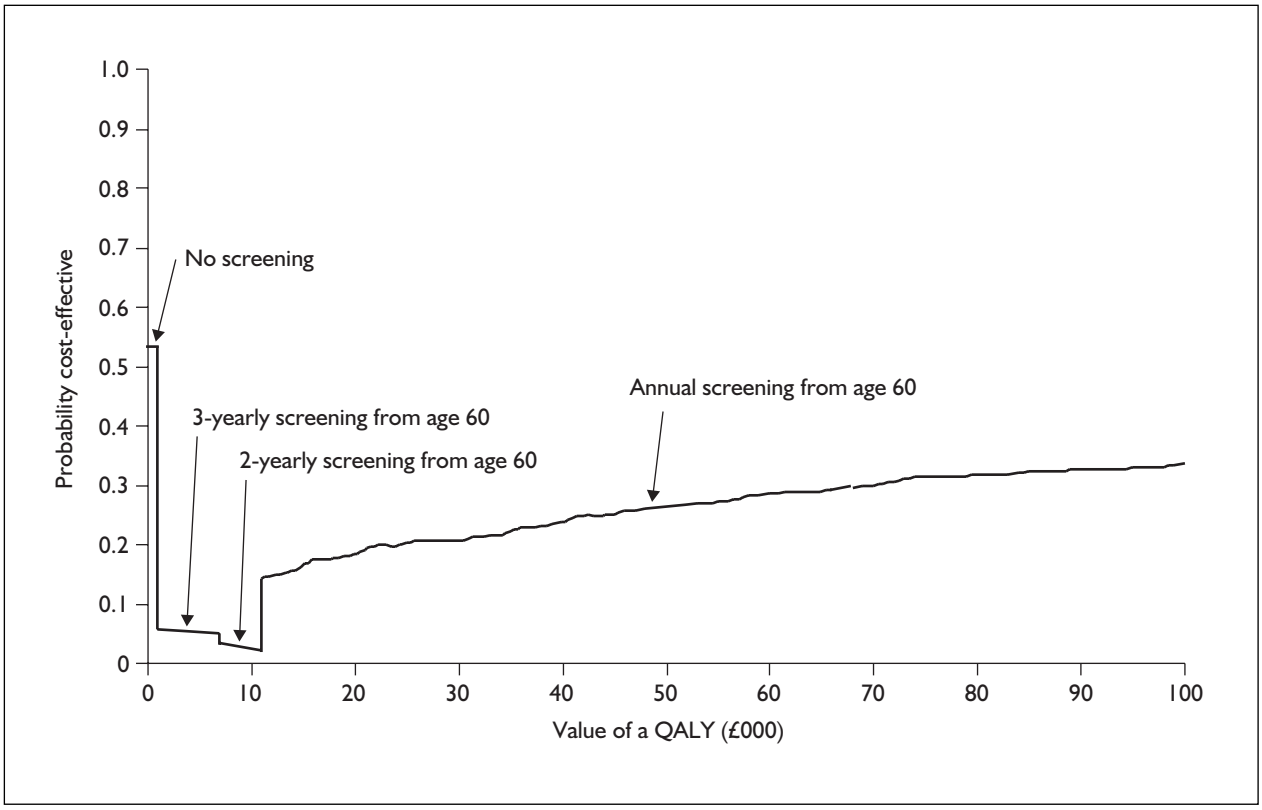

FIGURE 13 *Cost-effectiveness acceptability frontier for the cost per QALY for the sensitivity analysis of preventative interventions for wet AMD, assuming a cost per screen of £2*

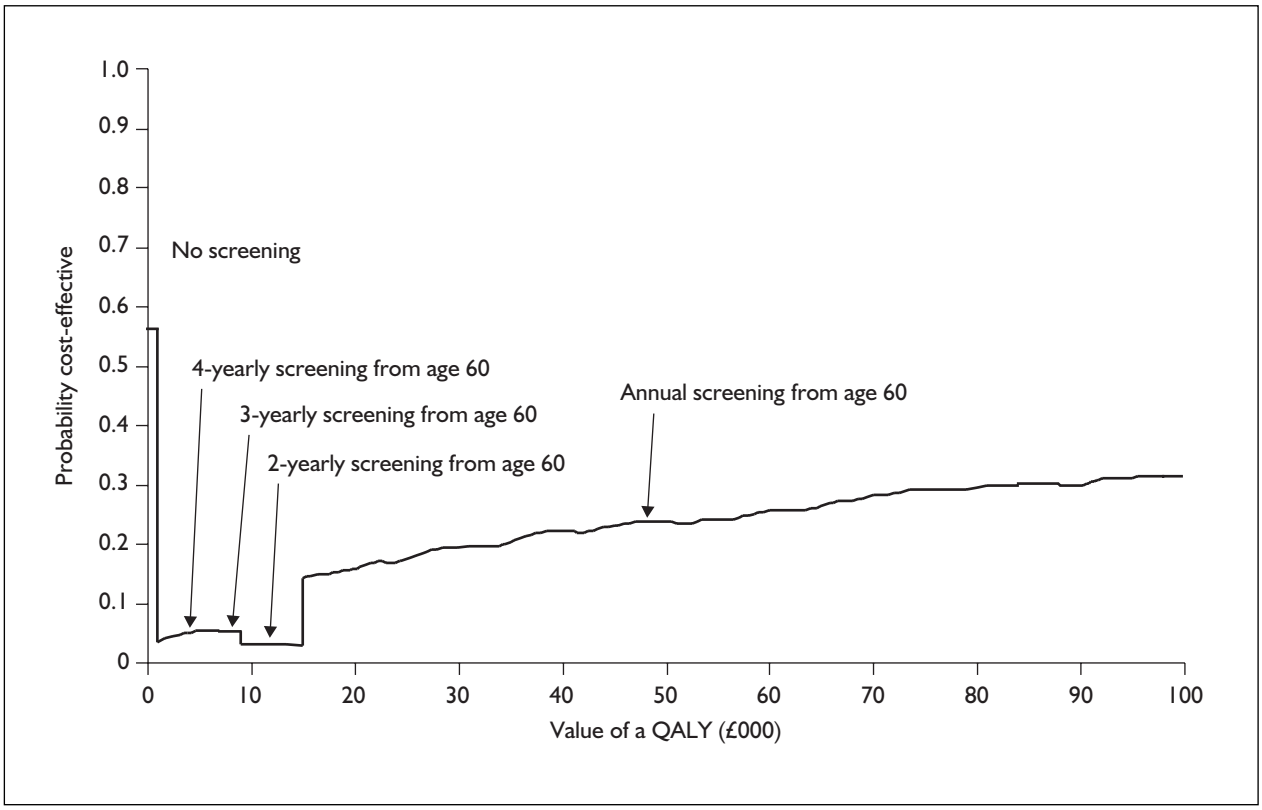

FIGURE 14 *Cost-effectiveness acceptability frontier for the cost per QALY for the sensitivity analysis of preventative interventions for wet AMD, assuming a cost per screen of £3*

preferred at low QALY values, whereas annual screening from age 60 years remains the option with the highest net benefits at all other QALY values. The probability that annual screening is the most cost-effective option is relatively low, at only 20% at a QALY value of £30,000.

Anti-VEGF therapy for JF or SF wet AMD (plus PDT for predominantly classic lesions)

The sensitivity analysis of AMD screening given the use of an anti-VEGF therapy for JF or SF wet AMD lesions shows that screening becomes slightly less cost-effective than when analysing current treatment options (based on non-age-specific utility values). The mean results presented in *Tables 74* and *75* show that the same screening options are included in the final analysis and that the mean ICERs are slightly higher than in the reference case analysis. The credible intervals remain significantly wide for most comparisons, although the upper interval for annual screening from age 60 years is now less than £100,000, and the lower interval for annual screening from age 50 years is within acceptable thresholds.

The cost-effectiveness acceptability frontiers, presented in *Figures 15* and *16*, show that all six screening options are included. In both cases, annual screening from age 60 years has an increasing probability of being cost-effective from a low value of a QALY gained, reaching around 45% at a value of a QALY of £50,000.

Summary

This chapter has presented the mean results, and the results of probabilistic sensitivity analyses, for a reference case specification of current treatment options, and also a range of potential treatment options that may be provided at some point in the future. The results show that, given the assumptions incorporated in the analyses, some form of screening may well be cost-effective, although there remains very large uncertainty around the presented estimates of cost-effectiveness. Of the screening options analyses, annual screening from age 60 years appears to consistently be the most cost-effective option.

The assumptions informing the input values for these parameters were described in previous chapters, and the relationship between these assumptions and the observed results are discussed in Chapter 8, which interprets the results in terms of identifying the key drivers of the cost-effectiveness results and the strength of the data and assumptions informing the key parameters.

TABLE 74 *Incremental cost per QALY results of screening for AMD for the analysis of anti-VEGF therapy for wet AMD, assuming a cost per screen of £2*

Age at first screen (years)	Screen interval	Aggregate costs (£)	QALYs	Differences		Incremental cost per QALY (£)		
				Costs (£)	QALYs	Mean	2.5th CI	97.5th CI
None		858	0	858	16.4765			
60	5-yearly	897	4.55	902	16.4841	5,773	Dominates	38,544
60	4-yearly	910	4.81	915	16.4852	12,306	Dominates	Dominated
60	3-yearly	931	6.20	938	16.4866	15,545	Dominates	Dominated
60	2-yearly	971	9.64	981	16.4889	19,410	Dominates	Dominated
60	Annual	1,053	19.96	1,073	16.4928	23,358	285	86,875
50	Annual	1,054	36.84	1,090	16.4930	141,476	11,254	Dominated

TABLE 75 *Incremental cost per QALY results of screening for AMD for the analysis of anti-VEGF therapy for wet AMD, assuming a cost per screen of £3*

Age at first screen (years)	Screen interval	Aggregate costs (£)	QALYs	Differences		Incremental cost per QALY (£)		
				Costs (£)	QALYs	Mean	2.5th CI	97.5th CI
None		858	0.00	858	16.4765			
60	5-yearly	897	6.83	904	16.4841	6,070	Dominates	39,123
60	4-yearly	910	7.22	917	16.4852	12,429	Dominates	Dominated
60	3-yearly	931	9.30	941	16.4866	16,014	Dominates	Dominated
60	2-yearly	971	14.46	986	16.4889	20,183	Dominates	Dominated
60	Annual	1,053	29.94	1,083	16.4928	24,658	1,214	91,984
50	Annual	1,054	55.26	1,109	16.4930	212,113	16,235	Dominated

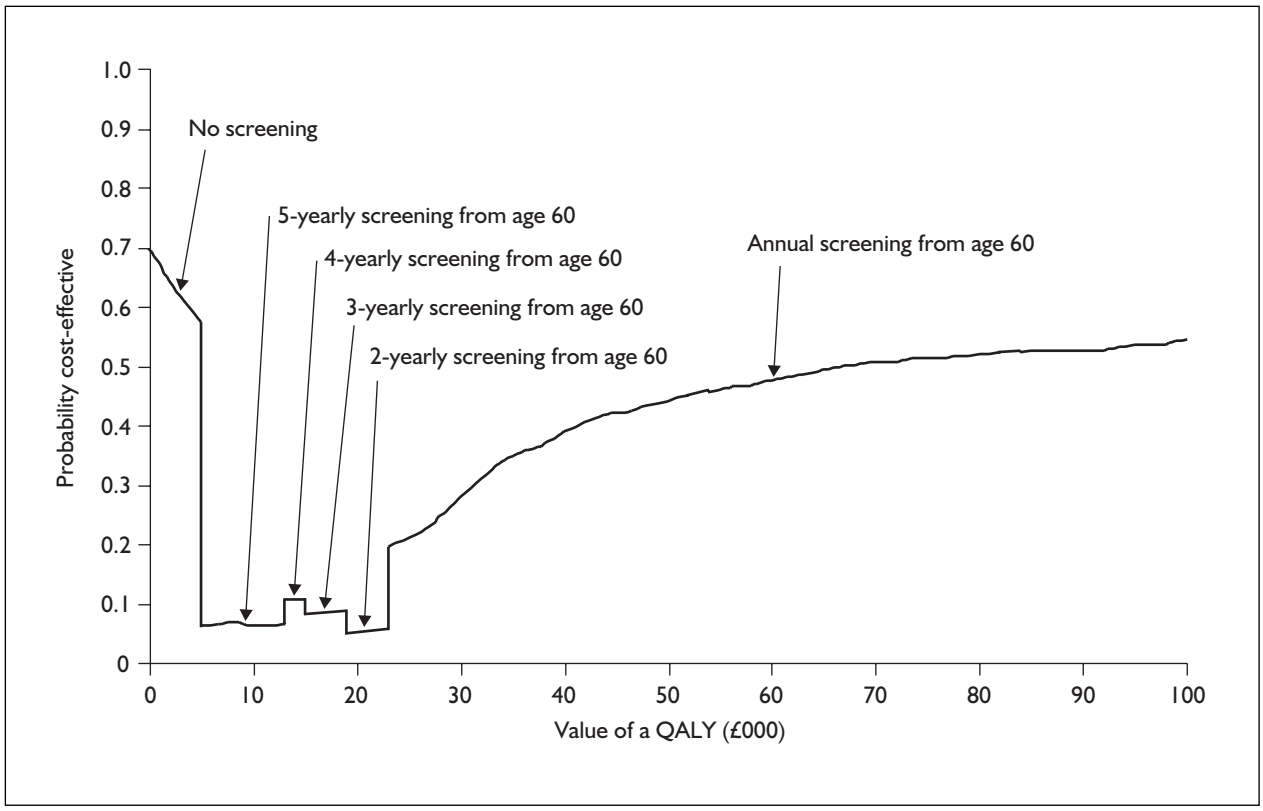

FIGURE 15 *Cost-effectiveness acceptability frontier for the cost per QALY for the analysis of anti-VEGF therapy for wet AMD, assuming a cost per screen of £2*

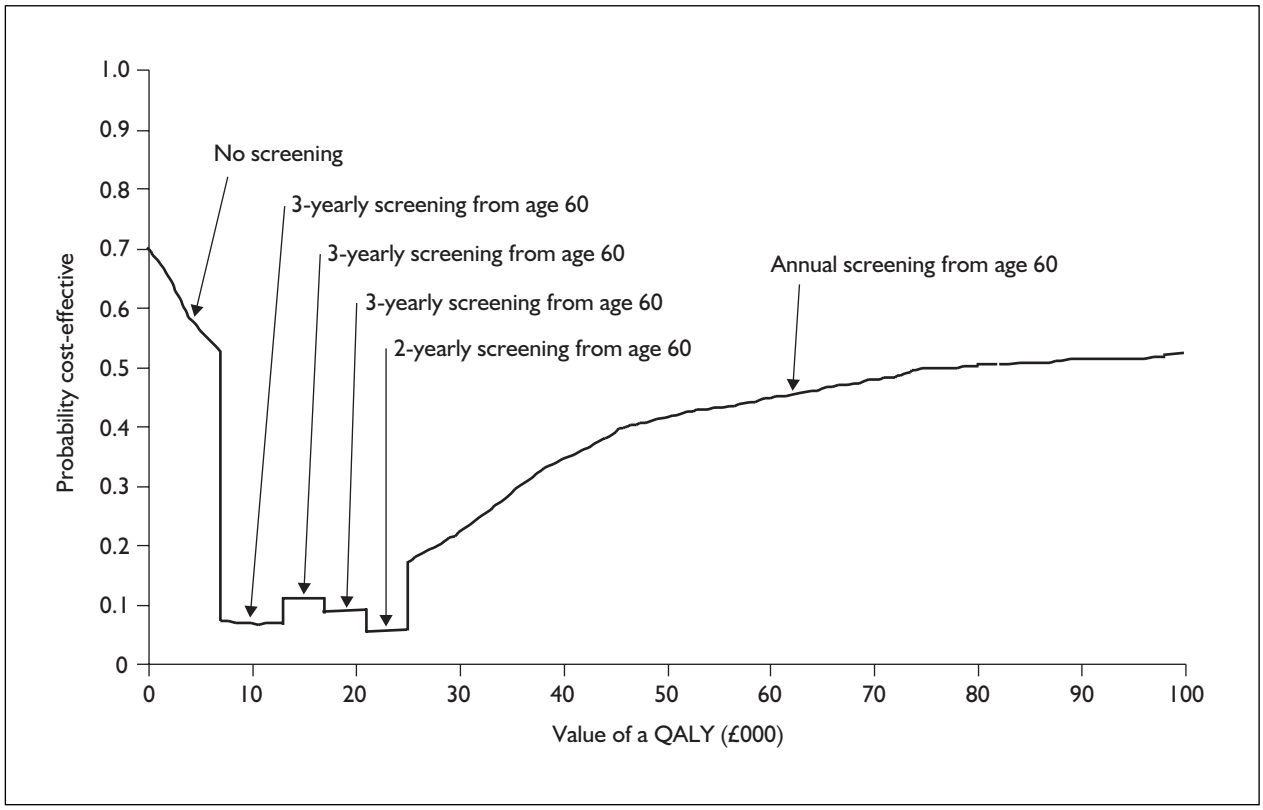

FIGURE 16 *Cost-effectiveness acceptability frontier for the cost per QALY for the analysis of anti-VEGF therapy for wet AMD, assuming a cost per screen of £3*

Chapter 8
Discussion

The results of the evaluation of screening for AMD presented in the previous chapter underline the *a priori* beliefs about the level of uncertainty around the mean cost-effectiveness results. The probabilistic sensitivity analyses that were undertaken for four alternative scenarios produced very wide credible intervals for the ICERs; most of the intervals ranged from one option costing less and being more effective to the other option costing less and being more effective.

The uncertainty around the utility values used in the model was well defined. Two relevant utility studies were identified, which reported very different values. In one study, 209 patients completed health status questionnaires including the Index of Visual Function (VF)-14 and three preference-based measures (HUI-3, EQ-5D and SF-6D) and the TTO.[76] Brown and colleagues[77] estimated utility values using the TTO method for a population of patients with actual visual loss due to AMD. The Sheffield study estimated lower utility values in the better VA categories (0.81 versus 0.89) and higher values in the worse VA groups (0.58 versus 0.40).

Rather than combine the studies, the reference case model was analysed separately using the two sets of utility values. Using the set that was more favourable to screening (i.e. that had a larger differential between levels of VA) suggested that annual screening from age 60 years provides the highest mean net benefits at commonly accepted ranges of the value of a QALY;[82] the mean cost-effectiveness results indicate that this screening programme should be adopted. However, the upper 95% credible interval for these analyses showed incremental costs per QALY of over £0.75 million.

The analysis based on the less favourable (age-specific) utility values predicted that screening from 60 years was cost-effective, although the screening interval should be at least every 3 years, and more likely every 5 years. The upper 95% credible intervals for these analyses were above £1 million per QALY gained.

The presented cost-effectiveness acceptability frontiers show that the screening options with the highest expected net benefits at different QALY values tend to have relatively low probabilities of being the most cost-effective option. In one of the reference case analyses, for example, annual screening from age 60 years had the highest net benefits from a QALY value of £20,000, but the probability of it being the most cost-effective option was less than 20% at a QALY value of £30,000. This result is to be expected given the large uncertainties in the analysis, combined with the fact that 15 alternative screening options are considered.

The two other scenario analyses incorporated the potential effect of treatments that may become available at some point in the future. These included treatments to prevent progression to wet AMD and the incidence of wet AMD in the fellow eye, and the availability of therapies that inhibit the VEGF (the anti-VEGFs) for the treatment of wet AMD. In the case of the anti-VEGF treatment option, the future is potentially very close as this class of treatments is currently being assessed by NICE.

The addition of a preventive treatment option for individuals detected with early-stage disease was found to have only a moderate effect on the cost-effectiveness of screening. The moderate impact on the cost-effectiveness of screening of potential preventive interventions that reduce progression rates to wet AMD is initially surprising because one might expect significant returns from interventions that are effective in preventing disease progression. However, the assumption in the reference case that first eyes are treated upon detection reduces the scope for further large benefits from preventive interventions. Screening is assumed to increase the detection of first eye wet AMD, such that a significant proportion of patients will receive treatment for wet AMD in both eyes. As utility is based solely on VA in the worst seeing eye, this means that screening provides two chances to maintain VA in at least one eye and thus maintain QoL. If treatment of the first eye was not considered appropriate (perhaps on the grounds of cost-effectiveness), then the impact of the preventive interventions would be expected to increase.

It is also worth noting that the preventive interventions are not 100% effective; the mean RR for vitamin supplements in preventing fellow eye incidence was 0.76.

The introduction of the new, more effective treatment options for wet AMD (the anti-VEGFs) had a smaller predicted effect on the mean estimates of the cost-effectiveness of screening. With the anti-VEGFs, the same non-dominated screening options were identified as in the reference case, although each mean ICER was slightly higher than in the reference case. These results were not surprising as the anti-VEGFs are significantly more expensive therapies, but also because this new therapy option improves vision in a proportion of patients, thus reducing the effects of late presentation in the absence of screening.

However, compared with the reference case, the probabilistic sensitivity analysis for the anti-VEGF analyses showed reduced credible intervals for screening compared with no screening, and for annual screening from age 60 years. This is most likely due to the increased certainty around the effectiveness of the anti-VEGFs relative to the certainty around the effectiveness of PDT. As the difference in QALYs between the alternative screening options is small, a minor change in the effectiveness of treatment leading to an even more minor change in QALYs can cause a relatively large change in the estimated ICER.

Unlike the other non-dominated screening options, the mean estimate of cost-effectiveness for annual screening from age 50 years compared with annual screening from age 60 years decreases (becomes more cost-effective) with an anti-VEGF treatment option. The credible interval also appears to widen as the lower bound shows screening from age 50 years to be potentially cost-effective. Most of the few individuals detected and treated in their 50s would remain alive and receive treatment in their 60s if screening commences at age 60 years. They therefore incur similar costs. However, it seems that the relative effect of treatment with the anti-VEGFs in individuals aged 50–60 years compared with individuals aged over 60 years is greater than the relative effect of PDT.

It should also be noted that the assumptions made about the long-term effectiveness of all of the interventions included in the analysis were favourable; in particular, it was assumed that the observed effect during the treatment period (a maximum of 2 years for PDT and the anti-VEGFs) was maintained over the course of a patient's lifetime.

The remainder of this discussion chapter focuses on the interpretation of the results from the perspective of defining the major areas of uncertainty. At the outset of the evaluation, it was intended to undertake a full expected value of information (EVI) analysis of the AMD screening model to inform quantitatively priorities for further research in this disease area. Two main factors persuaded us against undertaking an EVI analysis. First, as will be detailed in subsequent sections, there were such levels of uncertainty about certain aspects of the AMD screening model structure and population that the derivation of quantitative estimates to inform further research may provide a misleadingly definitive representation of the value of additional research. Second, although there are significant shortcomings in the structure and population of the model, and an innovative approach was adopted to reduce the analytic burden (i.e. the hybrid cohort/individual sampling approach), it remains a complex model that requires significant computer running time to analyse. The sensitivity analyses of two potential treatment scenarios required eight Pentium 4 processor PCs running from Friday afternoon to Monday morning to generate 2000 second-order iterations, each comprising only 200 first-order iterations. EVI analyses, even using short-cut Gaussian process techniques,[83] require significantly larger numbers of model iterations that were not feasible within the time frame of the evaluation.

It was decided that a qualitative appraisal of the major areas of uncertainty around the potential cost-effectiveness of a screening programme for AMD would be a more useful approach. Although no specific analyses of the contribution of the effects of individual parameters were undertaken, the understanding of the AMD screening model that has been developed over the course of the evaluation is an important output from the project that should be disseminated to inform future work in this area.

Areas of uncertainty

The following sections discuss the impact of particular aspects of the model structure and the data and assumptions used to populate key parameters, on the results of the AMD screening model, and how the screening model may be improved with respect to these issues:

- model structure
- rates of clinical presentation
- screening test and optometrist effectiveness
- treatment effectiveness
- costs of blindness.

Model structure

Recent guidelines on the use of decision analytic modelling suggest that "[health] states should not be omitted because of lack of data",[84] a statement with which we agree. It is generally preferable to define a model structure based on the best available evidence regarding the disease process, disaggregating the disease process into states that best represent the differential effects of the alternative stages of the disease on costs and outcomes (i.e. survival and QoL).

The initial stages of the model development process for the AMD screening model were based on discussions with expert ophthalmologists, reading the literature and previous research undertaken by the research team. This process indicated that VA was not the preferred marker of visual deterioration, as utility studies had shown that changes in CS provided a more accurate reflection of the impact of visual deterioration on QoL.[76] McClure and colleagues developed a visual functioning index [daily living tasks dependent on vision (DLTV)] that demonstrated that specific levels of vision as measured by VA, reading index and CS corresponded with different perceived amounts of difficulty in the performance of daily living tasks.[85] Thus, VA is unlikely to represent all of the potential QoL effects of AMD.

Ideally, therefore, the model would describe the progression of AMD in terms of progression of a range of measures of vision, but if only one were to be picked it would be CS. However, very few of the data sources used to populate the model (either primary or secondary sources) presented data describing the CS of eyes with AMD. Although expert elicitation was an integral part of this study, it was not considered feasible to ask experts to estimate levels of CS as a function of AMD lesion and time since incidence, which would have been required. Therefore, the model was built around progression of VA, despite a preference for CS.

Recent evidence shows that intact autofluorescence at the macula in wet AMD correlates with VA, lesion size and symptom length, and that in such cases VA might be rescued if treatment could suppress neovascular growth without damaging the RPE/retina complex.[86] Further developments to the model could include the representation of lesion size and treatment effect by symptom length, and also incorporating autofluorescence imaging as a diagnostic test that influences treatment strategy.

Rates of clinical presentation and reasons for non-presentation

The estimated rates of clinical presentation of ARM, by stage, were possibly the most important set of input parameters for the AMD screening model as these rates informed the main part of the model calibration process. These data were informed by local data from the Sheffield PDT clinic, which were extrapolated backwards to estimate the aggregate numbers of individuals referred to general hospital eye services by AMD lesion type, using responses from a survey of general ophthalmologists who referred to the PDT clinic. The main problems with these data included the fact that the sample of patients referred to the PDT clinic was small, the PDT database was not validated and the survey of ophthalmologists and inconsistencies was limited in the responses received.

The 'observed' rates of clinical presentation were much lower than the estimated population incidence rates that were primarily based on data reported by the Rotterdam study.[2] This imbalance meant that the calibration process estimated relatively low values for the probability of clinical presentation by AMD lesion; for example, the mean probability of clinical presentation for patients with the worst combination of AMD states (SF wet AMD in both eyes) was 0.10. The data from the Rotterdam study used to inform population incidence rates are not ideal; for example, UK data with more frequent, shorter and more complete follow-up intervals would be preferred. However, these data are of reasonable quality relative to the data used to estimate clinical presentation rates.

Given the role of the clinical presentation data in calibrating the model, we believe that serious consideration should be given to setting up a pilot study to estimate rates of clinical presentation. It may be possible to collate routinely collected data at relatively low expense.

The estimated difference between population prevalence and clinical presentation led the model to predict significant potential for screening to detect and successfully treat individuals who otherwise would not have presented. The model did not differentiate between the utility effects of

preventing VA loss in patients who would have presented clinically and those who would not have presented clinically. However, the accuracy of the model's results depends to a large degree on the explanation for why individuals do not present clinically (if that is the case). It may be that non-presenters are accepting of fate, in which case they would be unlikely to present following screening, which would affect the estimated screening detection rates. Alternatively, they may have a higher threshold for presentation due to experiencing lower utility effects. In this case, less utility gain should be assigned to an improved VA profile. Finally, non-presenters may perceive a lack of treatment options for AMD, such that the utility gain may be assumed to be constant across all individuals with AMD.

Screening and optometrist effectiveness

The effectiveness of the screening test (a reminder letter to undertake a cover test) is linked to the effectiveness of optometrists in dealing with individuals who present as a result of receiving a reminder letter. No data were identified that described the likelihood of individuals with particular combinations of ARM in both eyes (including no ARM) presenting as a result of receiving a letter advising them to undertake a cover test. Data were elicited from experts that described the probability that persons with different forms of ARM, who undertook the test, would identify abnormalities that might lead to them presenting at an optometrist's. These estimates cover only one of three of the required probabilities (that individuals undertake the test, notice an abnormality and present at an optometrist's) but the other two could not be feasibly informed by ophthalmologists.

No data were identified that described how effective optometrists are in diagnosing and referring on individuals who present to them with AMD. The AMD screening model incorporates the assumption that patients who present as a result of screening and do not have ARM do not impose costs on the screening programme. The model also assumes that optometrists accurately refer all cases of dry and wet AMD on to hospital ophthalmologists, while not referring any cases of early ARM.

Data to inform these parameters would require the setting up of pilot sites in which screening for AMD might be administered to a defined population. The study would need to be carefully designed to minimise bias, as it would be necessary to follow up all individuals who attend optometrists as a result of the screening programme. Ideally, diagnostic tests would be undertaken on a sample of the population in order to estimate the test characteristics, although useful information could be obtained from an age-weighted comparison of presentation rates with literature-based prevalence estimates.

Treatment effectiveness

The reference case analysis included only two forms of treatment: laser photocoagulation for EF wet AMD and PDT for PC JF or SF wet AMD. Although good quality trials inform both interventions, the laser photocoagulation trial for EF lesions describes effectiveness out to 5 years, but similar data are only available to 2 years for PDT. The lack of long-term follow-up data inevitably requires the use of weak assumptions to extrapolate the observed effectiveness data.

A similar approach was used to inform the effectiveness of both interventions. It was assumed that the additional proportion of patients who lost fewer than six lines at 5 years (laser photocoagulation) or two lines at 2 years (PDT) in the intervention group over the placebo group maintained their VA at that level over the remainder of their lifetime in the treated eye. The choice of threshold for laser photocoagulation was enforced by the limited publication of further results, while the tighter PDT threshold was defined as the patient-level data from the pivotal trial were made available.

With respect to the assumed intervention for early ARM, a key assumption concerns the role of optometrists in promoting the use of vitamin supplements and the likelihood that individuals comply. The assumption made in the model was that all individuals presenting with early ARM self-treat with the recommended supplement. The effectiveness of zinc in preventing progression was informed by published ORs describing the likelihood of individuals with bilateral drusen (early ARM) or unilateral AMD (dry or wet) experiencing AMD in eyes without AMD at baseline. The issue around the representation of effectiveness of vitamin supplements is not particularly around the stated levels of effectiveness in patients taking the supplement, as appropriate CIs were defined. Rather, the model assumes that no-one takes such supplements until they are advised to do so by an optometrist, whereas a proportion of the population at risk of AMD is likely to be taking such supplements.

Data informing these parameters could be collected as part of a screening pilot study, as

described in the previous section. The scope of the screening pilot study may be extended to incorporate rates of uptake of vitamin supplements and compliance as a result of initiation by an optometrist. Existing rates of vitamin usage aimed at preventing AMD could be estimated by a representative sample survey.

The main issue around the effectiveness of the potential interventions for dry and wet AMD is similar to that described for the current treatment options of laser photocoagulation and PDT – the need for long-term follow-up data. As and when these interventions are approved and implemented in the UK, longitudinal studies should be set up to monitor their longer term effectiveness. It is recognised that such longitudinal studies are not ideally suited to establishing long-term effectiveness, but extended follow-up in the relevant pharmaceutical company-sponsored clinical trials is unlikely. Longitudinal studies should provide some indication of the continued effectiveness of an intervention.

Costs of blindness

The described costs associated with blindness and deteriorating vision were a significant factor in the AMD screening model, especially in the anti-VEGF sensitivity analyses, where the no-screening option incurred higher lifetime costs due to the costs of blindness. The AMD screening model incorporates a binary threshold for costs associated with blindness: no such costs are incurred when the VA in the best-seeing eye is better than 6/60 or worse; significant costs are incurred once an individual crosses the threshold and VA in the best-seeing eye is 6/60 or worse. This is unlikely to be a true representation, as at least some of the costs associated with blindness and deteriorating vision would be more appropriately described on a continuum.

Costs to the NHS and local and central government associated with blindness and rapidly deteriorating vision were informed by the estimates presented in an HTA of PDT.[75] The mean annual cost of £6295 comprises a wide range of resources that are not specific to individuals who are registered as being blind. The cost estimates do not describe the **additional** proportion of individuals who experience events such as hip fractures, depression or the provision of community care. The main cost driver is admission to residential care, which is based on the proportion of residents with low vision, the total number of individuals in residential care and the estimated prevalence of AMD in the elderly, leading to the estimation that 30% of individuals with low vision are in residential care. This analysis does not appear to describe the additional proportion of individuals in residential care due to low vision.

Therefore, another potential area for further research is a costing study of the impact of low vision. Ideally, the analysis should describe costs as a function of age and vision, including the full range of visual ability (e.g. from 6/6 to 3/60). The cost analysis presented by Meads and Moore[75] provides a starting point for the range of resource items to be included in the study, although additional reviews of the literature and primary research may be necessary to increase the validity of the findings.

Conclusions

Well-defined criteria informing the provision of screening programmes have long been defined,[8] which have been adapted and adopted by the NSC. These criteria are interpreted in the light of the evidence identified as part of this study in Appendix 5. The conclusion is that there is probably not enough knowledge to justify the implementation of a screening programme for AMD at present.

It has been proposed that allocative decisions should be based on the mean results of economic evaluations of healthcare technologies.[87] However, the extent of the uncertainty around the mean results, and the additional resources and possible reorganisation of services required to implement screening, indicate that it may be preferable to reduce the level of uncertainty before implementing a *de novo* screening programme for AMD.

The evaluation of screening for AMD has identified an issue around the use of EVI analysis, which concerns a threshold of suitability of cost-effectiveness models for informing research priorities, let alone healthcare resource priorities. The AMD screening model has extreme levels of uncertainty around key input parameters, some of which cannot be feasibly estimated using expert elicitation techniques. We contend that the next stage in the evaluation of screening for AMD should identify, and cost, methods for improving the accuracy of these key parameters.

Research recommendations

Table 76 provides examples of the kind of studies that may be required to inform different key

TABLE 76 *Possible studies to inform key parameters in the AMD screening model*

Parameter	Study type	Cost level	Model impact
Incidence of ARM	Longitudinal population-based	High	Medium
Clinical presentation of ARM	IT study integrating routine data	Medium	High
AMD progression by factors other than visual acuity	Longitudinal patient-based; change in trial reporting standards	High	Low
Screening and optometrist referral effectiveness	Pilot study	Medium	High
Long-term treatment effectiveness	Longitudinal patient-based	Medium	Medium
Costs of blindness	Primary costing study	Low	Medium

parameters. It also provides a subjective assessment of the relative cost levels of implementing such studies, and the impact of improved data in reducing model uncertainty and increasing the suitability of the model to inform resource allocation decisions.

From the preliminary list presented in *Table 76*, initial actions may be best targeted at assessing how routine data may be used to describe clinical presentation rates of ARM. Other potential studies include a pilot study of the effectiveness of screening and optometrists' referral patterns for AMD, and a costing study of blindness as a continuum of association with deterioration in vision.

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Contribution of authors

Jon Karnon (Senior Research Fellow) led the project; developed, implemented, populated and analysed the model; contributed to the literature reviews; input to survey design and drafted and compiled the final report. Carolyn Czoski-Murray (Research Fellow) contributed to the literature reviews and organised the surveys and drafted sections of the report. Kevin Smith (Honorary Senior Clinical Lecturer in Public Health Medicine, Medical Advisor to the Yorkshire and the Humber Regional Specialised Commissioning Group) contributed to the literature reviews; contributed to data analyses and drafted sections of the report. Chris Brand (Consultant Ophthalmologist) was the main clinical contact for advice on the natural history, treatment and screening options for AMD; provided primary data and had an input to the survey design. Usha Chakravarthy (Professor of Ophthalmology and Vision Sciences) supplied advice on the natural history, treatment and screening options for AMD and provided primary data. Sarah Davies (Senior Health Economist) contributed to the data analyses. Nick Bansback (Health Economist) contributed to the literature reviews. Catherine Beverley (Knowledge Manager) informed and undertook literature searches. Alan Bird (Emeritus Professor), Simon Harding (Consultant Ophthalmologist), Iain Chisholm (Consultant Ophthalmologist) and YC Yang (Consultant Ophthalmologist) all gave advice on treatment options and screening for AMD and provided primary data.

References

1. Bird AC, Bressler NM, Bressler SB, Chisholm IH, Coscas G, Davis MD, *et al*. An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol* 1995;**39**:367–74.
2. van Leeuwen R, Klaver CC, Vingerling JR, Hofman A, de Jong PT. Epidemiology of age-related maculopathy: a review. *Eur J Epidemiol* 2003;**18**:845–54.
3. Leibowitz HM, Krueger DE, Maunder LR, Milton RC, Kini MM, Kahn HA, *et al*. The Framingham Eye Study monograph: an ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973–1975. *Surv Ophthalmol* 1980;**24** (Suppl):335–610.
4. Owen CG, Fletcher AE, Donoghue M, Rudnicka AR. How big is the burden of visual loss caused by age related macular degeneration in the United Kingdom? *Br J Ophthalmol* 2003; **87**:312–17.
5. Friedman DS, O'Colmain BJ, Munoz B, Tomany SC, McCarty C, de Jong PT, *et al*. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol* 2004; **122**:564–72.
6. Chang TS, Hay D, Courtright P. Age-related macular degeneration in Chinese-Canadians. *Can J Ophthalmol* 1999;**34**:266–71.
7. Bressler NM, Munoz B, Maguire MG, Vitale SE, Schein OD, Taylor HR, *et al*. Five-year incidence and disappearance of drusen and retinal pigment epithelial abnormalities. Waterman study. *Arch Ophthalmol* 1995;**113**:301–8.
8. Wilson J, Junger G. *Principles and practice of screening for disease*. Public Health Paper 34. Geneva: World Health Organization; 1968.
9. National Screening Committee. *NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme*. URL: http://www.nsc.nhs.uk/pdfs/Criteria.pdf. Accessed 7 July 2007.
10. Bartlett H, Eperjesi F. Age-related macular degeneration and nutritional supplementation: a review of randomised controlled trials. *Ophthalmic Physiol Opt* 2003;**23**:383–99.
11. Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, *et al*. Risk factors for age-related macular degeneration: pooled findings from three continents. *Ophthalmology* 2001;**108**:697–704.
12. Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. *JAMA* 1996;**276**:1141–6.
13. Christen WG, Glynn RJ, Manson JE, Ajani UA, Buring JE. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *JAMA* 1996;**276**:1147–51.
14. Age-Related Eye Disease Research Study Group. Risk factors associated with age-related macular degeneration. A case–control study in the age-related eye disease study: age-related eye disease study report number 3. *Ophthalmology* 2000;**107**: 2224–32.
15. Delcourt C, Diaz JL, Ponton-Sanchez A, Papoz L. Smoking and age-related macular degeneration. The POLA Study. Pathologies Oculaires Liées à l'Age. *Arch Ophthalmol* 1998;**116**:1031–5.
16. Vingerling JR, Hofman A, Grobbee DE, de Jong PT. Age-related macular degeneration and smoking. The Rotterdam Study. *Arch Ophthalmol* 1996;**114**:1193–6.
17. Delcourt C, Michel F, Colvez A, Lacroux A, Delage M, Vernet MH, *et al*. Associations of cardiovascular disease and its risk factors with age-related macular degeneration: the POLA study. *Ophthalmic Epidemiol* 2001;**8**:237–49.
18. Klein R, Klein BE, Tomany SC, Cruickshanks KJ. The association of cardiovascular disease with the long-term incidence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* 2003; **110**:636–43.
19. Klein R, Klein BE, Jensen SC. The relation of cardiovascular disease and its risk factors to the 5-year incidence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* 1997; **104**:1804–12.
20. Klein R, Klein BE, Wong TY, Tomany SC, Cruickshanks KJ. The association of cataract and cataract surgery with the long-term incidence of age-related maculopathy: the Beaver Dam Eye Study. *Arch Ophthalmol* 2002;**120**:1551–8.
21. Chaine G, Hullo A, Sahel J, Soubrane G, Espinasse-Berrod MA, Schutz D, *et al*. Case–control study of the risk factors for age related macular

degeneration. France–DMLA Study Group. *Br J Ophthalmol* 1998;**82**:996–1002.

22. Buch H, Nielsen N, Vinding T, Jensen G, Prause JU, la Cour M. 14-Year incidence, progression and visual morbidity of age-related maculopathy. *Ophthalmology* 2005;**112**:787–98.
23. Mitchell P, Wang JJ, Foran S, Smith W. Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study [published erratum appears in *Ophthalmology* 2002;**109**:1588]. *Ophthalmology* 2002;**109**:1092–7.
24. Tomany SC, Klein R, Klein BE. The relation of coffee and caffeine to the 5-year incidence of early age-related maculopathy: the Beaver Dam Eye Study. *Am J Ophthalmol* 2001;**132**:271–3.
25. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol* 2001;**119**:1417–36.
26. Sparrow JM, Dickinson AJ, Duke AM, Thompson JR, Gibson JM, Rosenthal AR. Seven year follow-up of age-related maculopathy in an elderly British population. *Eye* 1997;**11**(Pt 3):315–24.
27. Age-Related Eye Disease Study Research Group. Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS): AREDS report no. 19. *Ophthalmology* 2005;**112**:533–9.
28. Choroidal Neovascularization Prevention Trial Research Group. Laser treatment in eyes with large drusen. Short-term effects seen in a pilot randomized clinical trial. Choroidal Neovascularization Prevention Trial Research Group. *Ophthalmology* 1998;**105**:11–23.
29. Burgess DB, Hawkins BS, Jefferys JL, Bressler NM, Bressler SB, Hiner CJ, *et al*. 5-Year follow-up of fellow eyes of patients with age-related macular degeneration and unilateral extrafoveal choroidal neovascularization. *Arch Ophthalmol* 1993; **111**:1189–99.
30. Wilkinson CP, Hawkins BS, Javornik NB, Newhouse MM, Keller JA, Bressler NM, *et al*. Five-year follow-up of fellow eyes of individuals with ocular histoplasmosis and unilateral extrafoveal or juxtafoveal choroidal neovascularization. *Arch Ophthalmol* 1996; **114**:677–88.
31. Macular Photocoagulation Study Group. Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. Macular Photocoagulation Study Group. *Arch Ophthalmol* 1997;**115**:741–7.
32. Bressler NM, Frost LA, Bressler SB, Murphy RP, Fine SL. Natural course of poorly defined choroidal neovascularization associated with macular degeneration. *Arch Ophthalmol* 1988; **106**:1537–42.
33. Sunness JS, Gonzalez-Baron J, Bressler NM, Hawkins B, Applegate CA. The development of choroidal neovascularization in eyes with the geographic atrophy form of age-related macular degeneration. *Ophthalmology* 1999;**106**:910–19.
34. Pauleikhoff D, Radermacher M, Spital G, Muller C, Brumm G, Lommatzsch A, *et al*. Visual prognosis of second eyes in patients with unilateral late exudative age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2002;**240**:539–42.
35. Baun O, Vinding T, Krogh E. Natural course in fellow eyes of patients with unilateral age-related exudative maculopathy. A fluorescein angiographic 4-year follow-up of 45 patients. *Acta Ophthalmol* 1993;**71**:398–401.
36. Wang JJ, Foran S, Smith W, Mitchell P. Risk of age-related macular degeneration in eyes with macular drusen or hyperpigmentation: the Blue Mountains Eye Study cohort. *Arch Ophthalmology* 2003; **121**:658–63.
37. Holz FG, Wolfensberger TJ, Piguet B, Gross-Jendroska M, Wells JA, Minassian DC, *et al*. Bilateral macular drusen in age-related macular degeneration. Prognosis and risk factors. *Ophthalmology* 1994;**101**:1522–8.
38. Sarks JP, Sarks SH, Killingsworth MC. Evolution of geographic atrophy of the retinal pigment epithelium. *Eye* 1988;**2**:552–77.
39. Schatz H, McDonald HR. Atrophic macular degeneration: rate of spread of geographic atrophy and visual loss. *Ophthalmology* 1989; **96**:1551.
40. Ali F, Chan WC, Stevenson MR, Muldrew KA, Chakravarthy U. Morphometric analysis of angiograms of exudative lesions in age-related macular degeneration. *Arch Ophthalmol* 2004; **122**:710–15.
41. Sunness JS. The natural history of geographic atrophy, the advanced atrophic form of age-related macular degeneration. *Mol Vis* 1999;**5**:25.
42. Sunness JS, Gonzalez-Baron J, Applegate CA, Bressler NM, Tian Y, Hawkins B, *et al*. Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. *Ophthalmology* 1999; **106**:1768–79.
43. Stevenson MR, Hart PM, Chakravarthy U, MacKenzie G, Bird AC, Owens SL, *et al*. Visual functioning and quality of life in the SubFoveal Radiotherapy Study (SFRADS): SFRADS report 2. *Br J Ophthalmol* 2005;**89**:1045–51.

44. Zaidi FH, Cheong-Leen R, Gair EJ, Weir R, Sharkawi E, Lee N, *et al*. The Amsler chart is of doubtful value in retinal screening for early laser therapy of subretinal membranes. The West London Survey. *Eye* 2004;**18**:503–8.

45. Barthes A, Conrath J, Rasigni M, Adel M, Petrakian JP. Mathematical morphology in computerized analysis of angiograms in age-related macular degeneration. *Med Phys* 2001; **28**:2410–19.

46. Fine AM, Elman MJ, Ebert JE, Prestia PA, Starr JS, Fine SL. Earliest symptoms caused by neovascular membranes in the macula. *Arch Ophthalmol* 1986; **104**:513–14.

47. Schmitt NJ, Grover DA, Feldon SE. The Eger Macular Stressometer: pilot study. *Am J Ophthalmol* 2003;**136**:314–17.

48. Lafaut BA, De Backer E, Kohno T, De Laey JJ, Meire FM. Indocyanine green angiography in Sorsby's fundus dystrophy. *Graefes Arch Clin Exp Ophthalmol* 2000;**238**:158–62.

49. Macular Photocoagulation Study Group. Argon laser photocoagulation for neovascular maculopathy: five year results from randomized clinical trials. *Arch Ophthalmol* 1991;**109**:1109–14.

50. Evans JR. Antioxidant vitamin and mineral supplements for age-related macular degeneration (Cochrane Review) In *The Cochrane Library*, Issue 1. Chichester: Wiley; 2004.

51. Teikari JM, Laatikainen L, Virtamo J, Haukka J, Rautalahti M, Liesto K, *et al*. Six-year supplementation with alpha-tocopherol and beta-carotene and age-related maculopathy. *Acta Ophthalmol Scand* 1998;**76**:224–9.

52. ClinicalTrials.gov. *Open-label posterior juxtascleral injections of anecortave acetate 15 mg dose for long term use in patients with AMD*. URL: http://www.clinicaltrials.gov/ct/show/NCT00065728;jsessionid=547BE5D966347E4DA5750BE230BB9F66?order=1. Accessed 7 July 2007.

53. Pulido JS, Sanders DR, Klingel R. Rheopheresis for age-related macular degeneration: clinical results and putative mechanism of action. *Can J Ophthalmol* 2005;**40**:332–40.

54. Pulido JS, Multicenter Investigation of Rheopheresis for AMD (MIRA). Multicenter prospective, randomized, double-masked, placebo-controlled study of Rheopheresis to treat nonexudative age-related macular degeneration: interim analysis. *Trans Am Ophthalmol Soc* 2002; **100**:85–106.

55. Panel discussion. Evolving treatment strategies for exudative AMD. The combination of verteporfin PDT and triamcinolone is already changing practice patterns. *Retinal Physician* 2005. URL: http://www.retinalphysician.com/article.aspx?article=100108. Accessed 17 April 2008.

56. Jonas JB, Kreissig I, Degenring RF. Factors influencing visual acuity after intravitreal triamcinolone acetonide as treatment of exudative age related macular degeneration. *Br J Ophthalmol* 2004;**88**:1557–62.

57. Bhavsar A. Combined verteporfin photodynamic therapy and intravitreal triamcinolone in the treatment of minimally classic subfoveal CNV with or without RAP lesions. AAO poster presentation P0163. 2004.

58. Augustin AJ, Schmidt-Erfurth U. Verteporfin therapy combined with intravitreal triamcinolone in all types of choroidal neovascularisation due to age-related macular degeneration. *Ophthalmology* 2006;**113**:14–22.

59. Eye facts. *Anti-VEGF treatment for age-related macular degeneration*. URL: https://secure3.aao.org/pdf/057052.pdf. Accessed 7 July 2007.

60. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004;**351**:2805–16.

61. Genentech. *Genentech granted six-month priority review for ranubizimab for the treatment of wet AMD*. URL: http://www.mdsupport.org/. Accessed 7 July 2007.

62. Roberts D. *Avastin for wet AMD?* February 2007. URL: http://www.mdsupport.org/library/avastin.html. Accessed 7 July 2007.

63. Thomas MA, Ibanez HE. Subretinal endophotocoagulation in the treatment of choroidal neovascularization. *Am J Ophthalmol* 1993;**116**:279–85.

64. van Meurs JC, van den Biesen PR. Autologous retinal pigment epithelium and choroid translocation in patients with exudative age-related macular degeneration: short-term follow-up. *Am J Ophthalmol* 2003;**136**:688–95.

65. Moss SM, Gray A, Legood R, Henstock E. *Evaluation of HPV/LBC Cervical Screening Pilot Studies. First report to the Department of Health on evaluation of LBC*. London: Department of Health; 2002.

66. Roderick P, Davies R, Raftery J, Crabbe D, Bhandari P, Patel P. The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete event simulation model. *Health Technol Assess* 2003;**7**(6).

67. Goverdhan SV, Booth AJ, Luff AJ, Lotery AJ. Age-related macular degeneration. Where are we now? *Optometry Today* 2004; (17 December) 39–43.

68. Busbee B, Brown MM, Brown GC, Sharma S. CME review: a cost–utility analysis of laser photocoagulation for extrafoveal choroidal neovascularisation. *Retina* 2003;**23**:279–87.

69. Bonastre J, Le Pen C, Soubrane G, Quentel G. The burden of age-related macular degeneration: results of a cohort study in two French referral centres. *Pharmacoeconomics* 2003;**21**:181–90.

70. Sharma S, Bakal J, Sharma SM, Covert D, Shah GK. Drug pricing for a novel treatment for wet macular degeneration: using incremental cost-effectiveness ratios to ensure societal value. *Can J Ophthalmol* 2005;**40**:369–77.

71. van Leeuwen R, Chakravarthy U, Vingerling J, Brussee C, Hooghart A, Mulder P, *et al*. Grading of age-related maculopathy for epidemiological studies – is digital imaging as good as 35-mm film? *Ophthalmology* 2003;**110**:1540–4.

72. Pollack A. Genentech in competition with itself on eye drug. *New York Times* 27 September, 2005. URL: http://www.nytimes.com/2005/09/27/business/27place.html. Accessed 17 April 2008.

73. Cooke R. I can see clearly now. At last, therapies improve vision lost to macular degeneration. *AARP Bull* 2005. URL: http://www.aarp.org/bulletin/yourhealth/macular.html. Accessed 17 April 2008.

74. EyeTech. *Press release: Safety profile of Pegaptanib® (pegaptanib sodium injection) in the treatment of neovascular age-related macular degeneration (AMD) maintained for two years*. New York, 2 May, 2005. URL: http://www.mpmcapital.com/newsroom/news/050502ii.pdf. Accessed 7 July 2007.

75. Meads C, Moore D. The clinical effectiveness and cost utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2001;**7**(9).

76. Espallargues M, Czoski-Murray C, Bansback N, Carlton J, Lewis G, Hughes L, *et al*. The impact of age related macular degeneration on health state utility values. *Invest Ophthalmol Vis Sci* 2005; **46**:4016–23.

77. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. *Arch Ophthalmol* 2000;**118**:47–51.

78. Brown MM, Brown GC, Sharma S, Landy J, Bakal J. Quality of life with visual acuity loss from diabetic retinopathy and age-related macular degeneration. *Arch Ophthalmol* 2002;**120**:481–4.

79. Meads C, Hyde C. Photodynamic therapy with verteporfin is effective, but how big is its effect? Results of a systematic review. *Br J Ophthalmol* 2004;**88**:212–17.

80. Evans J, Wormald R. Is the incidence of registrable age-related macular degeneration increasing? *Br J Ophthalmol* 1996;**80**:9–14.

81. Karlsson G, Johannesson M. The decision rules of cost-effectiveness analysis. *Pharmacoeconomics* 2006; **9**:113–20.

82. Towse A, Devlin N, Pritchard C, editors. *Cost effectiveness thresholds: economic and ethical issues*. London: Office for Health Economics/King's Fund; 2002.

83. Stevenson M, Oakley J, Chilcott J. Gaussian process modelling in conjunction with individual patient simulation modelling. A case study describing the calculation of cost-effectiveness ratios for the treatment of osteoporosis. *Med Decis Making* 2004;**24**:89–100.

84. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, *et al*. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices – Modeling Studies. *Value Health* 2003;**6**:9–17.

85. McClure ME, Hart PM, Jackson AJ, Stevenson MR, Chakravarthy U. Macular degeneration: do conventional measurements of impaired visual function equate with visual disability? *Br J Ophthalmol* 2000;**84**:244–50.

86. Vaclavik V, Vujosevic S, Dandekar SS, Bunce C, Peto T, Bird AC. Autofluorescence imaging in age-related macular degeneration complicated by choroidal neovascularization. A prospective study. *Ophthalmology* 2008;**115**:342–6.

87. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ* 1999;**18**:341–64.

88. Woods RL, Tregear SJ, Mitchell RA. Screening for ophthalmic disease in older subjects using visual acuity and contrast sensitivity. *Ophthalmology* 1998;**105**:2318–232.

89. Vingerling JR, Dielemans I, Hofman A, Grobbee DE, Hijmering M, Kramer CF, *et al*. The prevalence of age-related maculopathy in the Rotterdam Study. *Ophthalmology* 1995;**102**:205–10.

90. Das BN, Thompson JR, Patel R, Rosenthal AR. The prevalence of eye disease in Leicester: a comparison of adults of Asian and European descent. *J R Soc Med* 1994;**87**:219–22.

91. Dickinson AJ, Sparrow JM, Duke AM, Thompson JR, Gibson JM, Rosenthal AR. Prevalence of age-related maculopathy at two points in time in an elderly British population. *Eye* 1997;**11**(Pt 3):301–14.

92. Vinding T. Visual impairment of age-related macular degeneration. An epidemiological study of 1000 aged individuals. *Acta Ophthalmol* 1990; **68**:162–7.

93. Klaver CCW, Wolfs RCW, Vingerling JR, Hofman A, De Jong PTVM. Age-specific prevalence and causes of blindness and visual impairment in an older population: the Rotterdam study. *Arch Ophthalmol* 1998;**116**:653–8.

94. Klaver CC, Assink JJ, van Leeuwen R, Wolfs RC, Vingerling JR, Stijnen T, *et al*. Incidence and progression rates of age-related maculopathy: the Rotterdam Study. *Invest Ophthalmol Vis Sci* 2001; **42**:2237–41.

95. Maguire MG. More pieces for the age-related macular degeneration puzzle, *Ophthalmology* 1997; **104**:5–6.

96. Schachat AP, Hyman L, Leske MC, Connell AM, Wu SY. Features of age-related macular degeneration in a black population. The Barbados Eye Study Group. *Arch Ophthalmol* 1995; **113**:728–35.

97. Weih LM, VanNewkirk MR, McCarty CA, Taylor HR. Age-specific causes of bilateral visual impairment. *Arch Ophthalmol* 2000;**118**:264–9.

98. Reidy A, Minassian DC, Vafidis G, Joseph J, Farrow S, Wu J, *et al*. Prevalence of serious eye disease and visual impairment in a north London population: population based, cross sectional study. *BMJ* 1998;**316**:1643–6.

99. Mitchell RA. Prevalence of age related macular degeneration in persons aged 50 years and over resident in Australia. *J Epidemiol Commun Health* 1993;**47**:42–5.

100. Munier A, Gunning T, Kenny D, O'Keefe M. Causes of blindness in the adult population of the Republic of Ireland. *Br J Ophthalmol* 1998; **82**:630–3.

101. Foran S, Wang JJ, Mitchell P. Causes of incident visual impairment: the Blue Mountains Eye Study. *Arch Ophthalmol* 2002;**120**:613–19.

102. Huang GH, Klein R, Klein BE, Tomany SC. Birth cohort effect on prevalence of age-related maculopathy in the Beaver Dam Eye Study. *Am J Epidemiol* 2003;**157**:721–9.

103. Gibson JM, Rosenthal AR, Lavery J. A study of the prevalence of eye disease in the elderly in an English community. *Trans Ophthalmol Soc UK* 1985; **104**(Pt 2):196–203.

104. Cruickshanks KJ, Hamman RF, Klein R, Nondahl DM, Shetterly SM. The prevalence of age-related maculopathy by geographic region and ethnicity. The Colorado–Wisconsin Study of Age-Related Maculopathy. *Arch Ophthalmol* 1997; **115**:242–50.

105. VanNewkirk MR, Nanjan MB, Wang JJ, Mitchell P, Taylor HR, McCarty CA. The prevalence of age-related maculopathy: the visual impairment project. *Ophthalmology* 2000;**107**:1593–600.

106. Foran S, Wang JJ, Mitchell P. Causes of visual impairment in two older population cross-sections: the Blue Mountains Eye Study. *Ophthalmic Epidemiol* 2003;**10**:215–25.

107. Buch H, Vinding T, Nielsen NV. Prevalence and causes of visual impairment according to World Health Organization and United States criteria in an aged, urban Scandinavian population: the Copenhagen City Eye Study. *Ophthalmology* 2001; **108**:2347–57.

108. Wang JJ, Foran S, Mitchell P. Age-specific prevalence and causes of bilateral and unilateral visual impairment in older Australians: the Blue Mountains Eye Study. *Clinical Exp Ophthalmol* 2000;**28**:268–73.

109. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1995; **102**:1450–60.

110. Javitt JC, Zhou Z, Maguire MG, Fine SL, Willke RJ. Incidence of exudative age-related macular degeneration among elderly Americans. *Ophthalmology* 2003;**110**:1534–9.

111. Klein R, Klein BE, Tomany SC, Moss SE. Ten-year incidence of age-related maculopathy and smoking and drinking: the Beaver Dam Eye Study. *Am J Epidemiol* 2002;**156**:589–98.

112. Rahmani B, Tielsch JM, Katz J, Gottsch J, Quigley H, Javitt J, *et al*. The cause-specific prevalence of visual impairment in an urban population: the Baltimore Eye Survey. *Ophthalmology* 1996;**103**:1721–6.

113. Farber MD. National Registry for the Blind in Israel: estimation of prevalence and incidence rates and causes of blindness. *Ophthalmic Epidemiol* 2003;**10**:267–77.

114. Frennesson CI. Photodynamic therapy with verteporfin in patients with age-related macular degeneration and juxtafoveal choroidal neovascularisation. *Acta Ophthalmol Scand* 2004;**82**:651–5.

Appendix 1

Literature search plans and results

Search strategies

A comprehensive literature search was undertaken during March 2004 (updated in January 2005) to identify relevant literature pertaining to screening for AMD. Four major searches were conducted which were designed to retrieve:

- high level evidence (i.e. guidelines, systematic reviews and RCTs) concerning AMD
- papers describing the epidemiology of AMD
- papers describing the diagnosis and diagnostic tests associated with AMD
- cost-effectiveness and health utility literature in the field.

The following electronic bibliographic databases were searched:

1. Cochrane Database of Systematic Reviews (CDSR)
2. Cochrane Central Register of Controlled Trials (CENTRAL)
3. EMBASE
4. MEDLINE
5. NHS Database of Abstracts of Reviews of Effects (DARE)
6. NHS Health Technology Assessment (HTA) database
7. Science Citation Index (SCI)
8. Social Sciences Citation Index (SSCI)
9. Turning Research into Practice (TRIP) database.

Attempts were also made to identify 'grey' literature by searching appropriate databases (e.g. Health Management Information Consortium, Index to Theses, Dissertation Abstracts), current research registers (e.g. National Research Register, Research Findings Register, Current Controlled Trials) and relevant websites (e.g. Macular Disease Society, Moorfields Eye Hospital, Royal National Institute for the Blind).

The reference lists of included studies and relevant review articles were also checked.

The search strategy used in MEDLINE (Ovid) was as follows:

1 exp macular degeneration/
2 macula$ degen$.tw
3 maculopath$.tw
4 AMD.tw
5 ARMD.tw
6 or/1-5

This strategy was combined with methodological search filters designed to retrieve the highest levels of evidence, for example:

Guidelines

7 guideline.pt
8 practice guideline.pt
9 health planning guidelines/
10 or/1-3

Systematic reviews

1 meta-analysis/
2 exp review literature/
3 (meta-analy$ or meta analy$ or metaanaly$).tw
4 meta analysis.pt
5 review academic.pt
6 review literature.pt
7 (systematic$ adj3 (review$ or overview$)).tw
8 or/1-7

RCTs

1 clinical trial.pt

The strategy was also combined with the following 'epidemiology' search terms:

1 exp epidemiology/
2 epidemiolog$.ti
3 inciden$.ti
4 prevalen$.ti
5 incidence/
6 prevalence/
7 or/1-6

Finally, the strategy was combined with the following 'diagnosis' search terms:

1 fluoresein.tw
2 amsler.tw
3 diagnos$.ti
4 screen$.ti
5 exp *mass screening/
6 diagnosis/
7 macula$ computer$ psychosphysical test$.tw

8 mcpt.tw
9 *angiography/
10 *fluorescein angiography/
11 angiograph$.ti
12 indocyanine green.tw
13 or/1-12

No date or language restrictions were applied to the searches.

In terms of cost-effectiveness and utility literature, searches were conducted in MEDLINE, EMBASE, NHS Economic Evaluations Database (EED) and OHE Health Economic Evaluations Database (HEED). Search filters designed to retrieve economic evaluations, economic models and QoL literature were applied to the MEDLINE and EMBASE searches. An example of the filter used in MEDLINE (Ovid) is provided below:

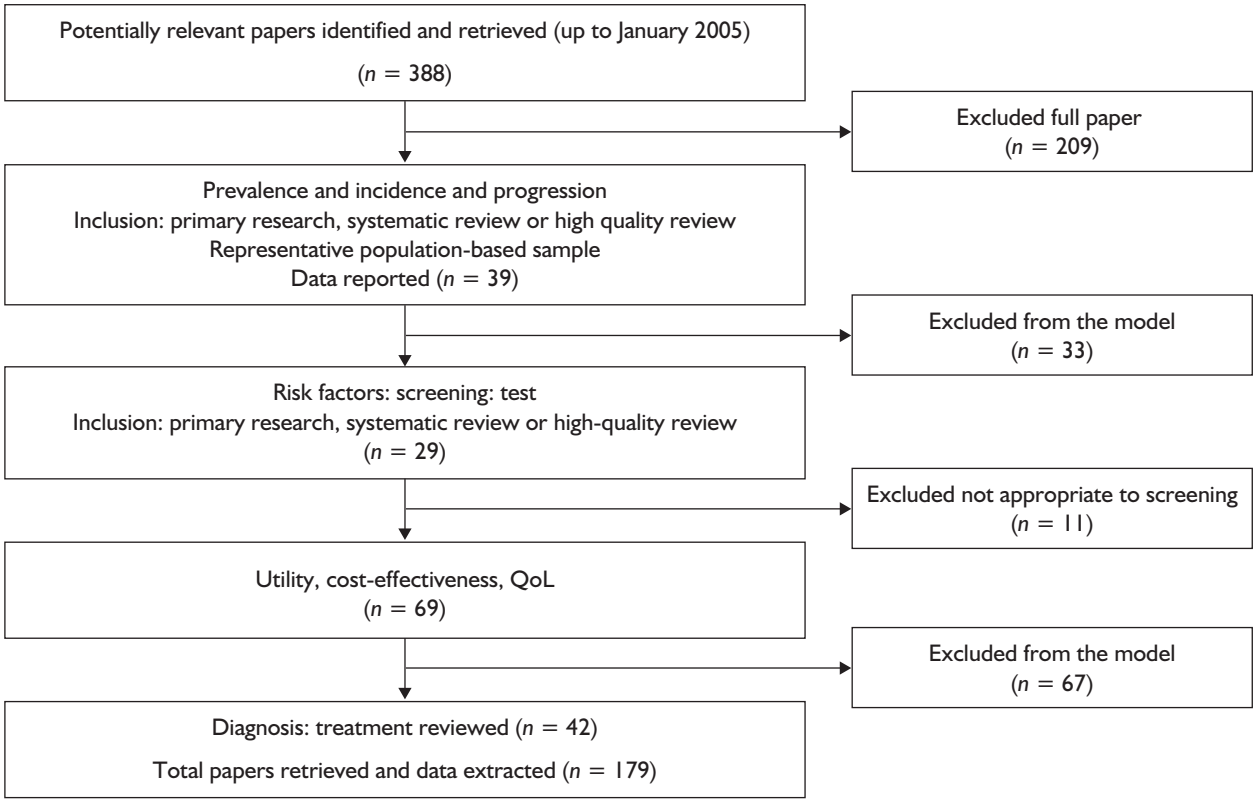
1 exp patient acceptance of health care/
2 exp "costs and cost analysis"/
3 cost$.ti
4 (cost$ adj2 (effective$ or util$ or benefit$ or minimi$)).ab
5 (economic$ or pharmacoeconomic$ or pharmaco-economic$).tw
6 quality adjusted life year/
7 quality adjusted life.tw
8 (qaly$ or qald$ or qale$ or qtime$).tw
9 disability adjusted life.tw
10 daly$.tw
11 health status indicators/
12 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw
13 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw
14 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw
15 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw
16 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw
17 (euroqol or euro qol or eq5d or eq 5d).tw
18 (hql or hqol or h qol or hrqol or hr qol).tw
19 (hye or hyes).tw
20 health$ year$ equivalent$.tw
21 health utilit$.tw
22 (hui or hui1 or hui2 or hui3).tw
23 disutil$.tw
24 rosser.tw
25 quality of wellbeing.tw
26 qwb.tw
27 willingness to pay.tw
28 standard gamble$.tw
29 time trade off.tw
30 time tradeoff.tw
31 tto.tw
32 exp models, economic/
33 *models, theoretical/
34 *models, organizational/
35 economic model$.tw
36 markov chains/
37 markov$.tw
38 monte carlo method/
39 monte carlo.tw
40 exp decision theory/
41 (decision$ adj2 (tree$ or analy$ or model$)).tw
42 or/1-41

Database	Host/system	Date searched	No. of hits	Location of search strategy	Notes
CDSR	Ovid	4 January 2004	9 (cdsrup.txt)	Paper copy only	
CENTRAL	Ovid	4 January 2004	13 (centup.txt)	Paper copy only	
MEDLINE 2004–	Ovid	4 January 2004	Guidelines: 4 (mamdupg.txt) Systematic reviews: 12 (mamdupsr.txt) Epidemiology: 25 (mamdupep.txt) Treatments (clinical trials): 31 (mamdupct.txt) Diagnosis: 43 (mamdupdiag.txt) Acceptability/utilities: 23 (mamduput.txt)	"cbmHTAAMD" in Ovid	
CENTRAL/CCTR	Ovid	3 March 2004	297 (cctramd.txt)	Paper copy only	Imported into Ref Man
CDSR	Ovid	3 March 2004	7 (cdsramd.txt)	Paper copy only	Imported into Ref Man
CINAHL 1982–	Ovid				
Citation Indexes (Science and Social Sciences) Author search	Web of Science	3 March 2004	175 (ciamdauthor.txt)	Paper copy only	Imported into Ref Man
CRD Databases	CRD Website http://agatha.york.ac.uk/welcome.htm	3 March 2004	35 (crdamd.txt)	Paper copy only	Imported into Ref Man
DARE	Ovid	3 March 2004	0	–	
EMBASE 1980–	SilverPlatter WebSPIRS		Guidelines: 43 (eamdg.txt) Systematic reviews: 15 (eamdsr.txt) Epidemiology: 289 (eamdep.txt) Treatments (clinical trials): 199 (eamdct.txt) Diagnosis: 887 (eamddiag.txt) Acceptability/utilities: 115 (eamdut.txt)	Paper copies only	Imported into Ref Man
HMIC	SilverPlatter WinSPIRS				
MEDLINE 1966–	Ovid	3 March 2004	Guidelines: 18 (mamdg.txt) Systematic reviews: 92 (mamdsr.txt) Epidemiology: 322 (mamdep.txt) Treatments (clinical trials): 381 (mamdct.txt) Diagnosis: 702 (mamddiag.txt) Acceptability/utilities: 62 (mamdut.txt)	"cbmHTAAMD" in Ovid	Imported into Ref Man
PreMEDLINE	Ovid				

Other sources searched

Other source	Date searched	No. of hits	Notes
Altavista or Google	3 March 2004	0 additional	
Citation/author searching			
Department of Health Website www.doh.gov.uk	3 March 2004	0	
Handsearching			
Index to Theses			
Macular Disease Society http://www.maculardisease.org/	3 March 2004	0 relevant	
Moorfields Eye Hospital http://www.moorfields.co.uk/Home	3 March 2004	1	Added to Ref Man
National Research Register http://www.update-software.com/national/	3 March 2004	Various	Majority added to Ref Man, others printed off and sent to JK
Research Findings Register (ReFeR) http://www.info.doh.gov.uk/doh/refr_web.nsf/Home?OpenForm	3 March 2004	0 additional	
RNIB	3 March 2004	0 additional	
ScHARR Library catalogue			
TRIP database	3 March 2004	Various	Relevant abstracts printed off and added to Ref Man

Flow chart of study identification



Appendix 2

Studies of prevalence of AMD

<table>
<tr><th>Study</th><th>Study design
Duration of study
Location
Total number</th><th>Subjects
Age range (years)
AMD
Gender
Ethnicity</th><th>Diagnostic test
Confirmation of disease
Exclusions</th><th>Results</th><th>Comments</th></tr>
<tr><td>Das et al. (1994)[90]</td><td>Prospective, randomised observational study
Leicester, UK
377</td><td>Patients 40+ from FPC lists
60–69
70+
M/F n not reported
Asian or European origin selected to represent Asian origin</td><td>VA, near and distant
Full refraction
Split lamp biomicroscopy
Macula = area clinically apparent pigmentation surrounding foveola
AMD = degenerative changes plus BC VA ⩽ 6/9
Exclusions diabetic retinopathy. Secondary causes and congenital macular disease, results from patients of West Indian origin</td><td><table><tr><th>Age</th><th>Asian F</th><th>Asian M</th><th>European F</th><th>European M</th></tr><tr><td>60–69</td><td>0%</td><td>0%</td><td>3%
(SE 3.1%)</td><td>3%
(SE 2.7%)</td></tr><tr><td>70+</td><td>23%
(SE 11.7%)</td><td>7%
(SE 6.4%)</td><td>28%
(SE 7.2%)</td><td>16%
(SE 7.3%)</td></tr></table>p-Values:
Age $p > 0.001$
Sex $p = 0.08$
Racial group $p = 0.51$</td><td>They also looked at the prevalence of diabetic retinopathy and age-related cataract
The FPC lists are out of date, which restricts recruitment
8 patients excluded from the analysis as they were of West Indian origin</td></tr>
</table>

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments
Dickinson *et al.* (1997)[91]	Retrospective/ prospective randomised 7-year follow-up Melton Mowbray, Leics, UK 529 and 88 at follow-up. Total of 158 eyes with data	Participants in a large epidemiology study in 1982–4 Over 75 in 1981 70% female European	Ophthalmic examination with fundus photography. Mydriatic ophthalmic Examinations in both the initial and follow-up studies. WARMGS VA 6/18 or worse 2 blinded observers	Prevalence AMD (total eyes *n* = 158): Initial testing (*n*) 23 (14.6%) % eyes ⩾6/18 50.0 Subsequent (*n*) 38 (24.1%) % eyes ⩾6/18 48.7 Prevalence of wet or dry AMD (total eyes *n* = 158): Initial wet (*n*) 3 (1.9%) Subsequent (*n*) 6 (3.8%) Initial dry (*n*) 3 (1.9%) Subsequent (*n*) 5 (3.2%)	Also data on drusen and severity of AMD which may be useable Only 50% of survivors in the sample Also broken down by VA available
Vinding (1990)[92]	Prospective random Follow-up 10 years District of Copenhagen 946 survivors, 924 in final analysis = 1848 eyes	Participants in large cardiac epidemiology study (1976–8 and 1981–3) 60–80 years European	Funduscopic Examination: Ophthalmoscopy and biomicroscopy with Goldmann 3mirror lenses. VA 6/9 or worse (Framingham definition). E-chart Single observer	AMD prevalence: No. of people: Total AMD 112/924 (173 eyes) %: Total AMD 12; VA 6/9–6/12 71.7; VA 6/18–6.36 15; VA 6/60 or less 13.3	There are additional graphs representing % of wet and dry AMD

continued

<table>
<tr><th>Study</th><th>Study design
Duration of study
Location
Total number</th><th>Subjects
Age range (years)
AMD
Gender
Ethnicity</th><th>Diagnostic test
Confirmation of disease
Exclusions</th><th>Results</th><th>Comments</th></tr>
<tr><td>Klaver et al. (1998)[93]</td><td>Prospective follow-up of Rotterdam study
6775 subjects</td><td>55+ years. 77.7% of those identified as eligible from the municipal register consented to initial interview</td><td>Medical record review
Diagnostic tests: ophthalmological examination, VA
Standardised grading protocol WHO: blind <0.05 (20/400), visual impairment <0.3 (20/60)
USA standard: blind <0.1 (20/200), visual impairment <0.5 (20/40)</td><td>Prevalence of AMD as cause of blindness and visual impairment:
<table><tr><th>Age (years)</th><th>Blind (64 eyes)</th><th>Visual impairment (192 eyes)</th></tr><tr><td>55–74</td><td>14% (2 eyes)</td><td>5% (1 eye)</td></tr><tr><td>75–84</td><td>56% (10 eyes)</td><td>28% (21 eyes)</td></tr><tr><td>85+</td><td>78% (25 eyes)</td><td>27% (26 eyes)</td></tr><tr><td>All ages (55+)</td><td>58% (37 eyes)</td><td>25% (48 eyes)</td></tr></table>Percentages of eyes rather than percentages of subjects</td><td>No explanation is provided for the 15.2% that did not participate in the ophthalmological examinations
The population examined was predominantly white
Possible problems with multiple (3) observers. No mention of blinding</td></tr>
<tr><td>Klaver et al. (2001)[94]</td><td>Population-based, prospective cohort study
Baseline: 6872
Follow-up: 4953
Rotterdam, The Netherlands</td><td>55+ years. 58.5% were women at follow-up
Exclusion: AMD at baseline excluding the incidence and progressive analyses (n = 105)</td><td>The screening for the presence of ARM followed the same protocol at baseline and follow-up. At follow-up side-by-side grading was used with the transparencies of the baseline phase</td><td>Age-specific incidence rates per 1000 person-years and 2-year cumulative incidences of AMD in the Rotterdam study
<table><tr><th>Age (years)</th><th>Person-years</th><th>No.</th><th>Incidence rate</th><th>95% CI</th><th>2-year cumulative incidence (%)</th></tr><tr><td>55–64</td><td>3546</td><td>0</td><td>0</td><td>0 to 1</td><td>0</td></tr><tr><td>65–74</td><td>4011</td><td>3</td><td>0.75</td><td>0.15 to 2.2</td><td>0.15</td></tr><tr><td>75–84</td><td>1952</td><td>6</td><td>3.07</td><td>1.1 to 6.7</td><td>0.61</td></tr><tr><td>85+</td><td>340</td><td>3</td><td>8.8</td><td>1.8 to 25.8</td><td>1.75</td></tr><tr><td>Total</td><td>9849</td><td>12</td><td>1.22</td><td>0.6 to 2.1</td><td>0.24</td></tr></table></td><td>In addition this paper has details of comparisons between Beaver Dam, Waterman and Rotterdam studies</td></tr>
</table>

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments

Stage	Criteria	At baseline	At follow-up	Selected for detailed grading
No AMD	No AMD or drusen ⩽63 μm	4038	3238	365
1a	Soft, distinct drusen	1485	1160	348
1b	Pigmentary irreg	307	217	193
2a	Soft, indistinct or reticular drusen	191	133	133
2b	Soft, indistinct drusen with pigmentary irregularities	209	158	158
3	Soft, indistinct or reticular drusen with pigmentary irregularies	83	47	47
4	Atrophic or neovascular macular degeneration	105	56	0

Vingerling *et al.* (1995)[89]

Follow-up study to the Rotterdam study

6251

55–98 years drawn from municipal register

59.7% women

63% non-attenders female

Photographs graded using WARMGS

Age- and sex-specific prevalence (%) of atrophic and neovascular AMD:

Age (years)	Atrophic AMD			Neovascular AMD			Total AMD		
	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes
	0.2	0	0.1	0.1	0.1	0.1	0.3	0.1	0.2
65–74	0.6	0.2	0.4	0.3	0.5	0.4	0.9	0.6	0.8
75–84	1.1	1.4	1.3	2.4	2.4	2.4	3.5	3.8	3.7
85+	2.7	4	3.7	6.8	7.5	7.4	9.6	11.5	11
Total	0.6	0.6	0.6	0.8	1.2	1.1	1.4	1.9	1.7

Only 6251 (64%) of the eligible 9774 made it to the final analysis with gradable fundus photographs

Table 2 in the journal article provides AMD and drusen definitions

continued

<table>
<tr><th>Study</th><th>Study design
Duration of study
Location
Total number</th><th>Subjects
Age range (years)
AMD
Gender
Ethnicity</th><th>Diagnostic test
Confirmation of disease
Exclusions</th><th>Results</th><th>Comments</th></tr>
<tr><td>Schachat et al. (1995)[96]</td><td>Prospective, random sample from resident population
Barbados, West Indies
Total 3444
Population-based study</td><td>Median age of all BES participants was 59 years
57% were female, 43% male
93% self-reported their race as black
40–84 years</td><td>Standardised examination
Automated refraction, best corrected VA, early treatment diabetic retinotherapy study protocol
Fundus photographs
Gradings from 30° stereoscopic macular photographs
Ophthalmological examination. Drusens were graded from the number of each type, confluence and predominant type. Focal hyperpigmentation, atrophy and exudative features were recorded
AMD changes: early (drusen >63 μm), late (exudative features)</td><td>Age- and sex-specific and overall % frequencies for any AMD features:
<table><tr><th>Age (years)</th><th>Both sexes</th><th>Male</th><th>Female</th><th>Overall frequency (%)</th></tr><tr><td>40–49</td><td>1073 (15.8%)</td><td>482 (16%)</td><td>591 (15.6%)</td><td>24.3</td></tr><tr><td>50–59</td><td>821 (24%)</td><td>339 (26.6%)</td><td>482 (22.2%)</td><td></td></tr><tr><td>60–69</td><td>541 (34.6%)</td><td>215 (35.8%)</td><td>326 (33.7%)</td><td>95% CI</td></tr><tr><td>70–79</td><td>192 (41.7%)</td><td>86 (44.2%)</td><td>106 (39.7%)</td><td>23.6 to 25.0</td></tr><tr><td>80+</td><td>16 (50%)</td><td>8 (50%)</td><td>8 (50%)</td><td></td></tr></table>
Age- and sex-adjusted prevalences and overall frequencies for early, late and any AMD features:
<table><tr><th>AMD</th><th>Age- and sex-adjusted prevalence (%) (95% CI)</th><th>Overall frequency (%) (95% CI)</th></tr><tr><td>Early</td><td>26.3 (24.4 to 28.2)</td><td>23.5 (22.8 to 24.2)</td></tr><tr><td>Late</td><td>0.6 (0.3 to 0.8)</td><td>0.6 (0.5 to 0.6)</td></tr><tr><td>Any</td><td>28.7 (26.4 to 30.9)</td><td>24.3 (23.6 to 25)</td></tr></table></td><td>The results are based on black BES participants with gradable photographs in both eyes
The frequency estimates for ARM changes may be less reliable in the older age groups as photograph gradability deteriorated as age increased</td></tr>
</table>

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments
Weih *et al.* (2000)[97]	Prospective Random selection from population-based study 5147	Random, cluster-stratified sample 40+ years	VA assessed using logMAR chart at 4 m. AMD were graded clinically and by photograph graders according to international classification schemes[1]	Cause-specific prevalence of vision less than driving vision: Age group (years) / Prevalence of AMD as cause of vision less than driving (estimate no. of Australians) 40–49: 0 (0) 50–59: 0 (0) 60–69: 0 (0) 70–79: 0.82 (8300) 80–89: 5.36 (23400) ⩾90: 16.56 (10200) Visual impairment classification by VA: Cause / No. of cases of visual impairment / No. (%) Classified by VA loss criteria / No. (%) Classified by visual field loss All causes: 364 / 333 (91) / 24 (9) 87 (100) / 0 (0)	Figure 2 in the article provides table of severity of AMD: mild, moderate, severe and profound in different age groups
Reidy *et al.* (1998)[98]	Prospective Cross-sectional survey North London, England 1547	65+ years and registered with one of the 17 GP groups defined	VA assessed with person's own spectacles and logMAR scale 4 VA groupings: 6/6+ (normal vision), 6/6–6/12 (adequate for driving), <6/12 (bilateral visual impairment), <6/60 (blindness). AMD: VA < 6/12	Population prevalence of eye disorders (for disorders other than AMD, see Table 1 in the article): Eye disorder / No. of cases in sample / Estimated population prevalence (95% CI) / Estimated no. of cases in population of 13,371 (95% CI) AMD: 133 / 8% (5.8 to 10.8) / 1108 (776 to 1440)	Also available breakdown by social class/deprivation score and cases of AMD

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments
Mitchell (1993)[99]	Prospective and retrospective examination of medical records Western Metropolitan Health Region of New South Wales, Australia 3283 (1478 male, 1805 female) participants	Stratified by age, sex and local government area GP practices randomly chosen. 50+ years who attended these practices	Patient history, record review and non invasive diagnosis??	Frequencies, % prevalence for persons with AMD (bilateral cases): Age (years) — Prevalence of AMD: total persons 50–64: 132 (9.6%) 65–74: 176 (14.8%) 75–84: 91 (18.8%) 85+: 29 (25.7%) Total: 428 (13%)	It is difficult to assess what is going on in this study. Unclear what methods other than ophthalmic records to diagnose AMD
Munier *et al.* (1998)[100]	Prospective Irish Republic 5002	100% representative of those legally registered as blind in Ireland at the time of study. 0.2% of total Irish population More than half of the patients were 65+ years and over, one-third were over 80 years	Legal registration of blindness VA of 6/60 (0.1) or worse (WHO definition of severe visual impairment)	% of those registered as blind caused by macular degeneration: Age (years) — Macular degeneration as cause of blindness 16–34: 2.3% of 732 patients 35–54: 3.1% of 1007 patients 55–64: 4.5% of 457 patients 65–79: 19.7% of 1350 patients 80+: 32.2% of 1486 patients Total: 16.2% of 5002 patients	Question: when does it become age-related?

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments
Foran *et al.* (2002)[101]	Prospective Blue Mountains, west of Sydney, Australia 2335	All non-institutionalised, permanent residents 50+ years Females 57.5%, mean age 64.5 years Follow-up 5 years BMES2	LogMAR, Beaver Dam classification and WHO ICD-10	Prevalence of ARM as the primary cause of incident unilateral visual impairment: Primary cause (non-correctable) <20/40 <20/70 <20/200 ARM 26 (19.4%) 27 (32.1%) 24 (54.5%) Age-specific primary attributable cause of incident unilateral visual impairment worse than 20/40: Primary cause: best correction / Age 49–59 years / Age 60–69 years / Age 70–79 years / Age 80+ years / All aged 49+ years ARM: 1 (8.3%) / 7 (15.2%) / 15 (23.8%) / 3 (23.1%) / 26 (19.4%) Total causes: 12 / 46 / 63 / 13 / 134 Primary causes of incident unilateral visual impairment worse than 20/40 and subsets: Primary cause: best correction / <20/40–20/70 / <20/70–20/200 / <20/200 / Total ARM: 11 (13.6%) / 4 (12.5%) / 11 (52.4%) / 26 (19.4%) Total causes: 81 / 32 / 21 / 134	Details about the sample population are published elsewhere

continued

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<tr><td>Huang et al. (2003)[102]</td><td>Prospective population-based longitudinal
5- and 10-year follow-up
Beaver Dam, Wisconsin, USA
4926</td><td>September 1987–May 1988, private census to identify residents of Beaver Dam
43–84 years old</td><td>Similar procedures were used at baseline and follow-up examinations
Reported elsewhere ?WARMGS
30° colour fundus photographs of both eyes: preliminary and detailed grading (drusen size, type and severity)
Definitions: soft drusen, early and late ARM</td><td>Age–cohort model for birth cohort effect on ARM, BDES 1988–2000:
<table><tr><th></th><th colspan="2">Early ARM in either eye</th><th colspan="2">Late ARM in either eye</th></tr><tr><th></th><th>Birth cohort effect</th><th>Age effect</th><th>Birth cohort effect</th><th>Age effect</th></tr><tr><td></td><td>8</td><td>10</td><td>7</td><td>8</td></tr><tr><td>Likelihood ratio statistic</td><td>22.25</td><td>41.85</td><td>3.72</td><td>45.89</td></tr><tr><td>p-Value</td><td>0.005</td><td><0.0001</td><td>0.81</td><td><0.0001</td></tr></table>Heagerty and Zeger's model for birth cohort effect on ARM, BDES 1998–2000:
<table><tr><th></th><th colspan="2">Late ARM in either eye</th></tr><tr><th></th><th>Birth cohort effect</th><th>Age effect</th></tr><tr><td>OR</td><td>1.23</td><td>1.79</td></tr><tr><td>95% CI</td><td>1.06 to 1.43</td><td>1.58 to 2.03</td></tr></table>Prevalence of ARM in either eye (%):
<table><tr><th></th><th>Early ARM</th><th>Late ARM</th></tr><tr><td>Baseline examination</td><td>20.4</td><td>1.74</td></tr><tr><td>5-year follow-up</td><td>24.7</td><td>2.11</td></tr><tr><td>10-year follow-up</td><td>22.8</td><td>2.78</td></tr></table></td><td>At 10-year follow-up (1998–2000) 2962 participated in examination. 59.8% of participants in initial examination
Figure 2 in the article shows the relation of age to log odds of ARM for different birth cohorts in the Beaver Dam Eye study</td></tr>
</table>

continued

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Exclusions</th><th>Results</th><th>Comments</th></tr>
<tr><td>Evans and Wormald (1996)[81]</td><td>Census records review
Data abstracted for the years 1950, 1960, 1970, 1980 and the standard year 1990
UK
13,950 records examined in 1990</td><td>Registered as blind in England
Causes of registered blindness: AMD, cataract, glaucoma and optic atrophy
Data taken from the Office of Population Censuses and Surveys
Age up to and including 85+ years</td><td>Sorsby pre-1980
Post-1980 ICD-9. Macular lesions description in 1970s corresponds to AMD</td><td>Proportion of annual new registrations for blindness in England and Wales attributed to AMD in England:
<table><tr><th>Year</th><th>% AMD</th></tr><tr><td>1933–43</td><td>6</td></tr><tr><td>1948–50</td><td>14</td></tr><tr><td>1951–4</td><td>20</td></tr><tr><td>1955–60</td><td>25</td></tr><tr><td>1970</td><td>24</td></tr><tr><td>1980–1</td><td>38</td></tr><tr><td>1990–1</td><td>49</td></tr></table>
Observed registrations for AMD and all registrations 1950–90 for males and females:
<table><tr><th></th><th colspan="2">1950</th><th colspan="2">1960</th><th colspan="2">1970</th><th colspan="2">1980</th><th colspan="2">1990</th></tr><tr><th></th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr><tr><td>Observed</td><td>549</td><td>780</td><td>1083</td><td>1824</td><td>1149</td><td>1464</td><td>1110</td><td>2283</td><td>2142</td><td>4438</td></tr><tr><td>All registrations
$p < 0.001$</td><td>4603</td><td>6541</td><td>4338</td><td>7343</td><td>4018</td><td>7184</td><td>4175</td><td>7466</td><td>5085</td><td>8481</td></tr></table>
Observed registrations for AMD 1950–90 for males and females: adjusting for the percentage of registrations analysed:
<table><tr><th colspan="2">1950</th><th colspan="2">1960</th><th colspan="2">1970</th><th colspan="2">1980</th><th colspan="2">1990</th></tr><tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr><tr><td>722</td><td>1026</td><td>1117</td><td>1880</td><td>1167</td><td>1487</td><td>1332</td><td>2739</td><td>2142</td><td>4438</td></tr></table></td><td></td></tr>
</table>

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Ethnicity</th><th>Diagnostic test
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Exclusions</th><th>Results</th><th>Comments</th></tr>
<tr><td>Gibson, et al. (1985)[103]</td><td>Prospective
Random
Melton Mowbray, Leics
1329</td><td>75+ years on 31 December 1980 on the GP register: follow-up still living in area 1982
147 male, 337 female. Mean age: 81.7 years</td><td>Ophthalmological examinations (optician and ophthalmologist). Criteria Framingham study</td><td>Prevalence of senile macular degeneration by age and sex:
<table><tr><th rowspan="2">Age group (years)</th><th colspan="2">Men</th><th colspan="2">Women</th><th colspan="2">Both sexes</th></tr><tr><th>No. examined</th><th>Positive in one or both eyes (prevalence, %)</th><th>No. examined</th><th>Positive in one or both eyes (prevalence, %)</th><th>No. examined</th><th>Positive in one or both eyes (prevalence, %)</th></tr><tr><td><85</td><td>132</td><td>54 (40.9%)</td><td>260</td><td>98 (37.7%)</td><td>392</td><td>152 (38.8%)</td></tr><tr><td>85+</td><td>15</td><td>6 (40%)</td><td>77</td><td>43 (55.8%)</td><td>92</td><td>49 (53.3%)</td></tr><tr><td>Total of all ages</td><td></td><td>–</td><td></td><td></td><td>484</td><td>201 (41.5%)</td></tr></table></td><td>677 persons available for examination, 484 were actually seen
2 methods were used to calculate prevalence rates, to allow for any discrepancies between the attenders and non-attenders</td></tr>
<tr><td>Cruickshanks, et al. (1997)[104]</td><td>Data from 2 population-based studies
SLVDS ($n = 1541$) and Beaver Dam ($n = 3999$)</td><td>Mean age: BDES 58.7, SLV (NHW) 54, SLV Hispanics 53.2 years</td><td>Colour stereoscopic fundus photographs. Graded using WARMGS
Both studies used similar methods. The same graders were used in both studies</td><td>Prevalence of any ARM by geographic location, ethnicity, age and gender: San Luis valley (Colorado) compared with Beaver Dam Eye Study (Wisconsin)
<table><tr><th rowspan="2">Age (years)</th><th colspan="3">San Luis Valley (non-Hispanic whites)</th><th colspan="3">San Luis Valley (Hispanics)</th><th colspan="3">Beaver Dam (non-Hispanic whites)</th></tr><tr><th>Male</th><th>Female</th><th>Both</th><th>Male</th><th>Female</th><th>Both</th><th>Male</th><th>Female</th><th>Both</th></tr><tr><td></td><td>67 (3.5%)</td><td>92 (8.5%)</td><td>159 (6%)</td><td>71 (10.6%)</td><td>88 (2.8%)</td><td>159 (6.7%)</td><td>0</td><td>0</td><td>0</td></tr><tr><td>43–59</td><td>187 (7.9%)</td><td>193 (6.5%)</td><td>380 (7.2%)</td><td>149 (12.1%)</td><td>183 (7.8%)</td><td>332 (9.8%)</td><td>982 (12.2%)</td><td>1115 (8.6%)</td><td>2097 (10.3%)</td></tr><tr><td>60–74</td><td>135 (14.9%)</td><td>136 (14.4%)</td><td>271 (14.6%)</td><td>104 (15.8%)</td><td>135 (23.9%)</td><td>239 (20.4%)</td><td>843 (19.9%)</td><td>1055 (20.3%)</td><td>1898 (20.1%)</td></tr><tr><td></td><td colspan="3">Age-, gender-adjusted prevalence (%): 10.4</td><td colspan="3">14.3</td><td colspan="3">14.5</td></tr></table></td><td>Low rate of AMD in Hispanics – ?due to low age limit (74) and may not survive to develop AMD</td></tr>
</table>

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments
VanNewkirk *et al.* (2000)[105]	Cluster stratified random sampling Victoria, Australia 5147	Mean age 60.2 years. 55% female, 45% male. Urban and rural population including NH residents	WARMGS was followed with minor modifications AMD was graded as wet or dry	Weighted prevalence (95% CI) of AMD lesions in either eye based on photographic grading:	For details on early ARM, see Table 5 in article [weighted prevalence (95% CI) of early ARM in either eye]. For comparison of the ARM prevalence with other population-based studies, see Table 7 in article

Age (years)	Neovascular ARM (wet)		Atrophic AMD (dry)		AMD	
	Male	Female	Male	Female	Male	Female
	0	0	0	0	0	0
50–59	0	0	0	0	0	0
60–69	0.35 (0 to 0.79)	0.20 (0 to 0.58)	0.23 (0 to 0.68)	0	0.58 (0.02 to 1.1)	0.20 (0 to 0.58)
70–79	1.7 (0.37 to 2.9)	0.86 (0 to 1.8)	0.27 (0 to 0.79)	0.70 (0 to 1.6)	1.9 (0.65 to 3.2)	1.6 (0.41 to 2.7)
80–89	1.6 (0 to 4.5)	4.7 (0.54 to 8.8)	0	3.8 (0.56 to 7.1)	2.0 (0 to 5.6)	7.0 (1.6 to 12.4)
90+	8.6 (0 to 27.8)	0	50 (0 to 111)	20.0 (0 to 45.1)	58.6 (0 to 120.1)	20.0 (0 to 45.1)
Age-standardised rate	0.41 (0.16 to 0.67)	0.38 (0.02 to 0.73)	0.17 (0 to 0.39)	0.35 (0 to 0.70)	0.58 (0.29 to 0.88)	0.76 (0.17 to 1.35)
Age-standardised rate (both sexes)	0.39 (0.20 to 0.58)		0.27 (0.04 to 0.50)		0.68 (0.30 to 1.1)	

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments
Mitchell *et al.* (2002)[23]	Population-based cohort study Blue Mountains Australia 2335 available at follow-up	Mean age 64.5 years 57.5% females	Baseline and 5-years follow-up retinal photographs graded by WARMGS Any participants (from either examination) with ARM lesions were re-graded using a modification side-by-side method developed for the Beaver Dam Eye Study	Incidence of early- and late-stage ARM by age and gender in the Blue Mountains Eye Study cohort (n = 2335): Age (years) — No. at risk (incidence, %) Late ARM: Males / Females / Both sexes Early ARM: Males / Females / Both sexes Under the age in the next row: 314 (0) / 407 (0) / 721 (0) / 310 (3.6) / 407 (3) / 717 (3.2) 60–69: 415 (0.2) / 525 (0.8) / 940 (0.6) / 402 (6.5) / 505 (8.1) / 907 (7.4) 70–79: 213 (2.4) / 328 (2.4) / 541 (2.4) / 193 (17.1) / 293 (19.1) / 486 (18.3) 80+: 43 (0) / 68 (8.8) / 111 (5.4) / 37 (10.8) / 51 (17.7) / 88 (14.8) Total: 985 (0.7) / 1328 (1.4) / 2313 (1.1) / 942 (7.9) / 1256 (9.4) / 2198 (8.7) p-Value: 0.02 / 0.001 / 0.001 / 0.001 / 0.001 / 0.001	The methods are described elsewhere The incidence of late ARM defined by appearance at follow-up of neovascular ARM or GA in persons in whom no late ARM was present at baseline Early ARM at follow-up indistinct soft or reticular drusen not detected at baseline
Foran *et al.* (2003)[106]	6-year cross-sectional study Blue Mountains, Australia 3508 at follow-up Including newly eligible due to age	Full details reported elsewhere (BMES2a + b): 57% female, 61.7% married and mean age 66.7 years	LogMAR VA was measured Blindness, <6/60; VA, <6/12 Subjective refraction performed according to the Beaver Dam Eye Study	Frequency of ARM as cause of bilateral and unilateral blindness and visual impairment: Cross-section 1 (BMES 1): Unilateral / Bilateral Cross-section 2 (BMES 2a + b): Unilateral / Bilateral Under the age in the next row: 46 (34.8%) / 13 (76.5%) / 34 (31.8%) / 5 (50%) Total cases of blindness: 132 (100%) / 17 (100%) / 107 (100%) / 10 (100%) ARM as cause of visual impairment: 95 (20.7%) / 48 (36.9%) / 85 (20.9%) / 32 (33.7%) Total cases of visual impairment: 459 (100%) / 130 (100%) / 406 (100%) / 95 (100%)	BMES2a, 75.1% of surviving eligible residents participated; BMES2b, a further 85.2% of newly eligible participants (moved to the area or now over 50 years old) ?Source of bias

continued

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<tr><td>Buch et al. (2001)[107]</td><td>Prospective cross-sectional study
Copenhagen, Denmark
946</td><td>Age- and gender-stratified subjects. 125 men and 125 women randomly selected from each age group (60–64, 65–69, 70–74, 75–80 years)
Mean age of participants was 69.8 years (SD ± 5.7)
481 women, 463 male participants
The mean age of subjects with visual impairment (US definition) was 74.7 years</td><td>Visual impairment defined by the WHO (20/60–20/400) and the most common criteria in the USA (worse than 20/40 but better than 20/200). Amsler chart, slit-lamp examination, direct ophthalmoscopy and biomicroscopy (Goldmanns 3 lenses) and colour fundus photographs</td><td>Prevalence of visual impairment in better eye caused by AMD according the WHO and US criteria:
<table><tr><th>Age (years)</th><th>No. of patients</th><th colspan="2">AMD WHO criteria (20/60–20/400)</th><th colspan="2">AMD US criteria (20/40–20/200)</th></tr><tr><th></th><th></th><th>No. (%)</th><th>95% CI</th><th>No. (%)</th><th>95% CI</th></tr><tr><td>Under the age in the next row</td><td></td><td>0</td><td>0.0 to 1.6</td><td>0</td><td>0.0 to 1.6</td></tr><tr><td>65–69</td><td>244</td><td>0</td><td>0.0 to 1.5</td><td>1 (0.41)</td><td>0.0 to 2.3</td></tr><tr><td>70–74</td><td>228</td><td>2 (0.8)</td><td>0.1 to 3.1</td><td>3 (1.3)</td><td>0.3 to 3.8</td></tr><tr><td>75–80</td><td>249</td><td>6 (2.4)</td><td>0.9 to 5.1</td><td>5 (2)</td><td>0.7 to 4.6</td></tr><tr><td>All</td><td>944</td><td>8 (0.85)</td><td>0.3 to 1.7</td><td>9 (0.9)</td><td>0.4 to 1.8</td></tr><tr><td>Age-adjusted %</td><td></td><td>0.69</td><td>0.2 to 1.2</td><td>0.82</td><td>0.3 to 1.4</td></tr></table>Distribution of AMD as cause of visual impairment (WHO criteria) by age and sex
<table><tr><th>Age (years)</th><th>Men</th><th>Women</th><th>Both sexes</th></tr><tr><td>60–69</td><td>0</td><td>0</td><td>0</td></tr><tr><td>70–80</td><td>4 (40%)</td><td>4 (50%)</td><td>8 (44.4%)</td></tr><tr><td>60–80</td><td>4 (40%)</td><td>4 (50%)</td><td>8 (44.4%)</td></tr></table></td><td>Comparison between US and WHO definitions</td></tr>
</table>

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<tr><td>Wang et al. (2000)[108]</td><td>Prospective
2 years
Blue Mountains, Sydney, Australia
3654</td><td>Reported elsewhere</td><td>WARMGS. Any visual impairment defined as 6/12 or worse. Moderate visual impairment 6/24–6/60 (the definition used in the Beaver Dam Eye Study) and severe 6/60 or worse (Australian definition of blindness)</td><td>ARM as cause of mild and moderate to severe bilateral and unilateral visual impairment:
<table><tr><th rowspan="2">Age (years)</th><th colspan="2">Bilateral visual impairment</th><th colspan="2">Unilateral visual impairment</th></tr><tr><th>Mild impairment (total n = 122)</th><th>Moderate–severe impairment (total n = 45)</th><th>Mild impairment (total n = 287)</th><th>Moderate–severe impairment (total n = 238)</th></tr><tr><td>Under the age in the next row</td><td>1 (20%)</td><td>0</td><td>0</td><td>2 (13%)</td></tr><tr><td>60–69</td><td>0</td><td>1 (25%)</td><td>5 (8.9%)</td><td>3 (5.8%)</td></tr><tr><td>70–79</td><td>7 (17%)</td><td>8 (80%)</td><td>14 (11%)</td><td>19 (28%)</td></tr><tr><td>80+</td><td>13 (20%)</td><td>18 (60%)</td><td>16 (18%)</td><td>38 (37%)</td></tr></table></td><td>BMES participants had a slightly higher socio-economic status, with a higher proportion gaining post-school qualifications and a slightly greater proportion owning their own homes, than non-participants</td></tr>
<tr><td>Mitchell et al. (1995)[109]</td><td>Reported elsewhere</td><td>Reported elsewhere</td><td>As above</td><td>Prevalence of ARM (wet or dry) by age and sex in the BMES, Australia, 1992–3:
<table><tr><th rowspan="2">Age (years)</th><th colspan="2">Female</th><th colspan="2">Male</th><th colspan="2">Total</th></tr><tr><th>%</th><th>No. at risk</th><th>%</th><th>No. at risk</th><th>%</th><th>No. at risk</th></tr><tr><td>Under the age in the next row</td><td>0</td><td>270</td><td>0</td><td>215</td><td>0</td><td>485</td></tr><tr><td>55–64</td><td>0.3</td><td>659</td><td>0</td><td>513</td><td>0.2</td><td>1172</td></tr><tr><td>65–74</td><td>0.9</td><td>682</td><td>0.6</td><td>527</td><td>0.7</td><td>1209</td></tr><tr><td>75–84</td><td>6.1</td><td>374</td><td>4.3</td><td>279</td><td>5.4</td><td>653</td></tr><tr><td>85+</td><td>21.8</td><td>87</td><td>12.5</td><td>48</td><td>18.5</td><td>135</td></tr><tr><td>Total</td><td>2.4</td><td>2072</td><td>1.3</td><td>1582</td><td>1.9</td><td>3654</td></tr></table></td><td>The study looked specifically at increase in risk with age. The table includes late and early AMD from other eye studies. Also prevalence of drusen in worst eye</td></tr>
</table>

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments
Javitt *et al.* (2003)[110]	Prospective Population-based cohort USA 1,041,009	5-years Medicare beneficiaries' data (1994–8) used to develop longitudinal cohort study. 3-year incidence measured Age 65+ years	Wet AMD ascertained using diagnosis and procedure codes contained in the claims files (laser, levels 1, 2 and 3) Analysed the surgical and laser procedure claims submitted by the ophthalmologists 3-year incidence of AMD defined as the proportion of beneficiaries who met one of the criteria	Three-year estimated incidence of exudative AMD in the Medicare population:	This study suffers from the obvious sources of bias and confounding in the sample collection. It is most likely to identify patients with the most advanced AMD Table 4 in the article provides further information for criterion levels 1–3 (CPT codes required for ARM ascertainment)

Age	Laser: no. with Wet ARM (incidence, %)		
	Men	Females	Both sexes
Under the age in the next row	159 (0.12) 95% CI: 0.1 to 0.13	222 (0.12) 95% CI: 0.10 to 0.14	381 (0.12) 95% CI: 0.11 to 0.13
70–74	237 (0.21) 95% CI: 0.19, 0.24	402 (0.25) 95% CI: 0.22 to 0.27	639 (0.23) 95% CI: 0.21 to 0.25
75–79	244 (0.35) 95% CI: 0.30 to 0.39	423 (0.35) 95% CI: 0.31 to 0.38	667 (0.35) 95% CI: 0.32 to 0.37
80–84	130 (0.39) 95% CI: 0.32 to 0.46	263 (0.33) 95% CI: 0.29 to 0.37	393 (0.35) 95% CI: 0.31 to 0.38
85+	43 (0.30) 95% CI: 0.21 to 0.39	137 (0.27) 95% CI: 0.22 to 0.31	180 (0.28) 95% CI: 0.23 to 0.32
Total	813 (0.22) 95% CI: 0.21 to 0.24	1447 (0.24) 95% CI: 0.23 to 0.25	2260 (0.23) 95% CI: 0.22 to 0.24

continued

<table>
<tr><th>Study</th><th>Study design
Duration of study
Location
Total number</th><th>Subjects
Age range (years)
AMD
Gender
Ethnicity</th><th>Diagnostic test
Confirmation of disease
Exclusions</th><th>Results</th><th>Comments</th></tr>
<tr><td>Klein et al. (2002)[111]</td><td>Prospective
Population-based cohort
10-year incidence Beaver Dam, Wisconsin
5924 eligible, 4926 at baseline examinations (83%). Of the survivors, 81.1% participated in 5-year follow-up and of these survivors 82.9% in 10-year follow-up</td><td>43–84 years</td><td>WARMGS used to grade stereoscopic colour fundus photographs</td><td>Relation of age and gender, by participant, to the 10-year incidence of early and late ARM in the Beaver Dam Eye Study:
<table><tr><th rowspan="2">Age (years)</th><th colspan="3">Incidence of early ARM (%)</th><th colspan="3">Incidence of late ARM (%)</th></tr><tr><th>Men</th><th>Women</th><th>Both sexes</th><th>Men</th><th>Women</th><th>Both sexes</th></tr><tr><td>43–54</td><td>4.7</td><td>3.7</td><td>4.1</td><td>0</td><td>0.1</td><td>0.1</td></tr><tr><td>55–64</td><td>10.6</td><td>10.7</td><td>10.7</td><td>1.5</td><td>0.6</td><td>1</td></tr><tr><td>65–74</td><td>21.7</td><td>24.8</td><td>23.6</td><td>4.6</td><td>4.3</td><td>4.4</td></tr><tr><td>75+</td><td>28.7</td><td>40.8</td><td>36.7</td><td>5.8</td><td>11.3</td><td>9.5</td></tr><tr><td>Total</td><td>10.9</td><td>13</td><td>12.1</td><td>1.7</td><td>2.4</td><td>2.1</td></tr></table>Relation of age and gender, by right eye, to the 10-year incidence of early and late ARM in the Beaver Dam Eye Study:
<table><tr><th rowspan="2">Age (years)</th><th colspan="3">Incidence of early ARM (%)</th><th colspan="3">Incidence of late ARM (%)</th></tr><tr><th>Men</th><th>Women</th><th>Both sexes</th><th>Men</th><th>Women</th><th>Both sexes</th></tr><tr><td>43–54</td><td>3</td><td>2.5</td><td>2.7</td><td>0</td><td>0</td><td>0.0</td></tr><tr><td>55–64</td><td>6.7</td><td>6.6</td><td>6.7</td><td>1.1</td><td>0.6</td><td>0.8</td></tr><tr><td>65–74</td><td>17.6</td><td>19.7</td><td>18.9</td><td>4.2</td><td>2.5</td><td>3.2</td></tr><tr><td>75+</td><td>17</td><td>34.5</td><td>28.9</td><td>1</td><td>9.1</td><td>6.6</td></tr><tr><td>Total</td><td>7.8</td><td>9.8</td><td>8.9</td><td>1.3</td><td>1.6</td><td>1.4</td></tr></table></td><td>82.9% of survivors in 10-years follow-up. 2764 final participants: 56% of all original participants
Table 2 in the article: both wet and dry numbers and drusen. Also Table 3, progression regression and disappearance of drusen</td></tr>
</table>

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments
Rahmani *et al.* (1996)[112]	Sample of 16 cluster areas East Baltimore 5300	A sample of 16 cluster areas was selected using a stratified sampling scheme designed to obtained approximately equal numbers of black and white residents 2911 blacks, 2389 whites	Visual impairment defined as BCVA worse than 20/40 but better than 20/200 (different from international criterion but the same as the criteria used by most states to restrict eligibility for driver licensing)	Distribution of ARM as cause of visual impairment by age and race:	

Age (years)	Visual impairment caused by AMD			All causes of visual impairment		
	Whites	Blacks	Total	Whites	Blacks	Total
Under the age in the next row	2 (9.1)	0 (0)	2 (2.9)	22 (100)	48 (100)	70 (100)
⩾65	33 (24.6)	10 (8.9)	43 (17.5)	134 (100)	112 (100)	246 (100)
Total	35 (22.4)	10 (6.3)	45 (14.2)	156 (100)	160 (100)	316 (100)

Values are no. (%) of eyes affected

Prevalence of visual impairment caused by AMD by age and race:

Age (years)	Whites		Blacks	
	No. of subjects	AMD	No. of subjects	AMD
Under the age in the next row	542	0 (0)	631	0 (0)
50–59	618	1 (1.6)	699	0 (0)
60–69	915	1 (1.1)	613	1 (1.6)
70–79	630	7 (11.1)	346	6 (17.3)
⩾80	206	11 (53.4)	100	1 (10)
Total	2911	20 (6.9)	2389	8 (3.3)

Values are no. (prevalence per 1000). Specified cause was present in one or both eyes

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments
Bressler *et al.* (1995)[7]	Follow-up study 483 Watermen on eastern shore of Maryland	30+ years. Men	Fundus photographs Eyes in which AMD appeared or disappeared were graded in a side-by-side fashion. The standardised grading of the fundus photographs has been described elsewhere	Appearance or disappearance of AMD-3: Age range in 1985 (years) / Participants with no AMD-3 in 1985: Total no. / No. (%) with AMD-3 in 1990 / Participants with AMD-3 in 1985: Total no. / No. (%) lost AMD-3 in 1990 Under the age in the next row: 126 / 9 (7) / 9 / 2 (22) 40–49: 83 / 3 (4) / 9 / 5 (56) 50–59: 95 / 7 (7) / 6 / 1 (17) 60–69: 78 / 11 (14) / 22 / 7 (32) 70+: 31 / 8 (26) / 15 / 2 (13) Total: 413 / 38 (9) / 61 / 17 (28) AMD level 3: eyes with large or confluent drusen, focal hyperpigmentation of the RPE or non-GA of the RPE within 1500 μm of the foveal centre	Only 483 (70%) showed the appearance or disappearance of AMD. Limitation: study composed of only men and biased towards a certain occupation (watermen). Also, almost half of the population were under 50 years of age
Farber (2003)[113]	Prospective Consecutive From the registry for the blind Israel 41,402	48.6% of the registered blind were male and 51.4% female. 84.3% of blind were aged over 40 years and 21.7% over 80 years	Registered as blind: identified as blind by an ophthalmologist – VA is ⩽0.05 (20/400), slightly less rigid than WHO definition (<0.05)	Number of persons (%) diagnosed as blind from 1987 to 1999 by age and AMD as cause of blindness: prevalence data: Age (years) / AMD cause of blindness / Total blind 0–4: 0 / 217 (1.2%) 5–24: 0 / 1258 (6.8%) 25–54: 122 (4.7%) / 3876 (21%) 55–74: 797 (30.8%) / 7200 (39%) 75+: 1665 (64.4%) / 5914 (32%) Total: 2584 (14%) / 18465 (100%)	

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments
				Number of persons (%) newly diagnosed as blind in 1999 by age and AMD as cause of blindness: incidence data: Age (years) / AMD cause of blindness / Total blind 0–4: 0 / 44 (1.8%) 5–24: 0 / 183 (7.3%) 25–54: 0 / 410 (16.3%) 55–74: 99 (19.7%) / 888 (35.4%) 75+: 404 (80.3%) / 983 (39.2%) Total: 503 (20.1%) / 2508 (100%) Blindness incidence rates, by AMD diagnosis, per 100,000 population, 1999: Age (years) / AMD as cause of blindness 25–54: – 55–74: 12.9 75+: 162.7 Total population: 8.2	
Chang *et al.* (1999)[6]	Prospective Vancouver, Canada 20,000	Canadian of Chinese ancestry	Reviewed the fluorescein angiograms Interpreted by retinal specialist and re-evaluated for primary diagnosis	AMD diagnosis for patients of Chinese and European ancestry who underwent fluorescein angiography December 1987–September 1990: Diagnosis / Ancestry: no. (%) of patients / Chinese (n = 417) / European (n = 417) AMD: 61 (14.6%) / 127 (30.4%), $p < 0.001$ Type of AMD among patients of Chinese and European ancestry who underwent fluorescein angiography December 1987–November 1993: Type of AMD / Ancestry: No (%) of patients / Chinese (n = 149) / European (n = 149) Wet[a]: 110 (73.8%) / 94 (63.1%) Active choroidal[b]: 39 (29.2%) / 55 (36.9%) [a] JF, EF and SF, CNVM, submacular haemorrhage and disciform scar [b] JF, EF and SF, CNVM only	Also table by age Methodology is vague with regard to participation rates and exclusion criteria (except for ethnicity)

continued

<table>
<tr><th>Study</th><th>Study design
Duration of study
Location
Total number</th><th>Subjects
Age range (years)
AMD
Gender
Ethnicity</th><th>Diagnostic test
Confirmation of disease
Exclusions</th><th>Results</th><th>Comments</th></tr>
<tr><td>Owen et al. (2003)[4]</td><td>Systematic review followed by a request for data used to establish a pooled prevalence for AMD
6 studies provided data:
Beaver Dam Eye Study
Blue Mountains Eye Study
Copenhagen City Eye Study
North London Eye Study
Rotterdam study
Melbourne Visual Impairment Project</td><td>Pooled data from 6 studies.
Excluded: studies including volunteers or specific professions due to possible selection biases
Age groups: <50, 50–90 (in 5-year bands), and 90+ years</td><td>Systematic review was conducted using published papers, abstracts, letters and review articles from the usual sources. 673 references yielded from search, 27 identified as having potential relevance; 19 studies were chosen (based on geographically defined, random sample populations, published from 1990 onwards) and the authors written to asking to provide data</td><td>Meta-analysis of GAMD, NVAMD and PS (caused by AMD) (see the last column): combined percentage prevalence for ages 65–79 years (95% CI):
<table><tr><th>Condition</th><th>Male</th><th>Female</th><th>Both sexes</th></tr><tr><td>GAMD (5 studies)</td><td>0.60 (0.35 to 0.85)</td><td>0.45 (0.26 to 0.64)</td><td>0.53 (0.37 to 0.68)</td></tr><tr><td>NVAMD (5 studies)</td><td>0.81 (0.52 to 1.11)</td><td>1.03 (0.49 to 1.58)</td><td>1.05 (0.57 to 1.52)</td></tr><tr><td>AMD caused by PS (6 studies)</td><td>0.15 (0.03 to 0.27)</td><td>0.21 (0.09 to 0.33)</td><td>0.35 (0.14 to 0.57)</td></tr></table>Prevalence figures applied to UK population predictions to give the expected number (in thousands) of AMD caused by PS, PS/B, B and VI (95% CI), stratified by age, for 2001 and 2011
<table><tr><th rowspan="2">Age range (years)</th><th colspan="2">No. of PS</th><th colspan="2">No. of PS/B</th><th colspan="2">No. of B</th><th colspan="2">No. of VI</th></tr><tr><th>2001</th><th>2011</th><th>2001</th><th>2011</th><th>2001</th><th>2011</th><th>2001</th><th>2011</th></tr><tr><td><55</td><td>0 (0 to 8)</td><td>0 (0 to 9)</td><td>0 (0 to 8)</td><td>0 (0 to 9)</td><td>0 (0 to 8)</td><td>0 (0 to 9)</td><td>0 (0 to 8)</td><td>0 (0 to 9)</td></tr><tr><td>55–59</td><td>0 (0 to 4)</td><td>0 (0 to 5)</td><td>0 (0 to 4)</td><td>0 (0 to 5)</td><td>1 (0 to 6)</td><td>1 (0 to 7)</td><td>1 (0 to 6)</td><td>1 (0 to 7)</td></tr><tr><td>60–64</td><td>0 (0 to 3)</td><td>0 (0 to 4)</td><td>0 (0 to 3)</td><td>0 (0 to 4)</td><td>0 (0 to 3)</td><td>0 (0 to 4)</td><td>0 (0 to 3)</td><td>0 (0 to 4)</td></tr><tr><td>65–69</td><td>3 (1 to 8)</td><td>4 (1 to 9)</td><td>0 (0 to 3)</td><td>0 (0 to 3)</td><td>0 (0 to 3)</td><td>0 (0 to 3)</td><td>3 (1 to 8)</td><td>4 (1 to 9)</td></tr><tr><td>70–74</td><td>5 (2 to 10)</td><td>5 (2 to 11)</td><td>1 (0 to 5)</td><td>1 (0 to 5)</td><td>1 (0 to 5)</td><td>1 (0 to 5)</td><td>8 (4 to 14)</td><td>8 (4 to 14)</td></tr><tr><td>75–79</td><td>19 (12 to 28)</td><td>19 (12 to 27)</td><td>5 (2 to 10)</td><td>5 (2 to 10)</td><td>7 (3 to 13)</td><td>7 (3 to 13)</td><td>30 (21 to 41)</td><td>30 (21 to 41)</td></tr></table></td><td>UK definitions: blindness, Snellen VA <3/60; partial sight, 6/60–3/60. For further details see article. Two definitions of AMD: NVAMD (neovascular/wet AMD) and GAMD (geographical/dry AMD)</td></tr>
</table>

continued

Study	Study design Duration of study Location Total number	Subjects Age range (years) AMD Gender Ethnicity	Diagnostic test Confirmation of disease Exclusions	Results	Comments

Age range (years)	No. of PS		No. of PS/B		No. of B		No. of VI	
	2001	2011	2001	2011	2001	2011	2001	2011
80–84	25 (16 to 36)	27 (18 to 39)	11 (6 to 19)	12 (6 to 21)	11 (6 to 19)	12 (6 to 21)	47 (35 to 61)	51 (38 to 67)
85–89	29 (18 to 44)	33 (21 to 50)	7 (2 to 15)	8 (2 to 17)	25 (15 to 39)	29 (17 to 44)	61 (45 to 80)	69 (51 to 91)
90+	28 (15 to 46)	33 (18 to 54)	11 (3 to 24)	13 (4 to 29)	26 (13 to 44)	30 (16 to 51)	64 (44 to 88)	75 (52 to 104)
Total	109 (65 to 187)	121 (72 to 208)	34 (13 to 92)	38 (15 to 103)	71 (38 to 140)	80 (43 to 157)	214 (151 to 310)	239 (168 to 346)

PS, partial sighted caused by AMD; PS/B, partial/blind; B, blind; VI, visual impairment. See Table 4 in journal article for definitions and further details on prevalence of GAMD and NVAMD
Only one of the six studies took place in the UK, so the validity of these predictions is questionable

BC, best corrected; BDES, best corrected eye sight; BES, best corrected sight; CNVM, choroidal neovascular membrane; CPT, Current Procedural Terminology; FPC, Family Practitioner Committee; NH, nursing home; NHW, Non-Hispanic White; SD, standard deviation; SE, standard error; SLV, San Luis Valley; SLVDS, San Luis Valley Diabetes Study; WARMGS, Wisconsin Age-Related Maculopathy Grading System; WHO, World Health Organization.

Appendix 3

Expert elicitation questionnaire

Expert survey to inform the evaluation of a screening programme for AMD

We are building a mathematical model to estimate the cost-effectiveness of a screening programme for AMD. To ensure that the defined screening programme is appropriate, and to overcome some limitations in the data available to populate the model, we are keen to incorporate the views of experts in the field.

The following survey is being distributed to six consultant ophthalmologists and will greatly assist our evaluation. It can either be completed over the telephone with a member of the research team (Carolyn Murray), and is expected to require 30 minutes of your time, or if you prefer we are happy to correspond via email or via the Royal Mail. Your contribution will be acknowledged in subsequent publications, which will include an NHS Health Technology Assessment monograph.

Screening

The following paragraphs lay out a possible screening process. Each paragraph is followed by questions regarding the appropriateness of the defined process.

1. A screening test for AMD is defined as providing the general population aged over 50 years with an annual reminder to self-test for AMD by covering one eye, and then the other eye. If they notice an abnormality (visual distortion) in either eye, they are instructed to present at an opticians.

   Q1.1 How would you describe 'an abnormality' in the context of the population-based screening test, i.e. how would you describe an abnormality in the reminder letter?

   Q1.2 We are assuming that the Amsler grid is an INAPPROPRIATE screening tool for the general population? Do you agree, and are there any other approaches that could be used?

Q1.3 Using the 'eye cover' test described above, or any other form of self-test, what proportion of people with the following types of AMD do you think would notice 'an abnormality' when self-testing?

AMD type	Proportion noticing visual distortion after self-completing a cover test	Proportion noticing visual distortion after self-completing another specified test (if any)
No AMD		
Drusen		
Dry AMD		
Extrafoveal CNV		
Juxtafoveal CNV		
Subfoveal CNV		

2. In the proposed screening programme, persons who notice an abnormality are instructed to present at an opticians. Opticians are instructed to examine the back of the eye of presenting patients, and if a macular haemorrhage is detected (indicating suspected CNV), the optician is instructed to refer the patient on to an ophthalmologist.

Q2.1 Is macular haemorrhage an appropriate indicator of CNV? If not, what other indicators could be used by opticians to identify suspected CNV?

Q2.2 What proportion of people with the following types of AMD do you think would be referred on to a consultant ophthalmologist on the basis of opticians detecting macular haemorrhage (or any specified alternative indicators)?

AMD type	Proportion referred to consultant ophthalmologist by opticians	
	Macular haemorrhage	Other indicator of CNV
No AMD		
Drusen		
Dry AMD		
Extrafoveal CNV		
Juxtafoveal CNV		
Subfoveal CNV		

Q2.2 As consultant ophthalmologists working for the NHS, do you only want to see patients with suspected CNV?

If not referred to a consultant ophthalmologist, how should patients with dry AMD (and no CNV) be treated? Should they be referred to an LVU or monitored by an optician? Should they be advised about diet and lifestyle changes, possible preventative interventions, and told to monitor their eyesight and present again at the opticians upon deterioration of eyesight?

Q2.3 Is a similar process to that for dry AMD recommended for patients presenting with drusen, but no AMD?

Treatment interventions

1. Treatment for CNV

We are describing VA scores over time by patient sub-group based on the patient's age and type of lesion at diagnosis (size – under or over 4 MPS DA; type – occult, minimally classic, or predominantly classic; location – extra-, juxta-, or subfoveal).

We have re-analysed the patient-level data from the TAP and VIP trials to estimate VA profiles for all subfoveal lesions.

Q1.1 What other interventions should we consider for subfoveal lesions?

We have identified studies reporting the use of laser photocoagulation, and PDT, in juxtafoveal lesions, with the PDT study (Frennesson[114]) stating that PDT is more effective than laser photocoagulation.

Q1.2 What treatment options should we consider for juxtafoveal lesions? Do treatment options differ by lesion size and type?

The only identified treatment for extrafoveal lesions is laser photocoagulation.

Q1.3 Would you treat all extrafoveal lesions with laser photocoagulation? If not, how would you treat extrafoveal AMD?

2. Treatment for dry AMD and drusen (ARM)

We want to model progression from dry AMD and ARM to CNV, as well as to describe VA scores over time for patients with dry AMD.

Q2.1 Are you aware of any data sources describing VA in patients with dry AMD who do not develop CNV? If not, could you estimate an average VA for patients presenting with dry AMD?

Q2.2 How quickly does VA deteriorate in patients with dry AMD who do not develop CNV, for example, what is the average VA loss over a year?

Q2.3 Are there any feasible treatments for dry AMD and ARM? For example, are IRIS Medical® OcuLight® Infrared Laser Photocoagulator, or the Rheopheresis® blood filtration procedure, likely to be treatment options now or in the future?

Q2.4 Are you hopeful that any interventions aimed at preventing progression to CNV will become available? If so, how effective do you think they might be, i.e. what is your estimate of the proportion of cases of CNV they could prevent?

Could the same level of effectiveness be applied to eyes with no AMD and those with early ARM, and to eyes whose fellow eyes have CNV and those whose fellow eyes have no CNV?

Many thanks for your time and opinions.

Appendix 4

Survey of ophthalmologists

ScHARR/PDT Users Group modelling of cost-effectiveness of AMD

Of 100 patients receiving their FIRST diagnosis of AMD or ARM, please estimate in your opinion how many are in each of the following categories:	
Unilateral ARM	/100
Unilateral dry AMD	/100
Unilateral extrafoveal AMD	/100
Unilateral juxtafoveal AMD	/100
Unilateral subfoveal AMD	/100
Bilateral ARM	/100
Bilateral ARM/AMD, worst eye has dry AMD	/100
Bilateral ARM/AMD, worst eye has extrafoveal AMD	/100
Bilateral ARM/AMD, worst eye has juxtafoveal AMD	/100
Bilateral ARM/AMD, worst eye has subfoveal AMD	/100
Of 100 patients that you diagnose in the following categories, how many do you refer on to a PDT clinic:	
Unilateral juxtafoveal AMD	/100
Unilateral subfoveal AMD	/100
Bilateral ARM/AMD, worst eye has juxtafoveal AMD	/100
Bilateral ARM/AMD, worst eye has subfoveal AMD	/100

Appendix 5

National Screening Committee's criteria for appraising the viability, effectiveness and appropriateness of a screening programme

The criteria, which are set out below, are based on the classic criteria first promulgated in a WHO report in 1966, but take into account both the more rigorous standards of evidence required to improve effectiveness and the greater concern about the adverse effects of healthcare; regrettably, some people who undergo screening will suffer adverse effects without receiving benefit from the programme.

These criteria have been prepared taking into account international work on the appraisal of screening programmes, particularly that in Canada and the USA. It is recognised that not all of the criteria and questions raised in the format will be applicable to every proposed programme, but the more that are answered will obviously assist the NSC to make better evidence-based decisions.

All of the following criteria should be met before screening for a condition is initiated.

The condition

1. The condition should be an important health problem.
   YES.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, or disease marker and a latent period or early symptomatic stage.
   THE NATURAL HISTORY IS POORLY QUANTIFIED, FIRST EYE DISEASE MAY BE DEFINED AS A LATENT PERIOD IN SOME INDIVIDUALS.

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
   THERE ARE ONGOING TRIALS OF VITAMIN SUPPLEMENTS, ALTHOUGH THERE IS NO CONCLUSIVE EVIDENCE ON THEIR EFFECTIVENESS AT PRESENT.

The test

4. There should be a simple, safe, precise and validated screening test.
   IT IS SIMPLE AND SAFE, BUT NOT PROVEN TO BE PRECISE AND VALIDATED.

5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
   NOT KNOWN.

6. The test should be acceptable to the population.
   NOT KNOWN, BUT PROBABLE.

7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
   THE DIAGNOSTIC PROCESS IS AGREED.

The treatment

8. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
   THERE IS SOME EVIDENCE OF EARLY TREATMENT BEING BETTER, ALTHOUGH A RANGE OF NEW INTERVENTIONS MAY HAVE DIFFERENT PROFILES. LONG-TERM TREATMENT EFFECTIVENESS DATA ARE MISSING.

9. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
   CURRENTLY UNDER DEBATE BY NICE.

10. Clinical management of the condition and patient outcomes should be optimised by all healthcare providers prior to participation in a screening programme.
    NOT APPLICABLE.

The screening programme

11. There must be evidence from high-quality RCTs that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
    NOT AVAILABLE.

12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.
    NOT AVAILABLE.

13. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
    NOT AVAILABLE.

14. The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).
    COST-EFFECTIVENESS NOT RELIABLY ESTABLISHED (I.E. HIGH UNCERTAINTY).

15. There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
    NOT APPLICABLE AT PRESENT.

16. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available prior to the commencement of the screening programme.
    NOT APPLICABLE AT PRESENT.

17. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.
    TREATMENT OPTIONS CURRENTLY IN A STATE OF FLUX.

18. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.
    NOT APPLICABLE AT PRESENT.

19. Public pressure for widening the eligibility criteria, for reducing the screening interval and for increasing the sensitivity of the testing process should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.
    NOT APPLICABLE AT PRESENT.

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