National Institute for Health and Care Excellence

Final

Age-related macular degeneration

Age-related macular degeneration: diagnosis and management

NICE Guideline NG82

Methods, evidence and recommendations

January 2018

Final

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Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Context

Age-related macular degeneration (AMD) is the most common form of macular degeneration and is the term given to ageing changes in the eye without any other obvious cause. These changes occur in the central area of the retina (macula). It is a painless eye condition that generally leads to the gradual impairment of vision, but can sometimes cause a rapid reduction in vision. AMD may be an incidental finding on a routine visit to the optometrist or people may present with difficulty in performing daily activities such as driving, reading and recognising faces.

Traditionally, AMD has been classified as early, intermediate or late according to the stage of disease progression. Late AMD can be further classified as either 'wet' AMD (neovascular) or 'dry' AMD (advanced geographic atrophy). Geographic atrophy may occur at the intermediate stage but is not considered to be late AMD until atrophic changes affect the fovea (an area in the retina where the centre of the field of vision is focused). Consequences of this condition can be severe: the Royal National Institute of Blind People (RNIB) reports that AMD is a leading cause of certification for vision impairment. In 1 Australian cohort study of people with early stage AMD the risk of progression to intermediate or advanced AMD within 5 years was 17%. However early AMD is not always significantly progressive as 83% did not progress within 5 years, and AMD lesions appeared to have improved and regressed in 8% of people.

Neovascular AMD can rapidly lead to severe loss of central vision but can be treated if people at risk are identified early; in people with untreated neovascular AMD, over half will become visually impaired or blind within 3 years. In American studies, more than 50% of patients treated for neovascular AMD failed to maintain near normal vision in their first affected eye after 2 years of treatment. People who developed neovascular AMD in their second affected eye maintained near normal vision in that eye over 90% of the time. The better outcome of the second affected eye is widely believed to be due to the increased monitoring that occurs during treatment of the first affected eye.

Geographic atrophy is the more common type of AMD. It usually develops slowly and causes a gradual change in the central vision. Geographic atrophy usually takes a number of years to reach its final stage and there is currently no proven treatment. Three lines of visual acuity are lost in 1 in 3 people within 2 years of diagnosis, and in 1 in 2 people within 4 years, with considerable variation between people in the rate at which visual loss happens.

Currently, the exact cause of AMD is not known but factors such as age, family origin (prevalence is higher in people of white and Chinese family origin), diet and nutrition, genetics, and smoking are thought to affect the risk of developing the disease. Socioeconomic factors also may result in later presentation and poorer outcomes. A qualitative study found that cost was seen as a significant barrier to accessing sight tests.

The prevalence of late AMD in the UK amongst those aged 50 years or more is 2.4% (from a meta-analysis applied to UK 2007−2009 population data). This increases to 4.8% in people aged 65 years or more, and 12.2% in people aged 80 years or more. The same study found the prevalence of geographic atrophy to be 1.3−6.7%, and the prevalence of neovascular AMD to be 1.2−6.3% (Owen et al., 2012). Estimates indicate that around 39,800 people develop neovascular AMD in the UK each year (Owen et al 2012); given a total UK population of 60 million, this equates to 663 new cases per million per year.

There has been a significant increase in hospital activity, including treatment and monitoring, in England for people with a primary diagnosis of AMD, from less than 10,000 visits in the years 2005−2006 to over 75,000 visits in the years 2013−2014 (Hospital Episode Statistics). The most common primary procedure in hospital visits of people with a primary diagnosis of macular degeneration involves intravitreal injection. The cost of aflibercept and ranibizumab,

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medicines for the treatment of late AMD (wet active), is significant. In 2015−16, ranibizumab was second and aflibercept was fourth in the list of medicines with positive NICE technology appraisals on which the NHS spent most money, between them accounting for a total of around £450 million expended (although some of these costs relate to use for other licensed indications) (NHS Digital, 2016).

This guideline provides advice on the management of people with AMD, including pharmacological and non-pharmacological treatments. It also provides guidance on tools available to diagnose and monitor AMD, and what information and support should be provided for people with AMD.

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1 Guideline Committee membership and ICG technical team

1.1 Guideline Committee membership and ICG technical team

1.1.1 Guideline Development Group

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2 Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Committee is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

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3 Methods

This guideline was developed in accordance with the process set out in 'Developing NICE guidelines: the manual (2014)'. There is more information about how NICE clinical guidelines are developed on the NICE website. A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' is available. In instances where the guidelines manual does not provide advice, additional methods are used as described below, organised by study type.

3.1 Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For continuous outcomes, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately. Methods for synthesising dichotomous outcome data are described in the individual sections for different types of review question below.

3.2 Evidence of effectiveness of interventions

3.2.1 Quality assessment

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines' (2014). Where RCTs were available, these are initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. The risk of bias of included RCTs was assessed using the Cochrane risk of bias tool (Higgins et al 2011). If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated a low quality and the quality of the evidence for each outcome was downgraded or not from this point. Risk of bias for cohort studies was assessed using the Critical Appraisal Skills Programme (CASP) cohort study checklist.

3.2.2 Methods for combining intervention evidence

Meta-analysis of interventional data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Dichotomous outcomes were pooled on the relative risk scale (using the Mantel–Haenszel method).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence, once pre-specified subgroup analyses had been undertaken to explore heterogeneity. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met (defined as $I^2 \geq 50\%$, and thus the presence of significant heterogeneity), random-effects results are presented.

Meta-analyses were performed in Cochrane Review Manager v5.3.

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3.2.3 Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline, which were considered along with any other published MIDs found during the clinical searches for the guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. MIDs found through this process and used to assess imprecision in the guideline are given in Table 1. No other MIDs for continuous outcomes were specified by the guideline committee other than those listed below, as the committee agreed it was not possible to set meaningful values for these outcomes without any reliable evidence.

Table 1: Identified MIDs

Outcome	Range	MID	Source
ETDRS letters (logMAR)	0 to 100 (1.7 to −0.3)	5 (0.1)	Amoaku WM, Chakravarthy U, Gale R, et al (2015) Defining response to anti-VEGF therapies in neovascular AMD. Eye, 29(6), 721-31
NEI-VFQ-25 total score	0 to 100	2.3	Gillespie BW, Musch DC, Niziol LM, et al (2014). Estimating minimally important differences for two vision-specific quality of fife measures. Investigative Ophthalmology & Visual Science, 55(7), 4206-12
POMS total score	0 to 200	5.6	Schwartz AL, Meek PM, Nail LM, et al (2002). Measurement of fatigue: determining minimally important clinical differences. Journal of Clinical Epidemiology, 55(3), 239-44
SF-36	0 to 100	5.0	Busija L, Pausenberger E, Haines T, et al (2011). Adult measures of general health and health-related quality of life. Medical outcomes study short form 36 item and short form 12-item. Arthritis Care & Research 63 (s11): s383-412.

LogMAR = logarithm of the maximum angle of resolution; NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire (25 items); POMS = Profile of Mood States; SF-36 = Short Form (36 items)

For applicable dichotomous outcome measures, the GRADE default MID interval for relative risks of 0.8 to 1.25 was used. This range refers to a 25% decrease or increase in the relative risk of an outcome.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

3.2.4 GRADE for pairwise meta-analyses of interventional evidence

The quality of the evidence for each outcome was downgraded where appropriate for the reasons outlined in Table 2.

Table 2: Rationale for downgrading evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	The quality of the evidence was downgraded if there were concerns about factors including the design or execution of the study, including concealment of allocation, blinding and loss to follow up. This was based on intervention checklists in the NICE guidelines manual (2012).

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GRADE criteria	Reasons for downgrading quality
Inconsistency	The quality of the evidence was downgraded if there were concerns about inconsistency of effects across studies: occurring when there is variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using visual inspection and the statistic, I^2 where; $I^2 < 50\%$ was categorised as no inconsistency, $I^2 \geq 50\%$ was categorised as serious inconsistency, and $I^2 \geq 50\%$ plus obvious additional heterogeneity on visual inspection categorised as very serious inconsistency.
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention, comparator and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	If MIDs (one corresponding to meaningful benefit; one corresponding to meaningful harm) were defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one MID, and twice if it crosses both MIDs. If an MID was not defined for the outcomes, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant).

3.2.5 Evidence statements

Evidence statements for pairwise intervention data are classified in to 1 of 4 categories:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence could not demonstrate a meaningful difference.
- Situations where the data are consistent, at a 95% confidence level, with an effect in either direction (i.e. one that is not 'statistically significant') but the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates no difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

3.3 Methods for combining direct and indirect evidence (network meta-analysis) for interventions

Network meta-analysis (NMA) was undertaken for 1 review in this guideline (chapter 10.1). The following provides an overview of the general principles adopted. Detailed methods are provided in Appendix G.

Conventional pairwise meta-analysis involves the statistical combination of direct evidence about pairs of interventions that originate from 2 or more separate studies (for example, where there are two or more studies comparing A vs B).

In situations where there are more than 2 interventions, pairwise meta-analysis of the direct evidence alone is of limited use. This is because multiple pairwise comparisons need to be performed to analyse each pair of interventions in the evidence, and these results can be difficult to interpret. Furthermore, direct evidence about interventions of interest may not be available. For example studies may compare A vs B and B vs C, but there may be no direct evidence comparing A vs C. NMA overcomes these problems by combining all evidence into a single, internally consistent model, synthesising data from direct and indirect comparisons,

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and providing estimates of relative effectiveness for all comparators and the ranking of different interventions.

3.3.1 Synthesis

Hierarchical Bayesian NMA was performed using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS code provided in the appendices of TSD 2 was used without substantive alteration to specify synthesis models.

Results were reported summarising 10,000 samples from the posterior distribution of each model, having first run and discarded 50,000 'burn-in' iterations. Three separate chains with different initial values were used.

Non-informative prior distributions were used in all models. Unless otherwise specified, trial-specific baselines and treatment effects were assigned N(0,1000) priors, and the between-trial standard deviations used in random-effects models were given U(0,5) priors (for dichotomous syntheses on a log-odds scale; see the recommendations in TSD 2). For syntheses on a continuous scale, priors for between-trial standard deviations were all uniform, and covered a range that could be considered uninformative for the measure in question; for instance, when synthesising visual acuity (ETDRS letters), U(0,50) priors were used.

3.3.2 Applying GRADE to network meta-analysis

A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses undertaken. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when modifying the GRADE framework to a network meta-analysis.

3.3.2.1 Unit of analysis for GRADE ratings and summary results

As there are up to 25 comparators in the NMAs undertaken for this guideline, it is not feasible to provide GRADE ratings for every possible pairwise comparison in each NMA, as recommended by some authorities (Puhan et al., 2014). This would produce multiple tables with up to 300 rows, from which it would be impossible to infer meaningful findings. On the other hand, it would be too reductive to summarise results as a single entity, with only 1 GRADE row per NMA. Therefore, results were assessed and presented at a 'meta-comparison' level, reflecting the following comparisons of interest:

- Antiangiogenic agent:
  - Photodynamic therapy compared with placebo
  - Anti-VEGF agents compared with placebo
  - Anti-VEGF agents compared with each other
  - Anti-VEGF agents compared with photodynamic therapy
- Anti-VEGF frequency:
  - PRN compared with routine injection
  - PRN with and without loading phase
  - Different frequencies of routine treatment
  - Treat-and-extend compared with routine injection
  - PRN-and-extend compared with PRN

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In this way, each NMA could provide information on up to 9 overarching comparisons. Because the NMA estimates all relevant comparisons simultaneously, outputs for each characteristic of interest are effectively adjusted for all others – for example, the intra-class comparison between anti-VEGF agents is adjusted for any differences in the regimens used while, at the same time, the comparison between PRN and routine administration is adjusted for any differences between the agents used in the trials providing the evidence.

3.3.2.2 Modified GRADE ratings for NMAs

3.3.2.2.1 Risk of bias

In addition to the usual criteria to assess the risk of bias or 'limitations' of studies for each pairwise analysis within a network, the risk of bias was assessed for each direct comparison and assessed to see how it would affect the indirect comparisons. In addition, there was an assessment of treatment effect modifiers to see if they differed between links in the network.

For NMAs with a large proportion of studies that were judged to be susceptible to bias, some downgrading decision rules were applied. If 50% or more RCTs in the direct comparison of interest and/or 50% or more RCTs in the whole network were inadequate or unclear for a particular parameter of quality, the outcome was downgraded by 1 level. If 50% of RCTs in the comparison or network were subject to a very serious risk of bias, the outcome was downgraded by 2 levels.

3.3.2.2.2 Inconsistency

Inconsistency was assessed for the heterogeneity of individual comparisons in the network, and also between direct and indirect comparisons where both were available (that is, where there were ‘loops’ in the network).

Heterogeneity across studies for each direct pairwise meta-analysis was assessed using I^2. This allowed for the assessment of heterogeneity within the included studies using the following decision rules:

- If there was considerable unexplained heterogeneity for 1 link or more in a network, the outcome was downgraded 1 level.
- If there was more than 1 link in the network with considerable, substantial or moderate unexplained heterogeneity, consideration was given to downgrading 2 levels.

To assess for consistency in each pairwise comparison where both direct and indirect evidence are available, the values of the direct and indirect estimates were compared to see if they were similar. ‘Inconsistency’ models were fitted to the data, and the residual deviance of each datapoint plotted against the analogous value from the NMA (see NICE DSU TSD4). These plots were visually inspected to identify signs of inconsistency between direct and indirect evidence – that is, conspicuous deviations from the x=y line. Where any unexplained inconsistency was noted, the comparison to which the anomaly related was downgraded for inconsistency. In the case of identified inconsistency that affected more than 1 comparison (due to multiple anomalous datapoints and/or because anomalous datapoint(s) were found in loops of evidence that were influential within the broader network), all comparisons from that NMA were downgraded for inconsistency. The overall values of tau was also assessed to assess heterogeneity across the network.

3.3.2.2.3 Indirectness

As with pairwise meta-analyses, studies included in a network were assessed for how well they fit the PICO (population, intervention, comparator, outcome) specified in the review protocol. If 50% or more RCTs in the direct comparison of interest and/or 50% or more RCTs in the whole network were judged to be subject to indirectness, the outcome was downgraded by 1 level.

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3.3.2.2.4 Imprecision

Imprecision was assessed with respect to the synthesised point-estimate for the meta-comparison in question, using the usual criteria (see Table 2).

3.4 Diagnostic accuracy evidence

In this guideline, diagnostic accuracy data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The 'raw' 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline are as follows:

- **Sensitivity** is the probability that the feature will be positive in a person with the condition.
  - sensitivity = TP/(TP+FN)
- **Specificity** is the probability that the feature will be negative in a person without the condition.
  - specificity = TN/(FP+TN)
- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared with people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.
  - LR^+ = (TP/[TP+FN])/(FP/[FP+TN])
- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared with people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.
  - LR^- = (FN/[TP+FN])/(TN/[FP+TN])

The following schema, adapted from the suggestions of Jaeschke et al. (1994), was used to interpret the likelihood ratio findings from diagnostic accuracy reviews.

Table 3: Interpretation of likelihood ratios

Value of likelihood ratio	Interpretation
LR ≤ 0.1	Very large decrease in probability of disease
0.1 < LR ≤ 0.2	Large decrease in probability of disease
0.2 < LR ≤ 0.5	Moderate decrease in probability of disease
0.5 < LR ≤ 1.0	Slight decrease in probability of disease
1.0 < LR < 2.0	Slight increase in probability of disease
2.0 ≤ LR < 5.0	Moderate increase in probability of disease
5.0 ≤ LR < 10.0	Large increase in probability of disease
LR ≥ 10.0	Very large increase in probability of disease

The schema above has the effect of setting a minimal important difference for positive likelihoods ratio at 2, and a corresponding minimal important difference for negative likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling between these thresholds were judged to indicate no meaningful change in the probability of disease.

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3.4.1 Inter-rater agreement

The reliability of agreement for diagnostic data between observers was evaluated using the kappa coefficient. The measure calculates the level of agreement in classification. The general rule of thumb to follow is: if there is no agreement among the classification, then kappa ≤0; if there is complete agreement then kappa=1 (Fleiss 1971). The following schema (see table 4), adapted from the suggestions of Fleiss, was used to interpret the level of agreement in diagnostic classification. It was not felt appropriate to meta-analyse studies due to the level of between-study heterogeneity, and therefore ranges of kappa coefficients are reported.

Table 4: Interpretation of kappa coefficient

Value of kappa coefficients	Interpretation
$\kappa < 0$	No agreement
$0 < \kappa \leq 0.20$	Poor agreement
$0.2 < \kappa \leq 0.4$	Fair agreement
$0.4 < \kappa \leq 0.7$	Good agreement
$0.7 < \kappa < 1.0$	Excellent agreement
$\kappa = 1.0$	Complete agreement

3.4.2 Modified GRADE for inter-rater agreement evidence

GRADE has not been developed for use with inter-rater agreement; therefore a modified approach was applied using the GRADE framework. Data from all study types was initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point.

Table 5: Rationale for downgrading evidence for inter-rater agreement

GRADE criteria	Reasons for downgrading quality
Risk of bias	Assessed according to the QUADAS2 bias tool for diagnostic cross-sectional studies, which was modified to remove non-applicable questions
Inconsistency	N/A (no pooling considered appropriate)
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, index feature or reference standard in the included studies and how directly these variables could address the specific review question. Studies were automatically downgraded if they had a reference standard of published criteria, as this was recognised by the GC as inferior to their preferred standard of expert clinician diagnosis.
Imprecision	Studies were downgraded if they presented unadjusted agreement rates, rather than accounting for levels of agreement expected by chance.

3.4.3 Methods for combining diagnostic accuracy evidence

Meta-analysis of diagnostic test accuracy data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Macaskill et al. 2010).

Where applicable, diagnostic syntheses were stratified by:

- Presenting symptomatology (features shared by all participants in the study, but not all people who could be considered for a diagnosis in clinical practice).
- The reference standard used for true diagnosis.

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Where 5 or more studies were available for all included strata, a bivariate model was fitted using the `mada` package in R v3.3.1, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data were not available (2–4 studies), separate independent pooling, treating the data as simple proportions, was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel. This approach is likely to somewhat underestimate test accuracy (see Macaskill et al., 2010).

Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Macaskill et al. 2010).

3.4.4 Modified GRADE for diagnostic evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework. GRADE assessments were only undertaken for positive and negative likelihood ratios, as the MIDs defined by the committee to assess imprecision were based on these outcomes, but results for sensitivity and specificity are also presented alongside those data.

Cross-sectional and cohort studies were initially rated as high-quality evidence if well conducted, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 6.

Table 6: Rationale for downgrading evidence for diagnostic accuracy questions

GRADE criteria	Reasons for downgrading quality
Risk of bias	This includes limitations in the design or execution of the study. Assessment was based on the QUADAS 2 checklist; studies were downgraded if there was evidence of bias in at least 2 domains or of serious bias in 1. Particular attention was paid to non-consecutive recruitment of participants and blinding of reference standard (in retrospective studies where the final diagnosis was known). Datasets with more than 1 study were downgraded for risk of bias if one-third or more of the weight in the meta-analysis came from studies that had been judged to have serious risk of bias (that is, datasets were downgraded if they did not have at least twice as much evidence from studies at low risk of bias as from studies with high risk of bias).
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 50%, the outcome was not downgraded. Serious: If the I^2 was greater than or equal to 50%, the outcome was downgraded one level. This approach is somewhat less conservative than that used in intervention studies (see Table 1 and Table 2), for the reason that heterogeneity is an unavoidable feature of diagnostic syntheses. The Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy states that 'Heterogeneity is to be expected in meta-analyses of diagnostic test accuracy. A consequence of this is that meta-analyses of [diagnostic] accuracy studies tend to focus on computing average rather than common effects…. In [diagnostic] accuracy reviews large differences are commonly noted between studies, too big to be explained by chance, indicating that actual test accuracy varies between the included studies, or that there is heterogeneity in test accuracy' (Deeks et al. 2010). For these reasons, it was considered unnecessarily conservative to doubly downgrade analyses with I^2 values ≥67%, or downgrade analyses with

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GRADE criteria	Reasons for downgrading quality
	I^2 values of 33–50% at all. Therefore, no two level downgrades where made for inconsistency in diagnostic reviews.
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, index feature or reference standard in the included studies and how directly these variables could address the specific review question. Studies were automatically downgraded if they had a reference standard of published criteria, as this was recognised by the GC as inferior to their preferred standard of expert clinician diagnosis. Datasets with more than 1 study were downgraded for indirectness if one-third or more of the weight in the meta-analysis came from studies that had been judged to have serious indirectness (that is, datasets were downgraded if they did not have at least twice as much evidence from directly relevant studies as from studies with serious indirectness).
Imprecision	If the 95% confidence interval for a positive likelihood ratio spanned 2, the outcome was downgraded one level, as the data were deemed to be consistent with a meaningful increase in risk and no meaningful predictive value. Similarly, negative likelihood ratio confidence intervals that spanned 0.5 led to downgrading for serious imprecision. Any likelihood ratio confidence intervals that spanned both 0.5 and 2 were downgraded twice, as this was taken to indicate very serious imprecision.

3.5 Association studies

In this guideline, association studies are defined those reporting data showing an association of a predictor (either a single variable or a group of variables) and an outcome variable, where the data are not reported in terms of outcome classification (i.e. diagnostic/prognostic accuracy). Data were reported as hazard ratios (if measured over time) or odds ratios (if measured at a specific time-point). Data reported in terms of model fit or predictive accuracy were not assessed using this method.

3.5.1 Methods for combining association study evidence

Hazard ratios were pooled using the inverse-variance method, and odds ratios were pooled using the Mantel–Haenszel method. Adjusted ratios from multivariable models were only pooled if the same set of predictor and confounder variables were used across multiple studies.

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, (defined as $I^2 \geq 50\%$, and thus the presence of significant heterogeneity), random-effects results are presented.

Meta-analyses were performed in Cochrane Review Manager v5.3.

3.5.2 Minimal clinically important differences (MIDs)

For odds ratios, adjusted odds ratios and hazard ratios, an MID interval of 0.8 to 1.25 was specified by the committee.

3.5.3 Modified GRADE for association studies

GRADE has not been developed for use with association studies; therefore a modified approach was applied using the GRADE framework. Data from cohort studies was initially

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rated as high quality, and data from case-control studies as low quality, with the quality of the evidence for each outcome then downgraded or not from this initial point.

Table 7: Rationale for downgrading evidence for association studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Concerns about the design or execution of the study, including in how either the predictor or outcome variables were assessed, or loss to follow up during the study. These were identified using checklists in the NICE guidelines manual (2014).
Inconsistency	The quality of the evidence was downgraded if there were concerns about inconsistency of effects across studies: occurring when there is variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using the statistic, I^2 where ; $I^2 < 50\%$ was categorised as no inconsistency, and $I^2 \geq 50\%$ was categorised as serious inconsistency
Indirectness	Concerns about the population, intervention and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	If an MID was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If an MID was not defined for the outcomes, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant).

3.6 Non-comparative studies

Throughout the guideline, wherever possible, data were always presented from comparative studies, with non-comparative studies only considered when this was the only data available. All non-comparative study designs (case series, audit data, surveys etc.) were analysed using the same statistical methods, regardless of the underlying question they sought to address.

3.6.1 Methods for combining non-comparative evidence

Where data were possible to meta-analyse, fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met (defined as $I^2 \geq 50\%$, and thus the presence of significant heterogeneity), random-effects results are presented.

Meta-analyses were performed in Cochrane Review Manager v5.3.

3.6.2 Modified GRADE for non-comparative evidence

GRADE has not been developed for use with non-comparative studies; therefore a modified approach was applied using the GRADE framework. Data from all study types was initially rated as low quality, with the quality of the evidence for each outcome then downgraded or not from this initial point.

Table 8: Rationale for downgrading evidence for non-comparative evidence

GRADE criteria	Reasons for downgrading quality
Risk of bias	Concerns about the design or execution of the study, including participant recruitment, retention and outcome measurement. For case series, the Joanna Briggs Institute case series checklist was used.

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GRADE criteria	Reasons for downgrading quality
Inconsistency	The quality of the evidence was downgraded if there were concerns about inconsistency of effects across studies: occurring when there is variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using visual inspection and the statistic, I^2 where ; $I^2 < 50\%$ was categorised as no inconsistency, and $I^2 \geq 50\%$ was categorised as serious inconsistency. No thresholds were set for very serious inconsistency and therefore no non-comparative evidence was downgraded twice for inconsistency.
Indirectness	Concerns about the population, intervention and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	If the upper and lower limits of the 95% confidence interval were such that, if they represented the true result, the committee agreed they would imply qualitatively different conclusions, the outcome was downgraded 1 level. If the mean estimate, and the upper and lower limits of the 95% confidence interval, were such that, if they represented the true result, the committee agreed they would all imply qualitatively different conclusions, the outcome was downgraded 2 levels.

3.7 Qualitative evidence

3.7.1 Methods for combining qualitative evidence

Where multiple qualitative studies were identified for a single question, information from the studies was combined using a thematic synthesis. By examining the findings of each included study, descriptive themes were independently identified and coded. Once all of the included studies had been examined and coded, the resulting themes and sub-themes were evaluated to examine their relevance to the review question, the importance given to each theme, and the extent to which each theme recurred across the different studies. The qualitative synthesis then proceeded by using these 'descriptive themes' to develop 'analytical themes', which were interpreted by the reviewer in light of the overarching review questions.

3.7.2 CERQual for qualitative studies

CERQual was used to assess the confidence we have in each of the identified themes. Evidence from all qualitative study designs (interviews, focus groups etc.) was initially rated as high confidence and the confidence in the evidence for each theme was then downgraded from this initial point as detailed in Table 9 below.

Table 9: Rationale for downgrading evidence for qualitative questions

CERQual criteria	Reasons for downgrading confidence
Methodological limitations	The extent to which there are problems in the design or conduct of the primary studies that contributed evidence to a review finding. Where the primary studies underlying a review finding are shown to have important methodological limitations, we are less confident that the review finding reflects the phenomenon of interest.
Relevance	Relevance is the extent to which the body of evidence from the primary studies supporting a review finding is applicable to the context specified in the review question. This may relate to, for example, the perspective or population researched, the phenomenon of interest or the setting. Where the contexts of the primary studies underlying a review finding are substantively different to the context of the review question, we are less confident that the review finding reflects the phenomenon of interest.
Coherence	Coherence was addressed based on two factors:

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CERQual criteria	Reasons for downgrading confidence
	• Between study – does the theme consistently emerge from all relevant studies • Theoretical – does the theme provide a convincing theoretical explanation for the patterns found in the data The outcome was downgraded once if there were concerns about one of these elements of coherence, and twice if there were concerns about both elements.
Adequacy of data	The outcome was downgraded if there was insufficient data to develop an understanding of the phenomenon of interest, either due to insufficient studies, participants or observations.

3.8 Mixed-quantitative and qualitative evidence

Where a review question identified both relevant quantitative and qualitative evidence, these two types of evidence were analysed separately, using the relevant GRADE, modified GRADE or CERQual criteria defined above.

3.9 Systematic review

Where systematic reviews were identified for a review question, synthesised evidence were assessed regarding relevance and the use of explicit, reproducible criteria in the selection of primary studies in the review, using the AMSTAR checklist including: the design of systematic review, study selection, database search, inclusion/exclusion criterion, characteristics of included studies, quality assessment of included studies and data synthesis (Shea 2007). Where systematic reviews were judged to be of sufficiently high quality and directly applicable to the review question, outcome data and risk of bias assessments for individual primary studies were taken directly from the included review, rather than from the primary studies. Data from additional primary studies identified was then added in to the data from the review.

3.10 Measures of visual acuity used in this guideline

Multiple interchangeable ways of quantifying visual acuity are used by the investigators whose research is included in this guideline. Table 10 shows how these different scales link to one another.

Table 10: Measures of visual acuity used in this guideline

LogMAR	Snellen		ETDRS		Decimal
	Metres	Feet	Letters	Lines	
-0.3	6/3	20/10	100	20	2.00
-0.2	6/4	20/13	95	19	1.60
-0.1	6/5	20/16	90	18	1.20
0.0	6/6	20/20	85	17	1.00
0.1	6/8	20/25	80	16	0.75
0.2	6/9	20/32	75	15	0.67
0.3	6/12	20/40	70	14	0.50
0.4	6/15	20/50	65	13	0.40
0.5	6/18	20/63	60	12	0.33
0.6	6/24	20/80	55	11	0.25
0.7	6/30	20/100	50	10	0.20
0.8	6/38	20/125	45	9	0.16

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LogMAR	Snellen		ETDRS		Decimal
	Metres	Feet	Letters	Lines	
0.9	6/48	20/160	40	8	0.13
1.0	6/60	20/200	35	7	0.10
1.1	6/75	20/250	30	6	0.08
1.2	6/96	20/320	25	5	0.06
1.3	6/120	20/400	20	4	0.05
1.4	6/150	20/500	15	3	0.04
1.5	6/190	20/630	10	2	0.03
1.6	6/240	20/800	5	1	0.03
1.7	6/300	20/1000	0	0	0.02

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4 Summary of recommendations

4.1 Recommendations summary

1. Classify age-related macular degeneration (AMD) using the following terms:

AMD classification	Definition
Normal eyes	• No signs of age-related macular degeneration (AMD) • Small ('hard') drusen (less than 63 micrometres) only
Early AMD	• Low risk of progression: ○ medium drusen (63 micrometres or more and less than 125 micrometres), or ○ pigmentary abnormalities • Medium risk of progression: ○ large drusen (125 micrometres or more), or ○ reticular drusen, or ○ medium drusen with pigmentary abnormalities • High risk of progression: ○ large drusen (125 micrometres or more) with pigmentary abnormalities, or ○ reticular drusen with pigmentary abnormalities, or ○ vitelliform lesion without significant visual loss (best-corrected acuity better than 6/18), or ○ atrophy smaller than 175 micrometres and not involving the fovea
Late AMD (indeterminate)	• Retinal pigment epithelial (RPE) degeneration and dysfunction (presence of degenerative AMD changes with subretinal or intraretinal fluid in the absence of neovascularisation) • Serous pigment epithelial detachment (PED) without neovascularisation
Late AMD (wet active)	• Classic choroidal neovascularisation (CNV) • Occult (fibrovascular PED and serous PED with neovascularisation) • Mixed (predominantly or minimally classic CNV with occult CNV) • Retinal angiomatous proliferation (RAP) • Polypoidal choroidal vasculopathy (PCV)
Late AMD (dry)	• Geographic atrophy (in the absence of neovascular AMD) • Significant visual loss (6/18 or worse) associated with: ○ dense or confluent drusen, or ○ advanced pigmentary changes and/or atrophy, or ○ vitelliform lesion
Late AMD (wet inactive)	• Fibrous scar • Sub-foveal atrophy or fibrosis secondary to an RPE tear • Atrophy (absence or thinning of RPE and/or retina) • Cystic degeneration (persistent intraretinal fluid or tubulations unresponsive to treatment) *NB Eyes may still develop or have a recurrence of late AMD (wet active)*

2. Do not refer to late AMD (wet inactive) as 'dry AMD'.
3. If you suspect AMD, recognise that the following risk factors make it more likely that the person has AMD:
    - older age
    - presence of AMD in the other eye

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- family history of AMD
- smoking
- hypertension
- BMI of 30 kg/m^2 or higher
- diet low in omega 3 and 6, vitamins, carotenoid and minerals
- diet high in fat
- lack of exercise.

4. Do not offer thermal laser therapy (for example, argon, diode) for treating drusen in people with early AMD.
5. Offer fundus examination as part of the ocular examination to people presenting with changes in vision (including micropsia and metamorphopsia) or visual disturbances.
6. Early AMD
    6.1. Confirm a diagnosis of early AMD using slit-lamp biomicrosopic fundus examination alone.
7. Late AMD (dry)
    7.1. Confirm a diagnosis of late AMD (dry) using slit-lamp biomicrosopic fundus examination.
8. Late AMD (wet active)
    8.1. Offer optical coherence tomography (OCT) to people with suspected late AMD (wet active).
    8.2. Do not offer fundus fluorescein angiography (FFA) to people with suspected late AMD (wet active) if clinical examination and OCT exclude neovascularisation.
    8.3. Offer FFA to people with suspected late AMD (wet active) to confirm the diagnosis if OCT does not exclude neovascular disease.
9. Make an urgent referral for people with suspected late AMD (wet active) to a macula service, whether or not they report any visual impairment. The referral should normally be made within 1 working day but does not need emergency referral.
10. Do not refer people with asymptomatic early AMD to hospital eye services for further diagnostic tests.
11. Refer people with late AMD (dry) to hospital eye services only:
    - for certification of sight impairment **or**
    - if this is how people access low-vision services in the local pathway (see recommendation 18) **or**
    - if they develop new visual symptoms that may suggest late AMD (wet active) **or**
    - if it would enable them to participate in research into new treatments for late AMD (dry).
12. For eyes with confirmed late AMD (wet active) for which antiangiogenic treatment is recommended (see recommendations 21–30), offer treatment as soon as possible (within 14 days of referral to the macula service).

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13. Ensure intraocular injections are given by suitably trained healthcare professionals, for example:
    - medical specialists, such as ophthalmologists
    - nurse practitioners, optometrists and technicians with experience in giving intraocular injections.

    If the injection is delivered by someone who is not medically qualified, ensure that cover is in place to manage any ophthalmological or medical complications.
14. Commissioners and providers should agree a clear local pathway for people with AMD, which should cover:
    - referral from primary to secondary care, with direct referral preferred
    - discharge from secondary to primary care, covering ongoing management and re-referral when necessary
15. Be aware that people with AMD are at an increased risk of depression. Identify and manage the depression according to the NICE guideline on depression in adults with a chronic physical health problem.
16. Be aware that many people with AMD have other significant comorbidities. For guidance on optimising care for adults with multiple long-term conditions, see the NICE guideline on multimorbidity.
17. Offer certification of visual impairment to all people with AMD as soon as they become eligible, even if they are still receiving active treatment.
18. Consider referring people with AMD causing visual impairment to low-vision services.
19. Consider a group-based rehabilitation programme in addition to a low-vision service to promote independent living for people with AMD.
20. Consider eccentric viewing training for people with central vision loss in both eyes.
21. Offer intravitreal anti-vascular endothelial growth factor (VEGF) treatment[1] for late AMD (wet active) for eyes with visual acuity within the range specified in recommendation 26.
22. Be aware that no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments[2] have been seen in the trials considered by the guideline committee.
23. In eyes with visual acuity of 6/96 or worse, consider anti-VEGF treatment for late AMD (wet active) only if a benefit in the person's overall visual function is expected (for example, if the affected eye is the person's better-seeing eye).

[1] At the time of publication (January 2018), bevacizumab did not have a UK marketing authorisation for, and is considered by the Medicines and Healthcare products Regulatory Agency (MHRA) to be an unlicensed medication in, this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines, and the MHRA's guidance on the supply of unlicensed medicinal products (specials), for further information. The guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation but does not amount to an approval of or a recommendation for such use.

[2] Given the guideline committee's view that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab), comparable regimens will be more cost effective if the agent has lower net acquisition, administration and monitoring costs.

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24. Be aware that anti-VEGF treatment for eyes with late AMD (wet active) and visual acuity better than 6/12 is clinically effective and may be cost effective depending on the regimen used[3,4].
25. Do not offer photodynamic therapy alone for late AMD (wet active).
26. Ranibizumab, within its marketing authorisation, is recommended as an option for the treatment of wet age-related macular degeneration if:
    - all of the following circumstances apply in the eye to be treated:
    - the best-corrected visual acuity is between 6/12 and 6/96
    - there is no permanent structural damage to the central fovea
    - the lesion size is less than or equal to 12 disc areas in greatest linear dimension
    - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

    and

    - the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012). [This recommendation is from Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (NICE technology appraisal guidance 155).]
27. Pegaptanib is not recommended for the treatment of wet age-related macular degeneration. [This recommendation is from Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (NICE technology appraisal guidance 155).]
28. People who are currently receiving pegaptanib for any lesion type should have the option to continue therapy until they and their clinicians consider it appropriate to stop. [This recommendation is from Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (NICE technology appraisal guidance 155).]
29. Aflibercept solution for injection is recommended as an option for treating wet age‑related macular degeneration only if:
    - it is used in accordance with the recommendations for ranibizumab NICE technology appraisal guidance 155 (re‑issued in May 2012 [see recommendation 26]) and
    - the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme. [This recommendation is from Aflibercept solution for injection for treating wet age‑related macular degeneration (NICE technology appraisal guidance 294).]

[3] At the time of publication (January 2018), bevacizumab did not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines, and the MHRA's guidance on the supply of unlicensed medicinal products (specials), for further information. The guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation but does not amount to an approval of or a recommendation for such use.

[4] Given the guideline committee's view that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab), comparable regimens will be more cost effective if the agent has lower net acquisition, administration and monitoring costs.

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30. People currently receiving aflibercept solution for injection whose disease does not meet the criteria in recommendation 29 should be able to continue treatment until they and their clinician consider it appropriate to stop. [This recommendation is from Aflibercept solution for injection for treating wet age‑related macular degeneration (NICE technology appraisal guidance 294).]
31. Do not offer photodynamic therapy as an adjunct to anti-VEGF as first-line treatment for late AMD (wet active).
32. Only offer photodynamic therapy as an adjunct to anti-VEGF as second-line treatment for late AMD (wet active) in the context of a randomised controlled trial.
33. Do not offer intravitreal corticosteroids as an adjunct to anti-VEGF for late AMD (wet active).
34. Consider switching anti-VEGF treatment for people with late AMD (wet active) if there are practical reasons for doing so (for example, if a different medicine can be given in a regimen the person prefers), but be aware that clinical benefits are likely to be limited.
35. Consider observation without giving anti-VEGF treatment if the disease appears stable (in this event, see section 11 for recommendations on monitoring and self-monitoring).
36. Consider stopping anti-VEGF treatment if the eye develops severe, progressive loss of visual acuity despite treatment as recommended in 13 and 21 to 30.
37. Stop anti-VEGF treatment if the eye develops late AMD (wet inactive) with no prospect of functional improvement.
38. Ensure that patients are actively involved in all decisions about the stopping or switching of treatment (see section 12 on patient information).
39. Do not routinely monitor people with early AMD or late AMD (dry) through hospital eye services
40. Advise people with late AMD (dry), or people with AMD who have been discharged from hospital services to:
    - self-monitor their AMD
    - consult their eye-care professional as soon as possible if their vision changes (see section 11.2)
    - continue to attend routine sight-tests with their community optometrist.
41. For people being monitored for late AMD (wet inactive), review both eyes at their monitoring appointments.
42. Discuss self-monitoring with people with AMD, and explain the strategies available.
43. Advise people with AMD to report any new symptoms or changes in the following to their eye-care professional as soon as possible:
    - blurred or grey patch in their vision
    - straight lines appearing distorted
    - objects appearing smaller than normal.
44. Encourage and support people with AMD who may lack confidence to self-monitor their symptoms.

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45. If people are not able to self-manage their AMD, discuss AMD monitoring techniques with their family members or carers (as appropriate).
46. Offer people with late AMD (wet active) ongoing monitoring with OCT for both eyes.
47. Offer fundus examination or colour photography if OCT appearances are stable, but:
    - there is a decline in visual acuity **or**
    - the person reports a decline in visual function.
48. Consider FFA to identify unrecognised neovascularisation if OCT appearances are stable, but:
    - there is a decline in visual acuity **or**
    - the person reports a decline in visual function.
49. If OCT results suggest macular abnormalities but the abnormalities are not responding to treatment, think about:
    - using alternative imaging
    - alternative diagnoses.
50. Provide information in accessible formats for people with AMD to take away at their first appointment, and then whenever they ask for it (see recommendation 53). The information should cover the following:
    - information about AMD and treatment pathways, including likely timescales
    - key contact details – for example, who to contact if appointments need to be altered
    - advice about what to do and where to go if vision deteriorates
    - available support (including transport and parking permits)
    - links to local and national support groups.
51. Allow enough time to discuss the person's concerns and questions about their diagnosis, treatment and prospects for their vision. Assess the person's priorities when making management decisions.
52. Promote peer support for people with AMD, particularly for people who are beginning intravitreal injections, who may be reassured by discussion with someone who has previously had the same treatment.
53. Provide people with AMD, and their family members or carers (as appropriate), with information that is:
    - available on an ongoing basis
    - relevant to the stage of the person's condition
    - tailored to the person's needs
    - delivered in a caring and sensitive fashion.

Be aware of the obligation to provide accessible information detailed in the NHS Accessible Information Standard. For more guidance on providing information to people and discussing their preferences with them, see the NICE guideline on patient experience in adult NHS services.

54. Provide opportunities to discuss AMD with the person. Topics to cover should include:
    - what AMD is and how common it is

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- types of AMD
- causes of AMD
- stopping smoking and other lifestyle advice
- how AMD may progress and possible complications
- the possibility of developing visual hallucinations associated with retinal dysfunction (Charles Bonnet syndrome)
- vision standards for driving
- tests and investigations
- treatment options, including possible benefits and risks
- who to contact for practical and emotional support
- where the person's appointments will take place
- which healthcare professionals will be responsible for the person's care
- expected wait times for consultations, investigations and treatments
- the benefits and entitlements available through certification and registration when sight impaired or severely sight impaired
- when, where and how to seek help with vision changes (see 11.2.5)
- signposting to other sources of information and support

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4.2 Research recommendations summary

The following research recommendations were agreed by the committee. It also agreed that research recommendations 1, 7, 14, 15 and 17 were of highest priority.

1. What is the effectiveness of antioxidant and zinc supplements on AMD disease progression for people with early AMD at high risk of progression in the context of a randomised controlled trial?
2. What is the diagnostic accuracy of the Amsler chart or other similar tools (digital or otherwise) for AMD?
3. What is the diagnostic accuracy of indocyanine green angiography (ICG) for diagnosing people with subtypes of AMD (in particular, polypoidal choroidal vasculopathy [PCV], a form of late AMD [wet active])? What is the impact of ICG on consequent treatment for PCV?
4. What is diagnostic accuracy of OCT-A for diagnosing people with late AMD (wet active), compared with FFA as the reference standard?
5. What is the diagnostic accuracy of OCT to exclude a diagnosis of late AMD (wet active) when offered in primary care?
6. What is the diagnostic accuracy of providing an electronic image with the initial referral of people with suspected late AMD (wet active)?
7. What is the long-term effectiveness, in terms of patient-relevant outcomes including visual acuity and quality of life, of different models of care that aim to reduce time from initial presentation to referral, diagnosis, and treatment?
8. What is the effectiveness and cost effectiveness of psychological therapies for the prevention of depression in people with AMD?
9. What is the impact of optimising low vision services on people with AMD?
10. What is the long-term effectiveness and cost effectiveness of 'treat-and-extend' regimen compared with alternative regimens (dosing frequencies)?
11. What is the long-term effectiveness and cost effectiveness of PDT as an adjunct to anti-VEGF as first-line treatment for polypoidal choroidal vasculopathy (PCV) (at least 2 years)?
12. What is the effectiveness and cost-effectiveness of PDT as an adjunct to anti-VEGF as second-line treatment for late AMD (wet active)?
13. How does patient preference impact on switching treatments, and how does switching affect quality of life?
14. When should anti-VEGF treatment be suspended or stopped in people with late AMD (wet)?
15. What is the long-term effectiveness, in terms of patient-relevant outcomes including best-corrected visual acuity and quality of life, of different review frequencies/strategies for people at risk of progression to late AMD (wet active)?
16. What is the effectiveness and cost-effectiveness of self-monitoring strategies in improving the long-term visual, functional and quality of life outcomes of people with early, indeterminate or late AMD (dry)?
17. Does earlier detection of the incidence of late AMD (wet active) by self-monitoring in people diagnosed with early AMD, indeterminate AMD or late AMD (dry) lead to earlier treatment and better long-term outcomes?

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18. What is the relative accuracy and cost of OCT-A compared with the reference standard of multimodal imaging?
19. What is the clinical effectiveness of OCT-A using test-and-treat approach (OCT(+/-FFA) -v- OCT+OCT-A)?
20. What terminology is clearest and most acceptable to patients to describe suspected or confirmed AMD throughout the pathway?
21. What is the impact of AMD on working people (aged<65 years or in paid/unpaid employment), and what information do they find useful and in what format and when?

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5 Classification

Age-related macular degeneration (AMD) is a progressive long-term medical condition, the management of which involves lifestyle changes, medical intervention and rehabilitation. It is also characterised by a number of distinct clinical manifestations and stages.

The aim of any classification is to reflect understanding of the disease processes, inform prognosis and to direct action. These aims are connected as a classification based on disease processes provides both predictive information and a basis for medical intervention. A useful classification should be simple enough for all – doctors, patients and carers – to understand but sufficiently sophisticated to support clinical decision-making. This also promotes good communication as each category in the classification is associated with both prognostic information and a plan of action.

The purpose of this review question was to develop a classification that was easy to understand while being clinically useful.

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5.1 Classification systems for AMD

Review question:

- What effective classification tool should be used to inform people with AMD?

5.1.1 Evidence review

The aim of this review was to establish the best available classification system or severity scale for people with diagnosed AMD. The review focused on identifying studies that fulfilled the conditions specified in Table 11. For full details of the review protocol please see Appendix C.

Table 11: PICO table – AMD classification

Population	Adults (18 years and older) with AMD
Interventions	Classification and stratification tools for AMD, including: • Wisconsin Age-Related Maculopathy Grading Scheme (WARMGS) • Modified International Classification system (MIC) • Age Related Eye Disease Study (AREDS) • Clinical Age-Related Maculopathy Staging System (CARMS) • International Classification for AMD (IC) • Other prediction models based on retinal, choroidal and/or functional features.
Comparator	N/A
Outcomes	Risk outcomes: adjusted odds ratios, adjusted relative risk, hazard ratios • The risk of progression (developing geographic atrophy or developing neovascularisation) • The risk of developing end stage vision problems (for example eligibility for certificate of vision impairment) • Validation outcomes • Patient understanding

Observational evidence was considered to be the highest quality evidence available to answer this question and was graded as high in the modified GRADE framework if well conducted and reported.

5.1.1.1 Description of included studies

A systematic search and a hand search of the reference lists of systematic reviews identified 4,711 references. The references were screened on their titles and abstracts and 50 references were ordered for full text. Reviewing the included and excluded studies in review question 2 for prognostic evidence and review question 4 for studies looking at the sub-classifications of late wet AMD resulted in the inclusion of 9 more studies.

Overall, 41 studies were excluded as they did not meet the eligibility criteria. Examples of common reasons for exclusion include study design (e.g. review article or meeting abstract), classification systems for individual clinical features (not AMD overall), no outcomes of interest (e.g. studies only reporting rates of advanced AMD incidence only), prediction models that incorporated demographic features (not clinical features alone). A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

In total, 18 articles were included. The studies fell into 2 different groups of outcomes:

- Validation outcomes for a classification system
- Risk of advanced AMD dependent upon classification system stage.

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Most of the classification systems found in this review presented validation outcomes for inter-observer and intra-observer agreement; however few studies reported adjusted risk outcomes to show the ability of the classification system to correlate increasing disease stage with increasing progression or worsening outcomes.

A brief summary of 18 included studies is provided in Table 12. References of included studies are listed in Appendix I.

Table 12 Summary of included studies for classification of AMD

Study [country]	Number included	Population	Outcomes reported
AREDS 17 (2006) [USA]	1230 eyes	Participants of the Age-Related Eye Disease Study.	Inter-observer and intra-observer agreement.
AREDS 6 (2001) [USA]	1225 eyes	Participants from the Age-Related Eye Disease Study (AREDS).	Inter-observer agreement.
Brader (2011) [USA]	15 photographic sets	Eyes with geographic atrophy and fundus photograph and angiography results	Inter-observer and intra-observer agreement.
Cohen (2007)	207 people	Patients with newly diagnosed exudative AMD	Inter-observer agreement
Coscas (2014)	193 eyes	Consecutive Japanese eyes and consecutive French eyes with exudative AMD	Inter-observer agreement
Danis (2013) [USA]	1335 eyes	Participants of the AREDS2 study	Inter-observer and intra-observer agreement.
Friedman (2000)	6 angiograms, 21 readers	6 fluorescein angiograms of choroidal neovascular membranes	Inter-observer agreement
Hamada (2006) [UK]	164 images of 106 patients	Consecutive patients with AMD referred to the Retinal Research Unit at King's College Hospital	Inter-observer agreement
Holz (2003)	40 patients, 16 readers	Neovascular AMD patients	Inter-observer and intra-observer agreement.
Jung (2014)	374 people	Treatment naïve patients with neovascular AMD in at least 1 eye	Inter-observer agreement
Klein (2011) [USA]	2846 participants	Participants in the Age-Related Eye Disease Study	Hazard ratios for advanced AMD
Klein (2014). [USA, Netherlands, Australia]	60 images of 60 eyes	Participants of the Beaver Dam Eye Study	Inter-observer agreement
Maguire (2008)	282 eyes	Eyes that developed late wet AMD in the CAPT trial	Inter-observer agreement
Olsen (2004)	200 cases	Neovascular AMD fluorescein angiograms from 2 centres	Inter-observer agreement
Perlee (2013) [USA]	2,415 participants	Participants of the Age-Related Eye Disease Study.	Hazard ratios for neovascular AMD Hazard ratios for geographic atrophy
Sandberg (1998) [USA]	127 people/eyes	Fellow eyes of people with unilateral neovascular AMD	Hazard Ratios for neovascular AMD

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Study [country]	Number included	Population	Outcomes reported
Seddon (2006) [USA]	492 eyes	People recruited for the Progression of Age-Related Macular Degeneration Study	Inter-observer and intra-observer agreement.
Van Leeuwen (2003)	91 subjects 131 images of eyes.	Participants of the EUREYE study	Inter-observer agreement

5.1.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. No references were identified as being relevant to this review question. Health economic modelling was not prioritised for this review question.

5.1.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

5.1.3.1 Agreement outcomes for classification systems

7 studies (n=4,597) provided validation outcomes for inter-observer and intra-observer agreement.

Inter-observer agreement

- Good agreement:
  - AREDS 9-step severity scale (moderate-quality evidence from 2 studies; κ=0.73 between graders)
- Good-to-excellent agreement:
  - Modified International Classification of ARM (moderate-quality evidence from 2 studies; κ range = 0.72–0.82 between graders).
  - Harmonized Three Continent AMD Consortium Severity Scale (moderate-quality evidence from 1 study; κ range = 0.66–0.86 between grading centres).
- Excellent agreement:
  - AREDS 4-step severity scale (moderate-quality evidence from 1 study; κ=0.88 between graders)
  - Clinical Age-Related Maculopathy Staging system (CARMS) (moderate-quality evidence from 1 study; κ = 0.86 between graders; κ = 0.78 between grading centres)

Intra-observer agreement

- Good agreement:
  - AREDS 9-step severity scale (moderate-quality evidence from 1 study; κ = 0.73)
- Excellent agreement:
  - AREDS 4-step severity scale (moderate-quality evidence from 1 study; κ = 0.88)
  - Clinical Age-Related Maculopathy Staging system (CARMS) (moderate-quality evidence from 1 study; κ = 0.97)

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5.1.3.2 Agreement outcomes for sub-classification systems of late AMD (wet)

Six studies (n=1,020) provided validation outcomes for inter-observer (6 studies) and intra-observer agreement (1 study).

Inter-observer agreement (kappa):

- Fair to good agreement:
  - Basic macular photocoagulation study (MPS)/Gass classification (very low-quality evidence from 3 studies; κ range = 0.37–0.64 between graders)
- Good agreement:
  - MPS/Gass classification with pigment epithelial detachment (PED) as a subgroup of occult (very low-quality evidence from 3 studies; κ=0.59 between graders)
- Excellent agreement:
  - MPS/Gass classification with serous pigment epithelial detachment (PED) as an additional criterion (very low-quality evidence from 3 studies; κ range = 0.75–1.00 between graders)

Agreement between classification systems

- Very low-quality evidence showed good agreement between the MPS/GASS classification with additional subgroup for retinal angiomatous proliferation (OCT) and the basic MPS/GASS classification (FFA) (1 study; κ = 0.65).

Inter-observer agreement (crude agreement %)

- Low-quality evidence from 2 cohorts reported in the same study found crude agreement with 'final diagnosis' to range between 33.3% and 100% for various types of late AMD (wet) using fundus photographs and FFA (with or without ICG and OCT) as investigations.

Intra-observer agreement:

- Good agreement:
  - MPS/Gass classification (very low-quality evidence from 1 study; κ=0.64).

5.1.3.3 Agreement outcomes for classification systems of late AMD (dry) alone

One study (15 photographic sets) provided validation outcomes for inter-observer and intra-observer agreement.

Inter-observer agreement:

- Good agreement:
  - CAPT classification of geographic atrophy alone (low-quality evidence from 1 study; κ=0.536 between graders).

Intra-observer agreement:

- Excellent agreement:
  - CAPT classification of geographic atrophy alone (low-quality evidence from 1 study; κ=0.84 within repeat grading).

5.1.3.4 Risk of progression to neovascular AMD

Two studies (n=2,542) provided outcomes for the risk of developing neovascular AMD with increasing stages of a classification system.

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- Very low-quality evidence from 1 study showed a higher risk for developing neovascular AMD with increasing stages of the Sandberg 4-Point Scale. (HR: 1.76 [1.18 to 2.73]).
- Low-quality evidence from 1 study showed a substantially higher risk for progression to neovascular AMD with increasing stages of the Simple Severity Score (SSS) (HR compared with a SSS of 0: SSS=1 4.76 [2.43 to 9.34]; SSS=2 12.66 [6.87 to 23.36]; SSS=3 26.56 [14.53 to 48.58]; SSS=4 35.89 [19.75 to 65.21]).

5.1.3.5 Risk of progression to geographic atrophy

One study (n= 2,415) provided outcomes for the risk of developing geographic atrophy with increasing stages of a classification system.

- Low-quality evidence from 1 study showed a substantially higher risk for progression to geographic atrophy with increasing stages of the Simple Severity Score (SSS) (HR compared with a SSS of 0: SSS=1 6.97 [3.01 to 16.14]; SSS=2 9.33 [4.13 to 21.05]; SSS=3 23.29 [10.59 to 51.22], SSS=4 34.81 [16.02-75.65]).

5.1.3.6 Risk of progression to advanced AMD

One study (n= 2,846) provided outcomes for the risk of developing advanced AMD with increasing stages of a classification system.

- Low-quality evidence from 1 study showed a substantially higher risk for progression to advanced AMD found with increasing stages of the Simple Severity Score (SSS) (HR compared with a SSS of 0: SSS=1 6.38 [3.48 to 11.69]; SSS=14.12 [8.06 to 24.75]; SSS=34.53 [19.79 to 60.26], SSS=50.65 [28.86 to 88.89]).

5.1.3.7 Health economic evidence

No cost–utility analyses were identified that were relevant to classification systems for AMD.

5.1.4 Evidence to recommendations

Relative value of different outcomes	**Validation and agreement outcomes** The guideline committee agreed that validation and agreement outcomes were helpful in showing which classification systems were workable in practice, and could be repeated with a reasonable degree of consistency. The classification system of interest should help inform people with AMD about their condition in a meaningful way (directing treatment) and help the committee use consistent terminology in the guideline. **Predictive outcomes** To maintain consistency between this review and section 6.1, the outcomes of interest for predictive outcomes in both were hazard ratios and time-adjusted odds ratios. This was agreed to be appropriate, because • They take into account duration of exposure to the risk factor • There is no arbitrary time cut-off, as in logistic regression, which can obscure differing rates of incidence over time Hazard ratios and time-adjusted odds ratios were considered high-quality outcomes for the reasons outlined in review question 2. The committee agreed that the hazard ratios reported were useful in showing an increase in the risk of progression as a person goes up the stages of any given classification or grading system. Due to considerable overlap in the evidence base between the 2 review questions, the evidence identified in section 6.1 (excluded or included) was searched to identify any other studies that may contribute useful information. The committee agreed that the purposes of the “risk models” presented differed from those of the classification systems that reported validation

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	outcomes. The objective of the risk models was to stratify people with early AMD into different risk classes for progression; the objective of the classification systems was to clearly define AMD in a meaningful way. Having reviewed the objectives of this review question in the corresponding protocol the committee agreed to focus on the classification systems that sought to produce a clear definition of AMD. This was considered to be more in line with the aim of this question i.e. “to inform people with AMD.”
Trade-off between benefits and harms	The committee considered that an agreed classification system would support consistency in practice nationally and would enable greater confidence in diagnosis of, and referral for, suspected AMD in first line services. Improvements in the volume of appropriate diagnosis and referral would result in a decreased risk of blindness due to late AMD (wet) through earlier initiation of treatment. Identification of people presenting with earlier stages of AMD and at risk of developing neovascular forms of AMD may help to enable early intervention and treatment with the potential to prevent end-stage visual problems. It may also be possible to slow or prevent the progression of AMD in these people. People who are correctly classified as not having developed AMD would receive reassurance or further investigation as appropriate. The consequences of falsely classifying a person as not having AMD include increased possibility of developing a treatable late AMD (wet active) that is not diagnosed early enough resulting in an avoidable loss of vision or blindness for that individual. The consequences of numerous false-positive classifications of AMD could include an overburdened retinal clinic, needlessly distressed patients, increased waiting times and poor monitoring of existing patients with neovascular AMD. In turn, overburdened retinal clinics could result in missed relapses, delayed treatments and increased risk of end-stage visual problems for other people. Because of the potential consequences for both the patient and the services, the committee agreed that any classification systems used as part of the guideline recommendations should be ones that are validated, with a high degree of usability in clinical practice. Risk stratification systems (for the purposes of risk stratification alone) had previously been discussed as being potentially harmful to the person with AMD by either giving a false sense of security or by unnecessarily causing anxiety in the person with early AMD.
Trade-off between net health benefits and resource use	No health economic evidence was found and this review question was not prioritised for health economic modelling. The committee was careful to consider the resource implications associated with any recommended classification system, taking into account the need for a classification system to aid consistent diagnosis of AMD and help prevent inappropriate referrals to second-line services. The committee agreed that the recommended classification system would not lead to many patients being reclassified and, critically, it will not affect the number of people eligible for treatment. Rather, it would clarify terminology to support consistent practice nationwide. As such, the committee felt that it would not have significant resource implications.
Quality of evidence	The committee considered the quality of studies reported in this review. The difficulty of quality assessment for studies reporting only agreement and validation outcomes was noted. The committee focused on evidence presented for validated classification systems. The committee agreed that it was important that any recommended validation system should be proven to have a high degree of inter-observer and intra-observer agreement since this would show that the system had usability and repeatability (consistency) in clinical practice. The committee further noted that any system employed to define fair, good, and excellent agreement using kappa levels was, in essence, arbitrary.

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Other considerations	After reviewing the evidence, the committee considered the studies that presented risk stratification models based upon pathological features presented such as drusen size. It was noted that there were very substantial hazard ratios, especially for the AREDS simple severity scale, which was unlikely to be explained by bias. This could be explained by the fact that the severity scale made use of important ocular risk factors (see section 6.1). The committee agreed that the main purpose of these risk stratification models was to inform the relationship between pathological features and development of AMD and to predict disease progression, while the key objective of this review was to identify a good classification system that is applicable to both clinicians and people with AMD, and can guide treatment. **Strengths and limitations of identified classifications** All of the systems reviewed used pigmentary irregularities, and drusen size or quantity as clinical variables to define the early stages of AMD. The committee noted that evidence on risk factors (see section 6.1) could be used to demonstrate that the expected risk of advanced AMD increases as drusen size increases and also with the presence of pigmentary abnormalities as outlined in the increasing stages of severity in all the classification systems presented. AREDS 9-step severity scale The committee noted that a classification system breaking early AMD down into a large number of categories, such as the AREDS 9-step severity scale, could be useful for research; however they had limited applicability as a classification system to inform people with AMD. The committee also noted the lower levels of agreement when compared with the kappa scores for the other classification systems. As such the AREDS 9-step severity scale was ruled out. The need for a classification system that was clinically meaningful was discussed and agreed. Patients should be able to draw a clear line from the “type” of AMD they have, to the kind of management they should expect. Clinical age-related maculopathy staging system It was noted that this system requires the healthcare professional to count the number of drusen in the eye. This was considered to be unwieldy in clinical practice where people may not be using fundus photographs. As such, this classification system was ruled out. Three Continent Consortium AMD severity scale and AREDS 4-step severity scale These classification systems had similar problems in that they required the use of fundus photographs and the positioning of circles of various size over the images in order to estimate total drusen area. This was judged as difficult and cumbersome to manage in clinical practice and these classification systems were ruled out. The Three Continent also includes medium-sized drusen and isolated pigmentary changes as 'no AMD.' Hyperpigmentation and medium drusen were identified risk factors for progression in review question 2, so the committee considered it was inappropriate to classify such people as not having AMD. Modified International Classification The remaining classification system was the Modified International Classification (MIC) which was shown to have the following strengths: 1) Drusen are classified in terms of maximum drusen size only (≥63 micrometres or ≥125 micrometres in diameter). These were values that could be estimated without the use of superimposed images or circles since 125micrometres is widely known to be roughly the width of the retinal vein where it crosses the optic disc, and 63micrometres is half this size. Size of drusen was noted to be estimated in this way (rather than measured) in practice; therefore, the committee agreed it was helpful to recommend a classification system that can be used in this manner.

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2) This was the only classification system that used all of the ocular risk factors found to be important in section 6.1, which found that drusen quantity/size, pigmentary abnormalities and the presence of reticular drusen were important risk factors. All the other classification systems only used drusen size/quantity and pigmentary abnormality as variables. It was noted that most systems of classification were developed before reticular pseudodrusen were recognised.

The committee therefore agreed to base its recommended classification on the Modified International Classification. It was noted, however, that this classification system only gives a broad overview of AMD (early and late).

Committee modifications

Early AMD

For early AMD, the committee discussed and agreed to incorporating drusen classification and AREDS risk stratification so the classification tool could not only provide pathological features of early AMD but also the risk of disease progression to inform a monitoring strategy for AMD.

Late AMD

For late AMD, the MIC pooled late wet and late dry AMD, which conflates 2 presentations with different prognoses. The committee agreed that late wet and late dry AMD should be separated out. The definitions of each were taken from the evidence on the modified international criteria. The committee agreed that dry AMD included geographic atrophy and significant visual loss (6/18 or worse) associated with confluent drusen, advanced pigment change and/or non-geographic atrophy, and adult vitelliform lesion.

Late AMD (wet)

The committee agreed an amendment to the MIC definition for late wet AMD as follows:

> "the presence of serous or haemorrhagic retinal PED, a subretinal neovascular membrane, a subretinal haemorrhage, a periretinal fibrous scar or a combination of the above"

The committee agreed that a distinction needed to be made between active and inactive wet AMD, with the latter representing fibrous scar, retinal pigment epithelial tear, atrophy and cystic degeneration. This distinction is important, as it has implications for the amenability of disease to antiangiogenic treatment. The committee agreed that a classification system for the subtypes of late AMD (wet active) was needed.

Evidence was presented on the validation of these classification systems (kappa and agreement outcomes). The committee considered that agreement levels remained generally in the 'fair to good' level of agreement. Levels of agreement increased more often to 'excellent' in the classification systems for early AMD. The committee discussed and agreed that the level of agreement can often be influenced heavily by the number of categories (though this effect is adjusted for in the weighted kappa statistic). It was also noted that the mixed pattern of late AMD (wet) can cause disagreement where there are 2 overlapping subtypes: a grader may choose to call it mixed or simply grade by the predominant lesion type. This was especially apparent in the paper by Coscas et al. where agreement levels were lower for mixed patterns. Most of the classification systems identified used some variation of the macular photocoagulation study (MPS) classification (classic/occult/mixed/scar).

Two studies used the 'anatomic' classification (type 1/type 2/type 3/mixed) whilst 1 study mapped the 2 classification systems together. Some studies also provided validation outcomes for classification systems that included polypoidal choroidal vasculopathy (PCV) and pigment epithelial detachment. The committee agreed the following subtypes were to be included as late wet AMD: retinal angiomatous proliferation, classic choroidal neovascularisation, mixed (predominantly and minimally classic

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CNV with occult CNV); occult CNV and serous pigment epithelial detachment with neovascularisation and polypoidal choroidal vasculopathy.

Indeterminate AMD

The committee discussed 1 subtype of AMD that was not identified in the evidence for this review: CSCR-pattern AMD (central serous chorioretinopathy). This was defined as the presence of degenerative AMD changes with sub- or intra-retinal fluid in the absence of neovascularisation, and may be referred to as a retinal pigment epitheliopathy. This subtype may be important and may not benefit from treatment; therefore the committee agreed that NICE should recognise an 'indeterminate' level above early AMD and below late AMD (wet) for which we would look for subgroup analysis in the treatment trials. Therefore this was added to the guideline classification by consensus agreement.

The committee also noted that serous pigment epithelial detachment without neovascularisation is between dry and wet AMD where there is fluid but no neovascularisation, and it should be included as indeterminate AMD.

The committee agreed that 'indeterminate' AMD was a good description of these conditions. It reflects the fact that management is uncertain. The committee was keen to avoid the alternative of 'intermediate' AMD, as this could be interpreted as implying something about expected progression whereas, in fact, relatively little is known about prognosis in this group of patients.

'Dry' AMD

The committee agreed that the term *dry AMD* should not be used on its own. This is because its use has become ambiguous, as it is used variously to describe 3 distinct clinical scenarios:

- Early AMD for patients with the presence of drusen, pigmentary change or small atrophic areas. Patients are often asymptomatic or mildly symptomatic and, as detailed elsewhere in this guideline, the only required intervention is lifestyle advice and an explanation of these common changes.
- Late AMD (dry) for patients who have developed central atrophy, confluent drusen or severe pigmentary change with visual loss, which can be profound. The required action is low-vision rehabilitation (see section 9.2).
- Late AMD (wet inactive) for patients who have had neovascular AMD, but now no longer require treatment with anti-VEGF agents. This may require ongoing monitoring (self or professional) and, commonly, rehabilitation.

The committee was particularly keen that ambiguity should not be perpetuated with respect to the last of these categories, as the experience of group members was that patients can become confused if they are told that their 'wet' disease has become 'dry'. For this reason, the committee made an additional, explicit recommendation that the term 'dry' should be avoided in these cases.

Exclusion of evidence

The committee discussed the evidence that was excluded for this review. This included papers on the Wisconsin Age-Related Maculopathy Grading Scheme (WARMGS) and the International Classification for AMD (IC). These 2 classification systems were excluded as they presented a series of classification systems for individual clinical features of AMD (e.g. drusen, drusen size, drusen type, hyperpigmentation, hypopigmentation) not a classification system for AMD as a whole. These classification systems were considered to be mostly for research purposes and, after consideration, their exclusion from the evidence base was agreed.

A further study looking at a classification system for polypoidal choroidal vasculopathy (PCV) was also excluded. It was unclear whether it was clinically meaningful for the management of AMD or to inform the person

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	with AMD to break the subgroup of PCV into a further 3 subgroups (A, B and C). The committee therefore agreed to exclude this study.

5.1.5 Recommendations

1. Classify age-related macular degeneration (AMD) using the following terms:

AMD classification	Definition
Normal eyes	• No signs of age-related macular degeneration (AMD) • Small ('hard') drusen (less than 63 micrometres) only
Early AMD	• Low risk of progression: ○ medium drusen (63 micrometres or more and less than 125 micrometres), or ○ pigmentary abnormalities • Medium risk of progression: ○ large drusen (125 micrometres or more), or ○ reticular drusen, or ○ medium drusen with pigmentary abnormalities • High risk of progression: ○ large drusen (125 micrometres or more) with pigmentary abnormalities, or ○ reticular drusen with pigmentary abnormalities, or ○ vitelliform lesion without significant visual loss (best-corrected acuity better than 6/18), or ○ atrophy smaller than 175 micrometres and not involving the fovea
Late AMD (indeterminate)	• Retinal pigment epithelial (RPE) degeneration and dysfunction (presence of degenerative AMD changes with subretinal or intraretinal fluid in the absence of neovascularisation) • Serous pigment epithelial detachment (PED) without neovascularisation
Late AMD (wet active)	• Classic choroidal neovascularisation (CNV) • Occult (fibrovascular PED and serous PED with neovascularisation) • Mixed (predominantly or minimally classic CNV with occult CNV) • Retinal angiomatous proliferation (RAP) • Polypoidal choroidal vasculopathy (PCV)
Late AMD (dry)	• Geographic atrophy (in the absence of neovascular AMD) • Significant visual loss (6/18 or worse) associated with: ○ dense or confluent drusen, or ○ advanced pigmentary changes and/or atrophy, or ○ vitelliform lesion
Late AMD (wet inactive)	• Fibrous scar • Sub-foveal atrophy or fibrosis secondary to an RPE tear • Atrophy (absence or thinning of RPE and/or retina) • Cystic degeneration (persistent intraretinal fluid or tubulations unresponsive to treatment) *NB Eyes may still develop or have a recurrence of late AMD (wet active)*

NB a detailed classification system agreed by the committee is provided in Appendix K

2. Do not refer to late AMD (wet inactive) as 'dry AMD'.

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6 Risk factors

A risk factor is any attribute, any event, any experience or any characteristic feature in a medical or socio-economic history, which specifically increases the probability of succumbing to a particular disease. Risk factors aid clinicians to predict disease, to anticipate disease progression, and to prevent disease. Suspicion of age-related macular disease, or the referral threshold to a retinal clinic, may be influenced by the presence or absence of risk factors. The advice given to a person with AMD, or at risk of this disease, is likely to be influenced by the presence or absence of these risk factors. Risk factors are a helpful resource for those in public health, commissioning, governments, third sector organisations, support organisations, health surveillance bodies, and funding bodies. Strategies that seek to maximise the effectiveness of care by targeting populations more likely to benefit will be easier to implement if awareness of the appropriate risk factors is increased.

Risk factors such as age, smoking and previous cataract surgery have been previously identified to be associated with AMD (Chakavarthy U et al 2010), but the evidence is not clear cut. This chapter seeks to search for and evaluate evidence for any modifiable or non-modifiable risk factors for macular degeneration. Specifically, the evidence base was searched for risk factors that are associated with the development or progression of AMD and for evidence of interventions that may slow the progression of AMD. The review questions aims to identify factors that could be influenced to prevent, or delay the onset of AMD, thus maintaining vision for as long as possible, or reducing the treatment burden on individuals. Where a diagnosis of AMD had been established, it looks at the evidence for strategies for the management of risk factors that may slow the progression of AMD (excluding those covered in the separate section on pharmacological management of AMD).

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6.1 Risk factors for development or progression of AMD

Review question:

- What risk factors increase the likelihood of a person developing AMD or progressing to late AMD?

6.1.1 Evidence review

The aims of this review were to determine which risk factors increase the likelihood of a person developing AMD, and to determine which risk factors increase the likelihood of progressing to late AMD in an eye that has early AMD. The review focused on identifying studies that fulfilled the conditions specified in Table 13. For full details of the review protocol please see Appendix C.

The purpose of this question was not to provide an ordered list of stronger or weaker predictors; it was simply to raise awareness of the factors that should raise suspicion of AMD. Therefore, results descriptions here do not focus on the specific difference in magnitude of effect between different predictors; but rather we simply identify when an association was found.

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Table 13: PICO table – risk factors

Population	• Adults (18 years and older) at risk of developing AMD. • Adults (18 years and older) who have been diagnosed with early AMD in either eye who have not yet progressed to late AMD.
Risk factors of interest	Ocular risk factors: • Refractive status (may be hard to interpret as neovascularisation could be as a result of myopia) • Iris colour • Cataract surgery (including lens replacement surgery) • Presence of AMD in the other eye • Drusen • Reticular pseudodrusen • Angioid streaks • Other pigmentary changes (RPE- retinal pigment epithelium) • Pseudovitelliform macular dystrophy • Pigment epithelial detachment (PED) • Cystoid macular oedema • Atrophy Lifestyle: • Smoking • Diet and nutrition • Obesity (BMI) • Alcohol consumption • Exercise • Sunlight exposure Medical risk factors: • Hypertension • Hypercholesterolemia • Hypertriglyceridemia • Coronary/vascular disease • Cerebrovascular disease • Diabetes • Family history • Anticoagulant medication • Anti-platelet medication Other: • Gender • Race • Age • Socio-economic status
Outcomes	Risk of developing any AMD, early AMD or progressing to late AMD (geographic atrophy or neovascular AMD), expressed as: • Hazard ratios • Time-adjusted odds ratios

Observational evidence was considered to be the highest-quality evidence available to answer this question and was graded as high in a GRADE framework if well conducted and reported. Papers were excluded it they:

- were not published in the English language.
- were abstracts, conference proceedings, narrative reviews, case-studies or non-comparative studies.

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6.1.1.1 Description of included studies

A systematic search and a hand search of the reference lists of systematic reviews identified 6,325 references. The references were screened on their titles and abstracts and 281 references were ordered for full-text screening.

Overall, 246 studies were excluded as they did not meet the eligibility criteria. Examples of common reasons for exclusion include non-full text paper (e.g. meeting abstract), non-primary studies (e.g. narrative review, editorial), studies not reporting outcomes of interest (time-adjusted odds ratios and hazard ratios), or studies based in countries outside those of interest (Europe, USA, Canada, Australia and New Zealand). A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

A large number of identified studies necessitated a strategy focusing on studies reporting the most relevant and informative evidence. Only studies with similar population characteristics (genetic background and ethnicity) and comparable quality of healthcare to the UK were included e.g. studies based in Europe, USA, Canada, Australia and New Zealand. The review only included outcomes that take into account the rate of AMD development and/or progression. These were hazard ratios and time-adjusted odds ratios for the development of AMD. These outcome measures:

- Take into account duration of exposure to the risk factor
- Do not require an arbitrary time cut-off, as in usual logistic regression, which can obscure differing incidence between exposed and non-exposed participants.

In total 35 articles were included. The studies fell into 6 different groups of risk outcomes:

- Risk of any AMD
- Risk of early AMD
- Risk of progression to late dry AMD
- Risk of non-exudative or dry AMD
- Risk of progression to late wet AMD
- Risk of progression to any late AMD

A brief summary of included studies was provided in the Table 14. References of included studies are listed in Appendix I. The Seddon (2011), Seddon (2013) and Seddon (2015) studies are all based on the same dataset (the AREDS study). All 3 are included here as they analyse the dataset in slightly different ways (e.g. adjusting for different confounding variables), but the dataset is only counted once in evidence tables.

Table 14 Included studies for risk factors

Study [country]	Number included	Population	Outcomes reported (HR-hazard ratio, OR-odds ratio)
Macular Photocoagulation Study Group (MPSG) (1997) [USA]	670	Unilateral CNV secondary to AMD (fellow eye study eye)	HR for late AMD (wet active))
Ajani (1999) [USA]	21,041	US male physicians in trial of aspirin and placebo	HR for any AMD HR for late AMD (wet active)
Boekhoorn (2008) [Netherlands]	4,229	All inhabitants ≥55years living in a suburb of Rotterdam	HR for late AMD HR for early AMD HR for late AMD (dry) HR for late AMD (wet active)

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Study [country]	Number included	Population	Outcomes reported (HR-hazard ratio, OR-odds ratio)
Bressler (1990) [USA]	127	Unilateral CNV due to macular degeneration (fellow eye study)	HR for late AMD (wet active)
Chew (2009) [USA]	2,880 right eyes, 2,961 left eyes	AREDs trial participants	HR for late AMD (dry) HR for late AMD (wet)
Chiu (2009) [USA]	2,924	AREDs trial participants	HR for late AMD HR for early AMD
Chiu (2007) [USA]	2,754	AREDs trial participants	HR for late AMD
Christen (2001) [USA]	22,071	US male physicians in trial of aspirin and placebo	HR for any AMD
Christen (2009) [USA]	39,876	Female health professionals in a trial of aspirin and placebo	HR for any AMD HR for late AMD
Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) Research Group, (2008) [USA]	1,052	Participants in a randomised controlled trial of laser treatment for late AMD	HR for late AMD (dry) HR for late AMD (wet active)
Finger (2014) [USA and Australia]	200	Consecutive subjects who presented with a newly diagnosed CNV secondary to AMD (fellow eye study)	HR for late AMD (dry) HR for late AMD (wet) HR for late AMD
Grunwald (2014) [USA]	1,024	Comparison of Age-related Macular Degeneration Treatments Trials (CATT) participants (fellow eye study)	HR for late dry AMD
Hahn (2013) [USA]	DM (6,621) NPDR (1,307) PDR (327)	Medicare beneficiaries aged 65 or older who were diagnosed with DM, NPDR, and PDR or dry AMD and wet AMD from 1991–2005.	HR for 'dry' AMD HR for late AMD (wet)
Howard (2014) [USA]	2,641	Census of the population of Beaver Dam, Wisconsin	HR for late AMD HR for early AMD
Klein (2012) [USA]	4,926	Participants free of the various type of AMD at baseline	HR for late AMD HR for early AMD HR for late AMD (dry) HR for late AMD (wet)
Klein (2011) [USA]	2,846	Participants in the AREDs study	HR for late AMD
Klein (2007) [USA]	3,917	Participants of the Beaver Dam eye study	OR for late AMD OR for early AMD OR for late AMD (dry) OR for late AMD (wet)
Klein (2008) [USA]	2,119	Participants of the Beaver Dam eye study	OR for late AMD OR for early AMD OR for late AMD (dry) OR for late AMD (wet)
Klein (2008)a [USA]	2,119	Participants of the Beaver Dam eye study	OR for early AMD OR for late AMD (dry) OR for late AMD (wet)

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Study [country]	Number included	Population	Outcomes reported (HR-hazard ratio, OR-odds ratio)
Klein (2013) [USA]	1,700	Participants of the Beaver Dam eye study and Epidemiology of Hearing Loss Study	OR for late AMD OR for early AMD OR for late AMD (dry) OR for late AMD (wet)
Knudtson (2006) [USA]	2,119	Participants of the Beaver Dam eye study	OR for early AMD OR for late AMD (dry) OR for late AMD (wet)
Lechanteur (2012) [Netherlands]	108	108 subjects selected by chart review from the European Genetic Database (EUGENDA) (fellow eye study)	HR for late AMD
Reynolds (2013) [USA]	2,128	Participants in the AREDS study	HR for late dry AMD
Sandberg (1998) [USA]	127	Participants with unilateral neovascular AMD (fellow eye study)	HR for late AMD (wet)
Seddon (2003) [USA]	261	Patients with AMD, seen for examination at the Massachusetts Eye and Ear Infirmary, Boston	HR for late AMD
Seddon (2003)a [USA]	261	Patients with AMD, seen for examination at the Massachusetts Eye and Ear Infirmary, Boston	HR for late AMD
Seddon (2011) [USA]	2,937	Participants in the AREDs study	HR for late AMD
Seddon (2013) [USA]	AREDs cohort (2,914) Validation cohort (980)	People in the Age-Related Eye Disease Study and an independent validation cohort	HR for late AMD
Seddon (2015) [USA]	2,951	Participants in the AREDs study	HR for late AMD
Stein (2011) [USA]	44,103 Asian Americans	Patients insured through one specific managed care network	HR for late AMD (wet) HR for non-exudative AMD
Submacular Surgery Trials Research Group (SST) (2009) [USA]	370	Participants in the submacular surgery trials who had a unilateral neovascular AMD at study (fellow eye study)	HR for late AMD
Van Leeuwen (2005) [Netherlands]	4,170	Cohort of all inhabitants aged 55 years or older in a middleclass suburb of Rotterdam.	HR for any AMD
van der Beek (2011) [USA]	1,535,008 whites, 78,315 blacks, 99,518 Latinos, and 44,103 Asian American	Patients insured through one specific managed care network	HR for late AMD (wet) HR for non-exudative AMD

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Study [country]	Number included	Population	Outcomes reported (HR-hazard ratio, OR-odds ratio)
Williams (2009) [USA]	male (n=29,532) and female (n=12,176)	Cohort of runners, 18 years old and older	HR for any AMD
Wilson (2004) [USA]	326	Diagnosed with AMD Followed in the SFVA eye and medical practice during the study period	HR for late AMD (wet)

6.1.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. No references were identified as being relevant to this review question. Health economic modelling was not prioritised for this review question.

6.1.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

6.1.3.1 Risk of development of any AMD

Five studies (n=128,866) reported risk factors for developing any AMD. Within this evidence, a decreased risk was found with:

- Increased exercise (very low- to low-quality evidence)
- Increased vitamin E intake (moderate-quality evidence)
- Increased zinc intake (moderate-quality evidence)
- Increased combined intake of vitamin C, vitamin E, beta-carotene and zinc (moderate-quality evidence).

6.1.3.2 Risk of development of early AMD

Nine studies (n=26,694) reported risk factors for developing early AMD. Within this evidence, an increased risk of early AMD was found with:

- Increased drusen size (moderate-quality evidence)
- Presence of soft, distinct (moderate-sized) drusen (moderate-quality evidence)
- Smoking (low- to moderate-quality evidence)
- Female gender (moderate-quality evidence)
- Increased age (moderate-quality evidence)

A decreased risk of early AMD was found with:

- Increased education (low-quality evidence)
- A history of diabetes (low-quality evidence)

6.1.3.3 Risk of progression to late AMD (dry) for people with early AMD

Twelve studies (n=31,374) reported risk factors for progression to late AMD (dry) for people with early AMD. Within this evidence, an increased risk was found with:

- Presence of hyperpigmentation (moderate-quality evidence)

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- Presence of depigmentation (moderate-quality evidence)
- Presence of pigmentary changes/abnormalities (low- to moderate-quality evidence),
- Increased drusen size (low- to moderate-quality evidence)
- Presence of soft indistinct (large) drusen (moderate-quality evidence)
- Presence of reticular pseudodrusen (low- to moderate-quality evidence)
- Worse baseline visual acuity (low-quality evidence)
- Presence of neovascularisation (moderate-quality evidence)
- Presence of geographic atrophy in the fellow eye (moderate-quality evidence)
- Presence of hypertension (moderate-quality evidence)
- Increased age (moderate-quality evidence)

6.1.3.4 Risk of late dry AMD

Three studies (n=1,809,302) reported risk factors for developing late AMD (dry). An increased risk was found with:

- Chinese ethnicity (low-quality evidence)
- Pakistani ethnicity (low-quality evidence)

A decreased risk of developing late AMD (dry) was found with:

- Japanese ethnicity (low-quality evidence)
- Black ethnicity (low-quality evidence)
- Latino ethnicity (low-quality evidence)

6.1.3.5 Risk of progression to late AMD (wet active)

Eighteen studies (n=1,859,815) reported risk factors for developing late AMD (wet active). An increased risk was found with:

- Presence of five or more drusen (low-quality evidence)
- Increased drusen size (low- to moderate-quality evidence)
- Presence of soft indistinct drusen (moderate-quality evidence)
- Presence of hyperpigmentation (low- to moderate-quality evidence)
- Presence of depigmentation (moderate-quality evidence)
- Presence of pigmentary changes/abnormalities (low- to moderate-quality evidence)
- Presence of systemic hypertension (low-quality evidence)
- Increased age (low- to moderate-quality evidence)

A decreased risk of developing late AMD (wet active) was found with:

- Increased exercise (low-quality evidence)

6.1.3.6 Risk of progression to any late AMD

Eighteen studies (n=78,914) reported risk factors for developing any late AMD. Within this evidence, an increased risk was found with:

- Presence of large drusen in the fellow eye (moderate-quality evidence)
- Presence of soft indistinct (large sized) drusen (moderate-quality evidence)
- Presence of reticular drusen (moderate-quality evidence)
- Increased drusen size (low- to moderate-quality evidence)
- Presence of hyperpigmentation (moderate-quality evidence)

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- Presence of pigmentary changes/abnormalities (low- to moderate-quality evidence)
- Presence of depigmentation (low- to moderate-quality evidence)
- Presence of hyperpigmentation in the fellow eye (moderate-quality evidence)
- Presence of neovascular AMD in the fellow eye (moderate-quality evidence)
- Presence of geographic atrophy in the fellow eye (moderate-quality evidence)
- Presence of late AMD in the fellow eye (low- to moderate-quality evidence)
- Obesity (BMI ≥30) (low- to moderate-quality evidence)
- Smoking (low- to moderate-quality evidence)
- Family history of AMD (low-quality evidence)
- Increased age (low- to moderate-quality evidence)
- Higher fat intake (moderate-quality evidence)
- Higher vegetable fat intake (moderate-quality evidence)
- Higher monounsaturated fat intake (low-quality evidence)
- Higher polyunsaturated fat intake (moderate-quality evidence)
- Higher trans-unsaturated fat intake (low-quality evidence)
- Higher dairy fat intake (low-quality evidence)
- Higher dietary glycaemic index (moderate-quality evidence)
- Higher intake of processed baked goods (moderate-quality evidence)

6.1.3.7 Health economic evidence

No cost–utility analyses were identified that were relevant to risk factors for development or progression of AMD.

6.1.4 Evidence to recommendations

Relative value of different outcomes	The committee did not distinguish between odds ratios and hazard ratios as being of greater or lesser value when compared to each other, and therefore both were given equal weight in decision making. For the relative value of studies reporting the risk of developing any AMD, the risk of developing early AMD, the risk of developing late AMD (wet), the risk of developing late AMD (dry) and the risk of developing any late AMD, the committee considered outcomes relating to the development of late AMD to be more important, since it is these types of AMD that lead to severe vision loss. The focus of this review was the use of risk factors to aid the diagnosis of AMD of all types. It was agreed, however, that the diagnosis of which "type" of AMD is not going to be made based upon risk factors alone, but rather by completing an ocular examination of the eye. The risk factors help to complete the clinical picture and for this reason the recommendations were not stratified by the type of AMD developed.
Trade-off between benefits and harms	The committee agreed that, in instances of a true positive, referral to appropriate services and appropriate care results in decreased risk of vision loss or blindness due to late AMD (wet), as treatment is initiated earlier. In instances of true negatives then reassurance and ongoing monitoring by healthcare professionals in the appropriate setting or service would be considered appropriate. The consequences of a false negative include the possibility of developing treatable neovascular AMD that is not diagnosed soon enough, resulting in an avoidable loss of vision for that individual. The consequences of numerous false positives could include overburdened retinal clinics, needlessly distressed patients, increased waiting times and poor monitoring of existing patients with

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neovascular AMD. For this last group of patients, the consequences of an overburdened retinal clinic could also be severe and result in missed relapses, delayed treatments and blindness.

Types of AMD

Because of the potential consequences for both the patient and the services, the committee agreed that any risk factors prioritised as part of the guideline recommendations should be ones that are either highly important or specific to AMD.

The committee agreed the risk factors identified would not, in isolation, enable a diagnosis to be made. This would be made upon ocular examination. For this reason, the recommendation states that the relevant factors should be considered where AMD is suspected.

Risk factors

Genetics

Very low-quality evidence showed that a family history of AMD increased the risk of developing AMD. The committee commented that the emerging evidence available on genetic risk factors for AMD would likely back this up and that this was in accordance with their own clinical experience. Family history was therefore added to the list of important risk factors in the recommendation.

Smoking

Smoking was consistently shown to increase the risk of all kinds of AMD. For this reason, it was added as an important risk factor for consideration in someone suspected of having AMD. The evidence also showed a clear risk reduction for those who were past smokers, as opposed to those who were current smokers. This showed that interventions to help people with AMD quit smoking could potentially help to prevent disease progression. For this reason, smoking cessation strategies would be considered for effectiveness in the review question on strategies for preventing or slowing the progression of AMD.

There was 1 study which only showed a non-significant effect of current smoking compared with non-smokers for the development of neovascular AMD (Klein et al., 2008) and the point estimate was in the direction of being protective. The committee considered this study and noted the very wide confidence intervals and the very low quality rating. For this reason the committee agreed that this single non-significant result should not influence its decision to make recommendations around the risks of AMD associated with smoking.

Age

Increasing age was also found to be a consistent risk factor for the development and progression of AMD. The committee did not find this surprising as the condition is known to be related to age.

Hypertension

The included evidence reported an association between the diagnosis of hypertension and the progression of AMD to late AMD. The committee considered this as consistent with current knowledge on hypertension as a risk factor for AMD. It was agreed that any known history of hypertension in a person suspected of having AMD would be easily obtained.

Weight

An incremental increase in BMI was not found to be associated with an increased risk for the development or progression of AMD. However BMI >30 (obesity) was more consistently found to be associated with the progression of AMD. The committee considered that there were a number of linked risk factors for the progression of

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AMD that included obesity, dietary fat intake, and the protective effect of exercise. The committee stated that this was consistent with their prior belief about the pathogenesis of AMD progression and that some consideration of healthy lifestyle should be taken into account when taking a history of a person with suspected AMD. For this reason exercise, which was found to be protective, BMI (>30) and dietary intake of fat were added to the list of risk factors associated with AMD.

Diet

The committee noted that many of the studies showing significant results for various dietary factors did not demonstrate a clear dose–response relationship between intake and risk of progression. The impracticality of asking a person about their diet, especially at the level of detail reported in some of the studies, was discussed.

Education

Education was found to be consistently protective of the development or progression of AMD. However the committee viewed this as a poor surrogate risk factor for socioeconomic status which was the risk factor of interest outlined in the protocol. They agreed that it was difficult to unpick the causative effect of this association, that confounding was likely and that it was not helpful for diagnosis of AMD in a person presenting to front-line services. It was also pointed out that the American “high school graduation” which was used in a number of the included studies differs from the UK “high school graduation” (in age and level of education).

Sex

One study showed an increased association of female sex with the development of AMD and an unclear association with the development of late AMD. The committee agreed that there was not sufficient evidence to show that female sex significantly raised the risk of AMD. Moreover, the committee was keen not to facilitate the under-diagnosis of AMD amongst men by recommending female sex as an important risk factor for AMD. It was queried whether the suggested increased risk for females was impacted by the greater life expectancy of females.

Ethnicity

One study showed that black ethnicity could be protective, that Latino ethnicity could be protective and that Asian ethnicity could raise the risk of exudative and non-exudative AMD. A further study looked at those of Asian ethnicity in greater detail (broken down by country) and found that being Japanese could be protective of non-exudative AMD and being Pakistani could raise the risk of non-exudative AMD. The committee agreed there was not sufficient evidence to say that all people of, for example, black ethnicity have a reduced risk of developing AMD. When the people of Asian ethnicity were broken down into their constituent countries, there appeared to be a wide range of risk estimates, and this added to the uncertainty of assigning a risk category based on ethnicity. Confounding due to a “westernised” diet for some ethnic groups living outside of their country of genetic origin was also a concern for the committee when looking at the evidence. The guideline committee agreed that they could risk doing greater harm if they were to recommend that any one ethnicity was protective of AMD on insufficient evidence. It was also noted that the American classification of “Asian” ethnicity differs from that of the UK classification.

History of diabetes

A history of diabetes was found to be protective against early AMD in 1 study. The committee discussed this finding and suggested that it

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	could be due to the increased surveillance of these patients and the greater potential for misclassification of early AMD as diabetic retinopathy (which could present very similarly at earlier stages). It was agreed that a history of diabetes should not be considered protective of AMD. Ocular risk factors Significant risk factors found to increase the risk of AMD or the risk of progression included: large drusen, soft indistinct drusen, reticular drusen, drusen size, hyperpigmentation, pigmentary changes/abnormalities, depigmentation, late AMD (wet) in the fellow eye, late AMD (dry) in the fellow eye and late AMD in the fellow eye. Identifying these features would all require an examination of the eye; therefore, they were mostly of value to questions on classification (section 5) and diagnosis (chapter 7). Unlike the other ocular risk factors that would require a professional to look in the eye, a person with prior AMD would be able to tell the front-line healthcare professional about having had a previous diagnosis of AMD. The committee agreed that the evidence showed a clear relationship between history of AMD in the fellow eye and the development of AMD. For this reason history of AMD in the fellow eye was added to the list of risk factors that are associated with an increased risk of AMD.
Trade-off between net health benefits and resource use	No health economic evidence was found and this review question was not prioritised for health economic modelling. The committee considered the substantial resource implications inherent in referring a greater number of people with suspected AMD to the retinal clinic. As outlined above the committee agreed that the recommended risk factors should be the ones that are either highly important or specific to AMD. The recommended risk factors should aid the appropriate diagnosis of AMD.
Quality of evidence	The committee considered the outcomes reported in this review. The decision to restrict the inclusion criteria to those studies reporting hazard ratios and time-adjusted odds ratios was agreed to be appropriate, given the large number of studies and the fact that no meta-analysis of the evidence was possible. The strength of these time-adjusted outcomes compared with those studies reporting logistic regression alone was agreed to be: • They take into account duration of exposure to the risk factor • There is no arbitrary time cut off, as in usual logistic regression, which can obscure differing rates of incidence between exposed and non-exposed participants. Further, it was agreed that the included studies provided a good coverage of the risk factors of interest The most common reasons for the quality of studies being downgraded were a lack of information being reported in the studies, in particular with relation to the study sample used and the amount of loss to follow up. Another common reason for downgrading was imprecision, and the resulting broad confidence intervals that would affect the ability of the guideline committee to make confident recommendations.
Other considerations	It was agreed that genetic risk factors for AMD would be a good review area for any future update of this guideline but it was acknowledged that the use of genetic risk factor is not currently used in clinical practice and the underpinning evidence base is not robust. However, studies in this area are currently in progress and the volume of evidence is likely to increase rapidly over the coming years. Therefore, it was not necessary to stimulate such research with an explicit research recommendation.

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6.1.5 Recommendations

3. **If you suspect AMD, recognise that the following risk factors make it more likely that the person has AMD:**
    - older age
    - presence of AMD in the other eye
    - family history of AMD
    - smoking
    - hypertension
    - BMI of 30 kg/m^2 or higher
    - diet low in omega 3 and 6, vitamins, carotenoid and minerals
    - diet high in fat
    - lack of exercise.

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6.2 Strategies to slow the progression of AMD

Review question:

- What is the effectiveness of strategies to reduce the risk of developing AMD in the unaffected eye or slow the progression of AMD?

6.2.1 Evidence review

The aim of this review was to establish the effectiveness of strategies to reduce the risk of developing AMD in the unaffected eye or slow the progression of AMD. The review focused on identifying studies that fulfilled the conditions specified in Table 15. For full details of the review protocol see Appendix C.

Table 15: PICO table – strategies to slow the progression of AMD

Population	a) Adults (18 years and older) with AMD in one eye and an eye without AMD; b) Adults (18 years and older) with early AMD in one or both eyes.
Interventions	Comparative or head to head trials of: • Smoking cessation • Antioxidant and carotenoids rich diet • Omega 3 fatty acid rich diet or supplementation • Vitamin supplementation • Mineral supplementation • Statins • Laser treatment of drusen • Exercise • Weight loss interventions
Comparator	Interventions above, placebo or usual care (including basic advice to stop smoking)
Outcomes	Clinical outcomes: • Development of late AMD (wet active) • Development of late AMD (geographic atrophy) • Development of VA loss due to AMD (LogMAR: for example, loss of 3 or more lines of visual acuity) • Safety and adverse events • Health related quality of life • Resource use and costs

In accordance with the review protocol, only randomised controlled trials (RCTs) and systematic review of RCTs were included if they compared interventions for slowing or preventing the progression of AMD with usual care (including basic advice) or placebo treatment. Papers were excluded if they:

- were not published in the English language
- had less than 1 year of follow-up (specified by the committee as a necessary length of follow-up to detect differences in progression caused by the strategies being tested).
- were abstracts or conference proceedings.

6.2.1.1 Description of included studies

This review was undertaken as a collaboration between the NICE Internal Clinical Guidelines Team and the Cochrane Eyes and Vision Group. Cochrane reviews on

- statins

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- omega 3 fatty acids
- laser treatment of drusen
- antioxidant and multivitamin supplements

were updated to identify new RCTs since their original publication, and a separate search was conducted for exercise, smoking cessation and weight management. For consistency with the rest of the guideline, some analyses have been adapted from those in the published Cochrane reviews; for example, where the effects were measured by odd ratios, relative risks were calculated based on following formula: RR=OR / (1-probablity of event + probability of event * OR), and therefore results may not be identical to all outcomes reported in the published Cochrane reviews.

One study met the inclusion criteria for the review on statins, 3 studies for the review on omega 3 fatty acids, 11 studies for the review on laser treatment of drusen and 14 studies for the review on antioxidant and multivitamin supplements, to slow progression to advanced AMD.

A systematic search identified 1,083 references on exercise, smoking cessation and weight management for slowing the progression of AMD. Eighteen studies were requested for full text review but none of the studies met inclusion criteria for this review question. For the list of excluded studies with reasons, see Appendix F.

A brief summary of included studies was provided in Table 16 to Table 19. References of included studies are listed in Appendix I.

Table 16 Summary of included studies – statins for preventing or slowing the progression of AMD

Study	Population	Intervention	Comparator	Outcomes
Guymer 2003	People with AMD in at least 1 eye (n=114)	Simvastatin (40mg daily)	Placebo	Progression of non-advanced AMD to either advanced AMD or higher severity scores of non-advanced AMD

Table 17 Summary of included studies – omega 3 fatty acids for preventing or slowing the progression of AMD

Study	Population	Intervention	Comparator	Outcomes
Ute E K 2015	People with early or intermediate AMD (n=79)	VitaluxOmega (lutein, omega-3 and vitamins)	VitaluxPlus (lutein and vitamins)	Contrast sensitivity; macular pigment optical density; change of visual acuity
AREDS2 2013	People at risk for progression to advanced AMD with bilateral drusen or large drusen in 1 eye and advanced AMD in the follow eye (n=4,203)	Omega 3 fatty acid	Placebo	Development of advanced AMD; progression to moderate vision loss (3 lines); serious adverse events
NAT2 2013	People with early lesions of AMD and visual acuity better than 0.4 logarithm of minimum angle of resolution units in the	Omega 3 fatty acid	Placebo	Time to occurrence of CNV in the study eye; percentage of patients in whom CNV developed;

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Study	Population	Intervention	Comparator	Outcomes
	study eye and neovascular AMD in the fellow eye (n=298)			changes in visual acuity

Table 18 Summary of included studies – laser treatment of drusen to prevent the progression of AMD

Study	Population	Intervention	Comparator	Outcomes
CAPT 2006	People had at least 10 drusen of size ≥ 125 µm within 3000 µm of FAZ centre; BCVA: 20/40 or more; aged ≥ 50 years (n=1,052 people)	Laser treatment	Observation	Loss of visual acuity (greater than 15 letters or more); change in visual acuity; change in contrast sensitivity; incident of late AMD (CNV, serous PED, geographic atrophy)
CNVPT 2001	People with bilateral or unilateral AMD (bilateral, n=156 people; unilateral, n=120 people)	Laser treatment	Observation of fellow eye	Visual acuity (EDTRS); development of CNV; development of geographic atrophy
DLS 2003	People with bilateral or unilateral AMD (bilateral, n=105 people; unilateral, n=177 people)	Laser treatment	Observation	Proportion of participants who developed CNV; visual acuity
Figueroa 1994	AMD with large confluent soft drusen involving the fovea (n=30 people)	Laser treatment	Observation	Occurrence of CNV, reduction of drusen, visual acuity
Frennesson 1995	People with soft drusen (n=38 people)	Laser treatment	Observation	development of CNV; Snellen VA
Frennesson 2009	People with soft drusen with or without mild pigmentary changes; VA ≥ 0.8 (20/25) in the study eye, aged ≥ 50 years (n=135 people)	Laser treatment	Unspecified control, possibly observation only	Visual acuity, occurrence of CNV
Laser to Drusen Study 1995	People with large drusen in study eye, evidence of late AMD (wet active) in fellow eye (n=99 people)	Laser treatment	Observation Subgroup (laser pattern)	Development of CNV; visual acuity;
Little 1995	People with symmetrical drusen; minimum drusen size 100 µm; at least 20 drusen or 10 drusen + 2 drusen at least 500 µm in diameter; drusen within 500 µm from foveola; VA at least 20/60 (n=27people)	Laser treatment	Observation	Snellen visual acuity

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Study	Population	Intervention	Comparator	Outcomes
Olk 1999	People had a diagnosis of AMD with ≥ 5 large (≥ 63 µm), soft drusen within 2250 µm in both eyes (bilateral study arm) or in 1 eye (unilateral study arm) if the fellow eye had evidence of exudative AMD; and VA of ≥ 20/63 on the ETDRS chart (bilateral, n=77 people; unilateral, n=75 people)	Slit-lamp integrated diode photocoagulator	Observation	Reduction of drusen; development of CNV; visual acuity
PTAMD bilateral 2009	People had BCVA of ≥ 20/63 on the ETDRS chart in both eyes; AMD with ≥ 5 drusen that were ≥ 63 µm in diameter and were located within 2250 µm of the centre of the fovea; unilateral participants must have had 1 eye ineligible due to vision loss that was attributed to advanced AMD (n=639 people)	Single-session of diode laser treatment	Observation	Drusen reduction, development of CNV. VA
PTAMD unilateral 2002	People had BCVA of ≥ 20/63 on the ETDRS chart; AMD with ≥ 5 drusen that were 63 µm in diameter and were located within 2,250 µm of the centre of the fovea; unilateral participants must have had 1 eye ineligible due to vision loss that was attributed to advanced AMD (n=244 people)	Single-session of diode laser treatment	Observation	Drusen reduction, development of CNV. VA

Table 19 Summary of included studies – antioxidant vitamin and mineral supplements for preventing or slowing the progression of AMD

Study	Population	Intervention	Comparator	Outcomes
AMDSG 1996	People with ophthalmic disease and clinically observable drusen, RPE disruption, and loss of macular reflex (n=71 people)	Antioxidant supplements	Placebo	Snellen acuity; near vision M units with dual sided Bailey-Lovie chart; contrast sensitivity; retinal grading score; subjective perception of vision; adverse

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Study	Population	Intervention	Comparator	Outcomes
				gastrointestinal reactions
AREDS 2001	People had 20/32 or better visual acuity in at least one eye; at least one eye free from eye disease that could complicate assessment of AMD (n=3,640 people)	Antioxidants (vitamin C, vitamin E, beta-carotene, and zinc)	Placebo	Progression to advanced AMD; 15 letters or more decrease in visual acuity; reported adverse events
AREDS2 2013	People at high risk of progression to advanced AMD with bilateral large drusen or non-foveal geographic atrophy or large druse or non-foveal geographic atrophy in one eye and advanced AMD in the fellow eye (n=4,203 people)	Lutein/zeaxanthin	Placebo	Progression to advanced AMD in people at moderate to high risk for progression; Progression to moderate vision loss; adverse events; progression of lens opacity or incidence of cataract surgery
Bartlett 2007	People with presentation of ocular pathology in at least 1 eye, or no ocular pathology other than soft hard drusen, and areas of increased or decreased pigment associated with drusen (n=30 people)	Lutein/retinol/ vitamin C/vitamin E, zinc, copper	Placebo	Distance and near Visual Acuity (VA); contrast sensitivity (CS); colour vision; macular Mapping (MM) test; Eger macular stressometer (EMS) used to assess glare recovery; fundus photographs of the macular will be assessed using colour and edge analysis software
Berrow 2013	People with best-corrected distance VA of 0.2 LogMAR or better (for good mfERG central fixation) (n=14 people)	Antioxidant multivitamin	No treatment	multifocal electroretinogram amplitudes and latencies, assessed every 20 weeks for a period of 80 weeks; macular pigment optical density
CARMA 2013	People with any severity of early AMD in one eye and late AMD (wet active or central geographic atrophy) in the fellow eye. The study eye was the eye free of late-stage AMD (n=433 people)	Antioxidant multivitamin	Placebo	Distance visual acuity; retinal visual acuity
CARMIS 2011	People with a diagnosis of late AMD (dry) in at least one	Antioxidant multivitamin	No dietary supplement	Change in BCVA (the number of letters

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Study	Population	Intervention	Comparator	Outcomes
	eye having extensive (as measured by drusen area) intermediate (>= 63 mm, <125 mm) drusen; and at least one large (>=125 mm) drusen or geographic atrophy not involving the centre of the macula (n=145 people)			read on the logMAR chart)
CLEAR 2013	People with AMD grade 0 to 4 in one eye (Rotterdam grading) (n=84 people)	Lutein	Placebo	Visual acuity and MPOD
Huang 2015	People with a diagnosis of early AMD (defined as the presence of soft drusen, presence of retinal pigmentary abnormalities with no signs of late AMD, or both) according to the Age-Related Eye Disease Study System (n=112 people)	Lutein/zeaxanthin	Unspecified in the study	VFQ (Chinese version)
Newsome 1988	People with macular degeneration (clinically visual drusen with varying degrees of pigmentary change with visual acuity in one eye of 20/80 or better) (n=174 people)	Zinc	Placebo	Visual acuity (ETDRS charts), changes in visual pigment; adverse effect of zinc
Stur 1996	People with AMD in one eye and early AMR with visual acuity 20/40 or better in other eye (n=112 people)	Zinc sulphate	Placebo	Visual acuity; contrast sensitivity; incidence of choroidal neovascularisation; progression of disease
VECAT 1999	People with at least 1 eye available for documentation for lens and retina (n=1,204 people)	Vitamin E	Placebo	Development of early AMD
Veterans LAST study 2004	People with late AMD (geographic atrophy) (n=90 people)	Lutein/lutein plus additional antioxidants	Placebo	Macular pigment optical density
Wang 2004	Unknown (n=400 people)	Zinc oxide	Placebo	Not specified

6.2.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of

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3,163 unique references was returned. Two references were retained. Health economic modelling was not prioritised for this review question.

6.2.2.1 Antioxidant vitamin and mineral supplements

Rein et al. (2007) compared the effectiveness of vitamin therapy added to best-supportive care with no vitamin therapy using a computerised, stochastic, agent-based model. The model simulated the progression of AMD using data from the Age-Related Eye Disease Study (AREDS). The treatment effect of vitamin supplements was simulated by modifying by a 25% relative risk reduction of disease progression compared with taking a placebo. Outcomes included costs of routine ophthalmology appointments, treatment, vitamin prophylaxis and nursing home care, and QALYs. Costs and benefits were from the US healthcare service perspective, discounted at a rate of 3% per year. The base-case results are shown in Table 20.

Table 20: Rein et al. (2007) – base-case cost–utility results

	Cost ($US)			Years of VI & blindness	QALYs	ICER ($/QALY)
	AMD	Nursing home	Total			
Conventional treatment	583.41	265.55	848.96	0.26049	15.6221	-
Vitamin therapy	720.87	216.51	937.38	0.22501	15.6263	-
Incremental	137.46	-40.94	88.42	-0.0355	0.004	21,887

The base-case model produces an ICER of $21,887 per QALY gained. Model outputs were most sensitive to the cost of vitamin supplementation and the discount rate. Doubling vitamin costs increased discounted total costs per person by $279, resulting in an ICER of $61,683 per QALY gained. Using the minimum observed prices made vitamin therapy dominant.

6.2.2.2 Zeaxanthin supplementation

Olk et al. (2015) conducted a CUA alongside an interventional comparative study of zeaxanthin supplement versus no supplement alongside triple combination therapy (PDT + bevacizumab + dexamethasone). The study enrolled 424 participants (543 eyes) with wet AMD. Patients were treated initially with the triple therapy. Oral zeaxanthin was added to on the basis of evidence suggesting that it might be effective. All patients also took a multivitamin and an AREDS-I antioxidant regimen.

First-eye treated, second-eye treated and combined-eye models were run over a 9-year timeframe, with a mean patient age at baseline of 81 years. It is assumed that zeaxanthin therapy is used continuously over the 9-year period, and that its observed effectiveness in categorical VA gains continues over that time. Costs include treatment, diagnosis, monitoring and administration, from the US healthcare system perspective. Brown et al. (2003) TTO utilities are used to estimate QALYs, alongside small estimates of disutility due to AEs.

Table 21: Olk et al. (2015) – base-case cost–utility results

Zeaxanthin daily + triple therapy	Incremental cost (compared with triple therapy)	Incremental QALY gain (compared with triple therapy)	ICER ($/QALY)
First-eye treated model	$859	0.115	$7,470
Second-eye treated model	$859	0.253	$3,395
Combined-eye model	$859	0.162	$5,302

The base case ICER is $5,302 per QALY gained. The model was sensitive to assumptions the duration of maintained treatment effect, increasing to $23,892 per QALY gained when zeaxanthin had no benefit after 2 years.

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6.2.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively. All the findings below are against a comparator of either placebo or usual care.

6.2.3.1 Statins for AMD

Low-quality evidence could not differentiate progression of AMD between participants receiving simvastatin and those receiving placebo at 3 years' follow-up (RR 0.78 [95%CI 0.50 to 1.02]; 1 RCT of 114 people).

Low-quality evidence showed a reduction in adverse events for people receiving statins compared with people in the placebo group (RR 0.64 [95%CI 0.39 to 0.92]; 1 RCT of 114 people).

6.2.3.2 Omega 3 fatty acid for preventing or slowing the progression of AMD

Low-quality evidence could not differentiate visual acuity (loss of 3 or more lines) between omega 3 fatty acid and placebo at 3 years' follow-up (RR 1.25 [95%CI 0.69 to 2.26]; 1 RCT of 236 people).

High-quality evidence showed that omega 3 supplements do not slow the progression of AMD at 3–5 years' follow-up (HR 0.96 [95%CI 0.84 to 1.10]; 2 RCTs of 2,343 people).

Low-quality evidence could not differentiate incidence of choroidal neovascularisation between omega 3 fatty acid and placebo at 3 years' follow-up (RR 1.12 [95%CI 0.53 to 2.38]; 1 RCT of 195 people).

High-quality evidence showed there is no difference in the number of adverse events between omega 3 fatty acid and placebo at 3–5 years' follow-up (RR 1.01 [95%CI 0.94 to 1.09]; 2 RCTs of 2,343 people).

6.2.3.3 Laser treatment of drusen to prevent progression to advanced AMD

Moderate-quality evidence with 2–3 years' follow-up could not differentiate between laser photocoagulation and control in progression to late AMD (wet active) (RR 1.03 [95%CI 0.83 to 1.27]; 11 studies of 2,159 people, 3,580 eyes) or late AMD (geographic atrophy) (RR 1.27 [95%CI 0.41 to 3.94]; 2 RCTs of 148 people, 148 eyes).

Moderate-quality evidence showed there is no difference in visual acuity (loss of 2 or 3 more lines) between laser photocoagulation and placebo at 3 years' follow-up (RR 0.99 [95%CI 0.83 to 1.18]; 9 studies of 2,002 people, 3,486 eyes).

Moderate-quality evidence showed people receiving laser photocoagulation were more likely to have drusen reduction than those in control treatment at 1–3 years' follow-up (RR 4.47 [95%CI 1.64 to 12.19]; 3 studies of 570 people, 944 eyes).

6.2.3.4 Antioxidant vitamin and mineral supplements for slowing AMD

6.2.3.4.1 Multivitamin supplement

Moderate-quality evidence showed people taking a multivitamin supplement (antioxidant vitamin plus zinc) were less likely to progress to late AMD (wet active or geographic atrophy) at 6 years' follow-up (RR[5] 0.77 [95%CI 0.67 to 0.89]; 3 studies of 2,410 people).

[5] Estimation of the effect used an odds ratio, which was converted to a relative risk based on the following formulation: RR=OR / (1-probablity of event + probability of event * OR).

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Moderate-quality evidence showed people taking a multivitamin supplement were less likely to progress to late AMD (wet active) at 6 years' follow-up (RR 0.67 [95%CI 0.53 to 0.85]; 1 study of 1,206 people).

Moderate-quality evidence could not differentiate progression to late AMD (geography atrophy) between multivitamin supplements and control at 6 years' follow-up (RR 0.76 [95%CI 0.53 to 1.10]; 1 study of 1,206 people).

Moderate-quality evidence could not demonstrate a meaningful difference in probability of visual loss (3 or more ETDRS lines) between multivitamin supplements and control at 6 years' follow-up (RR 0.83 [95%CI 0.70 to 0.97]; 1 study of 1,807 people).

6.2.3.4.2 Lutein/zeaxanthin supplement

Moderate-quality evidence with 5 years' follow-up could not detect a difference between lutein/zeaxanthin supplements and other supplement formulations (including beta-carotene instead) on preventing progression to late AMD (wet active) (RR 0.92 [95%CI 0.84 to 1.02]; 1 study of 6,891 people) or late AMD (geography atrophy) at 5 years' follow-up (RR 0.92 [95%CI 0.80 to 1.05]; 1 study of 6,891 people).

Moderate-quality evidence could not differentiate visual function score between lutein/zeaxanthin supplements and control at 2 years' follow-up (MD 1.48; [95%CI -5.53 to 8.49]; 1 study of 108 people).

6.2.3.4.3 Zinc supplement

Moderate-quality evidence could not differentiate progression to late AMD (wet active or geographic atrophy) between zinc supplements and control at 2–6 years' follow-up (RR 0.87 [95%CI 0.77 to 0.98]; 2 studies of 3,718 people).

Moderate-quality evidence showed people taking a zinc supplement were less likely to progress to late AMD (wet active) at 6 years' follow-up (RR 0.80 [95%CI 0.67 to 0.94]; 1 study of 3,640 people).

Moderate-quality evidence could not differentiate progression to late AMD (geographic atrophy) between zinc supplements and control 6 years' follow-up (RR 0.85 [95%CI 0.66 to 1.09]; 1 study of 3,640 people).

Moderate-quality evidence showed zinc supplements had no effect on slowing the progression of visual loss (loss of 3 or more lines) at 2–6 years' follow-up (RR 0.90 [95%CI 0.82 to 1.00]; 2 studies of 1,942 people).

6.2.3.5 Health economic evidence

Two partially applicable cost–utility analyses with very serious limitations compared usual care with the addition of antioxidant multivitamin and mineral supplements. One analysis, based on the AREDS study, estimates that vitamin supplements incur an additional cost of $88 per patient and generate 0.004 additional QALYs compared with conventional care, with an ICER of $21,887 per QALY gained. The second analysis reports that zeaxanthin given as a supplement to combination PDT, bevacizumab and dexamethasone costs an additional $859 per patient and generates 0.162 additional QALYs, with an ICER of $5,302 per QALY gained.

6.2.4 Evidence to recommendations

Relative value of different outcomes	All included RCTs presented progression to AMD as a primary outcome. The committee agreed that this is the critical factor in determining the effectiveness of strategies to slow AMD progression. In addition, the included evidence on the use of statins and omega-3 fatty acid reported the incidence of adverse events, which is

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	important in assessing whether harms may attenuate or outweigh benefits. The committee noted that the effect of treatment on risk of disease progression was sometimes expressed as an odds ratio. The committee commented that odd ratios can be difficult to interpret. Therefore, they were converted to relative risks where necessary.
Trade-off between benefits and harms	**Statins** For statins, only 1 study with a high dropout rate was included. However this study did not provide a strong evidence base for the effect of statins on AMD progression. The committee noted that lipids are known to be implicated in the pathogenesis of AMD, but there is a lack of evidence on the association between lipid deposits in AMD and disease progression. **Omega-3 fatty acid** The committee agreed that the presented evidence indicated that omega-3 fatty acid had no meaningful effect on AMD progression and visual acuity, and that therefore no recommendations could be made on this topic. **Laser treatment** The evidence presented demonstrated that laser treatment reduces drusen size; however there was no evidence of an associated effect on AMD progression or vision. The committee agreed that laser treatment is still used in clinical practice, especially to reduce drusen size, but noted that patient-relevant benefits have never been demonstrated. Therefore, the committee agreed by consensus that laser (e.g. argon, diode) should not be offered to treat drusen in people with early AMD. **Antioxidant vitamin and mineral supplements** The committee discussed the possible mechanism of action of antioxidant vitamin and mineral supplements and suggested that this was likely to be due to a reduction of oxidative stress levels that contribute to AMD. The review of the evidence suggested a positive effect of antioxidant vitamin and zinc supplements on slowing progression from early AMD to late AMD (either wet active or dry). The committee was, however, sceptical about the treatment effects reported by the included studies. Its reservations were based on the following reasons: • Firstly the pooled effect of antioxidant vitamins on AMD progression was largely based on the AREDS1 study (assigned approximately 84% of the weight in meta-analysis), and the committee noted that a proportion of participants (20%) had been taking multivitamins containing a supplement supplied via the study protocol prior to enrolment in the study. Therefore, participants were unlikely to be representative of the general population, and the generalisability of the study findings is unknown. • Secondly, the analysis of AMD progression and rate of vision loss was based on a subgroup of study participants, who were at high risk of progressing to advanced AMD (including eyes with intermediate and large drusen or non-central GA and those with visual acuity worse than 6/9.5 with no presence of neovascular features) which suggests that the true effect of slowing AMD progression was likely to have been affected by selection bias. • Finally, although treatment effects were reported in the AREDS trial, there was no evidence showing the same effect in the other included AMD prevention trials. The committee discussed the antioxidant supplementation formulation used in the AREDS studies. In AREDS1 the formulation is a combination of beta carotene, vitamin E and vitamin C. Beta

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	carotene is associated with a possible risk of lung cancer amongst smokers. Additionally the AREDS1 study reported the effect of the combined antioxidant supplementation whilst the effects of each of the formula components on AMD progression are unknown. Therefore based on the available evidence, the committee agreed that it is not possible to conclude whether the treatment benefits of such a formula outweigh the potential risks that could be caused by individual components of the antioxidant supplements. The committee noted that there is no beta carotene in the AREDS2 formula, but due to a complicated study design involving a secondary randomisation protocol, the effect of AREDS2 formulation on AMD disease progression is not clear. Therefore, the committee agreed to make a research recommendation for a large RCT to evaluate the effectiveness of the AREDS2 formula on AMD progression, comparing AREDS2 formula with no treatment (i.e. normal diet).
Consideration of health benefits and resource use	**Antioxidant vitamin and mineral supplements** The committee agreed that it was difficult to relate the 2 US-based cost–utility analyses to the NHS perspective as the pricing and reimbursement structures are widely different. <u>Zeaxanthin supplementation</u> The committee discussed the evidence from the Olk et al. (2015) study and agreed that it was not directly applicable to the question of preventing onward progression of AMD as the mean VA of the cohort was 20/200, indicating significant ocular morbidity. It was also mindful of that the included clinical evidence had not demonstrated a benefit for this form of supplementation. Accordingly, it was implausible that it could provide cost-effective benefits. <u>Antioxidant vitamin and mineral supplements</u> With regard to Rein et al. (2007) the committee was sceptical of the way in which the assumed benefit of the AREDS vitamin supplementation had been parameterised to affect transitions between states reflecting pathological manifestations of early AMD, rather than preventing transitions from those early AMD states to more advanced and visually debilitating states (as per the AREDS trial data). Another key assumption of the analysis is that all patients are identified at standard optometry appointments, and the committee agreed that additional resources may be needed to screen patients for their suitability for vitamin treatment. In spite of these limitations (which, the committee agreed, would tend to overstate the cost effectiveness of supplementation), the intervention was reported to confer an extremely small benefit of only 0.004 additional QALYs compared with standard treatment. The committee considered that, even if 0.004 QALY represents an accurate description of the benefit, the cost effectiveness of supplementation would be very sensitive to the cost of prescribing high-dose vitamin supplements. In the UK, a prescription-only multivitamin supplement based on the AREDS studies has been available since March 2016. MacuLEH Light may be prescribed by a GP only if they are asked to by a consultant, because MacuLEH is not suitable for all AMD patients but only those at a specific stage of AMD. The NHS price in November 2016 is £9.95 for 90 capsules (1 month's supply). This amounts to £120 per year, a cost that – absent of other savings – would need to confer at least 0.006 QALYs in order to be associated with an ICER £20,000/QALY or less. On a balance of these considerations, the committee agreed that it was unlikely to represent good value for money to offer an intervention with an uncertain – but, in any event, limited – effect on people's quality of life. The committee's caution, in this regard, was increased by the large population for which the intervention would

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	potentially be indicated, meaning that the overall resource impact could be significant, even if the cost per person was perceived to be small. **Other interventions (statins; omega-3 fatty acid; laser treatment)** The committee agreed that, as it had seen no evidence that these interventions had meaningful benefits, there was no prospect of them providing good value for money. As laser treatment for drusen is used to some degree in the NHS, some savings may be achievable if the practice is discontinued. However, the major cost associated with such treatment is the acquisition and maintenance cost of the laser device and these costs will not be reduced, as they are still needed for other non-AMD indications.
Quality of evidence	The committee noted that quality of evidence on strategies to slow AMD progression varied widely. **Statins** Only 1 included study (Guymer 2013) examined the effect of statins on AMD progression but was judged to be at high risk of bias due to a significant potential for attrition bias: data were missing for 34/114 (30%) of participants at 3 years follow-up – 20/57 (35%) in the statins groups and 14/57 (25%) in the placebo groups. In addition, 12% (n=7) of participants in the placebo group started taking statins due to an abnormal lipid profile, potentially contaminating treatment effect. **Omega-3 fatty acid** Of the included studies on omega-3 fatty acid, AREDS 2 compared disease progression between people receiving omega-3 fatty acid supplements and control treatment, but the control group participants were given either non-randomised AREDS supplement or were randomly assigned to receive 1 of the 4 variations of AREDS supplement in the secondary randomisation (AREDS supplement: vitamin C (500mg), vitamin E(400IU), beta carotene(15mg), zinc (80mg, as zinc oxide) and cooper (2mg as cupric oxide). **Antioxidant vitamin and mineral supplements** The committee noted that the quality of evidence on antioxidant vitamin and mineral supplements varied. There was some moderate- and high-quality evidence on the effect of multiple vitamins on AMD progression, whilst low- and moderate-quality evidence showed the effect of zinc supplements on AMD progression. Based on GRADE, evidence from the AREDS study was rated as moderate quality, containing some limitations which have been discussed earlier. The committee agreed that these limitations were important and should be taken into account when interpreting the estimated treatment effect. Therefore, the committee agreed that the current clinical evidence was not able to demonstrate a clear treatment benefit of antioxidant vitamin and mineral supplement for people with early AMD and was therefore not sufficient to make a strong recommendation for the use of antioxidant, vitamin and mineral supplements. However the committee agreed that was also insufficient evidence to make a strong recommendation against the use of such supplements. The committee instead agreed to recommend further research in this area. **Laser treatment** Evidence for laser treatment was of moderate quality: it comprised 11 RCTs that were generally judged to be at low risk of bias and had follow-up of up to 3 years. Therefore, the committee had a degree of confidence that any patient-relevant benefits associated with treatment should be evident from the data.

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Other considerations	The committee noted that there was no clinical evidence on the effect of exercise, weight management and smoking cessation on AMD progression. Smoking is generally understood to be an important risk factor that is associated with AMD progression and the committee noted that there is likely to be value in smoking cessation interventions to reduce the risk of AMD progression.

6.2.5 Recommendations

4. **Do not offer thermal laser therapy (for example, argon, diode) for treating drusen in people with early AMD.**

6.2.6 Research recommendations

1. **What is the effectiveness of antioxidant and zinc supplements on AMD disease progression for people with early AMD at high risk of progression in the context of a randomised controlled trial?**

Why this is important

Age-related eye disease study (AREDS 2001) examined the effect of antioxidant supplementation on AMD progression using the ARDES formation, which included beta carotene, vitamin E, vitamin C and zinc. Although the study showed some beneficial effects of the combined antioxidant supplementation in a subgroup of participants, the effects of each of the formula components on AMD progression were unclear. Additionally 1 of the ingredients (beta carotene) in the AREDS 2001 formulation is associated with a possible risk of lung cancer amongst smokers. The AREDS research group introduced a new formulation that excluded beta carotene in the AREDS2 study, but the effect of AREDS2 formulation on AMD disease progression is unknown because of a complicated study design involving secondary randomisation and no placebo control. Therefore, a well conducted randomised trial would provide an evidence base for the benefits and risks of individual components of the antioxidant supplements, and provide the ability to establish the treatment effect of antioxidant supplementation (the AREDS2 formula) on AMD progression by comparing AREDS2 formula with no treatment (for instance normal diet).

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7 Diagnosis

Diagnosing AMD involves differentiating macular aging changes from degenerative abnormalities which threaten, or are affecting vision. In particular the identification of wet AMD is important, as timely and appropriate treatment can save sight. Patients with wet AMD often have symptoms which can alert healthcare professionals to a macular problem rather than non-specific “blurry vision”. Those with the skills and equipment to examine the macula can also find signs suggestive of wet AMD. It is important that these symptoms and signs are recognised as red flags requiring urgent action to enable referral for timely definitive diagnosis and treatment.

However diagnosis of wet AMD does not just involve separating it from dry AMD, as other conditions can have similar signs on the macula as wet AMD and need to be identified. Specialist imaging and its interpretation are required to do this by identifying new blood vessel growth (neovascularisation).

Neovascularisation in or under the macular retina is the hallmark of wet AMD. However AMD is not the only disease which can lead to these new vessels, although it is the most common. Inflammatory, genetic, degenerative and idiopathic diseases of the macula can also lead to neovascularisation but usually in a younger age-group. Therefore it is important to make a positive diagnosis of wet AMD using clinical history, examination and the appropriate ocular imaging tools.

Ocular imaging is a rapidly changing area with intense development in new technologies. It takes time for the interpretation of the images produced by new technologies to become established and for evidence of their benefit and role to emerge.

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7.1 Signs and symptoms of AMD

Review question:

- What signs and symptoms should prompt a healthcare professional to suspect AMD in people presenting to healthcare services?

7.1.1 Evidence review

The aim of this review was to establish what signs and/or symptoms should raise suspicions about AMD in a person presenting to healthcare services. The review focused on identifying studies that fulfilled the conditions specified in Table 22. For full details of the review protocol see Appendix C.

Table 22: PICO table for signs and symptoms

Population	Adults (18 years and older) suspected of having AMD
Index test	Symptoms - development of: • Straight lines appearing crooked (distortion, metamorphopsia) • Painless loss or blurring of central vision • Scotoma • Difficulty reading • Difficulty driving • Difficulty seeing fine detail (such as facial expressions and features and the need for brighter light than previously to read small print.). • Light glare • Loss of (or decreased) contrast sensitivity (the ability to discern between different shades or 'luminances') • Objects appearing smaller than they really are (micropsia) • Delayed dark and light adaption (e.g. difficulty adjusting from bright to dim lighting) • Visual hallucinations (Charles Bonnet syndrome). Signs: • Reduced visual acuity (uniocular) • Breaks, waviness, or missing portions of the lines when looking at graph paper or Amsler grid (metamorphopsia) On fundus examination (handheld diagnostic lens, biomicroscopy, slit lamp fundoscopy,): • Drusen • Pigmentary, exudative, haemorrhagic, or atrophic changes affecting the macula. • Cystoid macular oedema and (rarely) choroidal polyps • Pigment epithelial detachment • Breaks in Bruch's membrane (angioid streaks, lacquer cracks, choroidal splits) • Pseudo-vitelliform degeneration
Reference test	Confirmed diagnosis of AMD • Early AMD or geographic atrophy diagnosis based on colour photos or fundoscopy, • Neovascular AMD diagnosed based on fundus fluorescein angiography (FFA).
Outcomes	Diagnostic accuracy of any one feature or group of features for AMD, neovascular AMD or geographic atrophy: • Accuracy metrics (sensitivity, specificity, likelihood ratios)

Diagnostic cross-sectional evidence was considered to be the highest quality evidence available to answer this question, and studies were excluded if they did not provide sufficient

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data to be able to construct a 2x2 table to evaluate diagnostic accuracy. Papers were also excluded if they:

- were not published in the English language.
- were abstracts, conference proceedings, narrative reviews, case-studies or non-comparative studies.

7.1.1.1 Description of included studies

A systematic search and a hand search of the reference lists of systematic reviews identified 6,766 references. The references were screened on their titles and abstracts and 51 references were ordered for full-text screening.

Fifty studies were subsequently excluded as they did not meet the agreed eligibility criteria. Examples of common reasons for exclusion include non-full text paper (e.g. meeting abstract), study type (e.g. review, editorial), studies not reporting diagnostic outcomes of interest (or where it was not possible to derive diagnostic outcomes from data provided), studies testing the sensitivity or specificity of a specific test and not a clinical feature, and automated computerised diagnosis. A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

None of the identified studies reported the diagnostic accuracy of clinical features found on fundus examination (handheld diagnostic lens, biomicroscopy, slit lamp fundoscopy, ophthalmoscopy). This may be because many of the clinical features of interest (drusen; pigmentary, exudative, haemorrhagic, or atrophic changes affecting the macula; cystoid macular oedema; choroidal polyps; pigment epithelial detachment) are already part of the diagnostic definition of early AMD, indeterminate AMD, late AMD (dry, wet active, wet inactive). As a result, proving the diagnostic accuracy of such features would follow a circular argument.

In total 1 article was included. This study (Hessellund, 2012) reported:

- Diagnostic outcomes for detecting “treatable” neovascular AMD

A summary of included study was provided in Table 23. References of included studies are listed in Appendix I.

Table 23: Included studies for signs and symptoms

Author	Number included	Population	Reference standard	Outcomes reported
Hessellund (2012) [Denmark]	1682 patients	All patients referred to the AMD clinic at the Department of Ophthalmology.	The clinical examination consisted of: • a measurement of visual acuity using ETDRS charts and fundoscopy, to identify central macular oedema, retinal haemorrhages, and exudates. • In all patients, an OCT scan was carried out. • When macular oedema was present, a fluorescein angiography was performed.	Diagnostic accuracy of blurred vision, central dark spot, metamorphopsia, micropsia, and dyschromatopsia symptoms for “treatable” neovascular AMD.

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7.1.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. No references were identified as being relevant to this review question. Health economic modelling was not prioritised for this review question.

7.1.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

7.1.3.1 Signs and symptoms for the diagnosis of choroidal neovascularisation

7.1.3.1.1 Increasing the probability of choroidal neovascularisation

On their own, the presence of the following signs increases the probability that a person has treatable neovascular AMD to a degree that is most likely to be **small**:

- Very low-quality evidence (1 study of 1,683 people):
  - Blurred vision
  - A central dark spot
  - Metamorphopsia
  - Sudden onset vision symptoms
  - Worsening of vision symptoms

On its own, the presence of the following sign increases the probability that a person has treatable neovascular AMD to a degree that is most likely to be **small**; however, at a 95% confidence level, data are also consistent with a **moderate** increase in probability:

- Very low-quality evidence (1 study of 1,683 people):
  - Dyschromatopsia

On its own, the presence of the following sign does not alter the probability that a person has treatable neovascular AMD:

- Very low-quality evidence (1 study of 1,683 people):
  - Micropsia

7.1.3.1.2 Decreasing the probability of choroidal neovascularisation

On their own, the absence of the following signs decreases the probability that a person has treatable neovascular AMD to a degree that is most likely to be **small**:

- Very low-quality evidence (1 study of 1,683 people)
  - Blurred vision
  - A central dark spot
  - Metamorphopsia
  - Dyschromatopsia
  - Sudden onset vision symptoms
  - Worsening of vision symptoms

7.1.3.2 Health economic evidence

No cost–utility analyses were identified that were relevant to signs and symptoms of AMD.

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7.1.4 Evidence to recommendations

Relative value of different outcomes	The committee considered both sensitivity and specificity to be important qualities of any component of the diagnostic process. The focus of this review was the use of clinical features, signs and symptoms to aid the diagnosis of AMD of all types. However, the committee considered it particularly important to be able to identify late AMD (wet active), because this both causes visual loss and can be treated. Although the committee agreed that it is important that the first-line healthcare professional knows the signs and symptoms for any kind of AMD, they recognised that a diagnosis of AMD is not going to be made based upon symptoms alone, but rather by completing an ocular examination of the eye.
Trade-off between benefits and harms	The committee agreed that, in instances of a true positive, referral to appropriate services and appropriate care resulted in decreased risk of blindness due to late AMD (wet active) through earlier initiation of treatment. In instances of true negatives, reassurance and ongoing monitoring by healthcare professionals in the appropriate setting or service would be considered good practice. The consequences of a false negative include delay in treating late AMD (wet active), resulting in an avoidable loss of vision. The consequences of numerous false positives could include an overburdened retinal clinic, needlessly distressed patients, increased waiting times, and poor monitoring of existing patients with neovascular AMD. For this last group of patients, the consequences of an overburdened retinal clinic could result in missed relapses, delayed treatments and loss of vision/blindness. Mindful of these potential consequences for both the patient and the services, the committee was keen to emphasise any signs or symptoms the presence or absence of which were particularly suggestive of AMD (i.e. signs or symptoms with strong positive or negative likelihood ratios). However, the evidence presented did not show a high diagnostic accuracy for any of the symptoms of interest. The committee was therefore keen to stress in the recommendations that diagnosis should not be made on the basis of signs and symptoms alone but that anyone presenting with visual disturbances or changes in vision should receive fundoscopy, a test that is simple to perform and that would more be much more likely to reveal the underlying pathology. Based on the clinical experience and expertise of its members, the committee agreed by consensus that the symptoms of micropsia and metamorphopsia were particularly suggestive of neovascular AMD, and these were referenced in the recommendation. It was noted micropsia, while rare, should be taken seriously, especially if the symptoms were reported voluntarily rather than elicited by the healthcare professional.
Trade-off between net health benefits and resource use	No health economic evidence was found and this review question was not prioritised for health economic modelling. The committee noted that fundoscopy is an inexpensive and simple to perform test, and therefore represented a sensible use of funds, as it is likely to reduce the number of inappropriate referrals to retinal clinics, and therefore be cost-saving compared with referral based on clinical features alone.
Quality of evidence	Only 1 study was included in the review, and the evidence it provided was judged of very low quality for all outcomes. It was at high risk of bias, as it did not report clear information about whether the reference test was reviewed without knowledge of the index test. There was also clear indirectness, since the study only showed how good the symptoms were at indicating ‘treatable’ neovascular AMD,

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	and potential participants were excluded if they had scarring or low visual acuity.
Other considerations	The committee was made aware of some studies on the Amsler grid comparing people with diagnosed AMD with healthy controls. These studies were agreed to be likely to give inflated estimates of specificity. It was also noted that people with diagnosed (as opposed to suspected) AMD were not the population of interest for this question. Therefore, the committee agreed that these studies did not constitute useful evidence and they were excluded from the review. However, the committee noted that Amsler grids are still used in practice, so it agreed a research recommendation should be made to elicit more robust evidence in this area.

7.1.5 Recommendations

5. **Offer fundus examination as part of the ocular examination to people presenting with changes in vision (including micropsia and metamorphopsia) or visual disturbances.**

7.1.6 Research recommendations

2. **What is the diagnostic accuracy of the Amsler chart or other similar tools (digital or otherwise) for AMD?**

Why this is important

Although there was evidence on the accuracy of the Amsler grid for diagnosing AMD, the quality of evidence available to make recommendations as part of this guideline was low, due to the use of case-control study designs comparing people with an existing diagnosis of AMD with healthy individuals. This is not the optimal approach to validate a diagnostic tool, as it is not calculating diagnostic accuracy in the population of interest, those suspected of having the condition. It was agreed that as Amsler grids are still used in practice (for instance in general practice) for diagnosing people suspected of having AMD, and therefore future research on the diagnostic accuracy of the Amsler grid would enable an evaluation of how well the grid performs in people with suspected AMD ,who would been excluded from case-control studies. The optimal study design for this question would be a cohort or cross-sectional study of people presenting with suspected AMD.

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7.2 Tools for triage, diagnosis and informed treatment

Review questions:

- What tools are useful for triage, diagnosis, informing treatment and determining management in people with suspected AMD?

7.2.1 Evidence review

The aim of this review was to establish the risks, benefits and accuracy of tools to assess and diagnose early AMD and late AMD including dry and wet active. The review focused on identifying studies that fulfilled the conditions specified in Table 24. For full details of the review protocol see Appendix C.

Table 24: PICO table – diagnostic tools for people with AMD

Population	Adults (18 years and older) with suspected AMD including early, indeterminate and late AMD		
	For diagnosing early AMD	**For diagnosing geographic atrophy**	**For diagnosing late AMD (wet)**
Index text	• Focus fundoscopy (slit-lamp fundoscopy, biomicroscopy)	• Focus fundoscopy (slit-lamp fundoscopy, biomicroscopy) • Fundus fluorescein angiography (FFA) • Indocyanine green angiography (ICG) • Fundus autofluorescence	• Focus fundoscopy (slit-lamp fundoscopy, biomicroscopy) • Optical coherence tomography (OCT) • ICG • Fundus autofluorescence
Reference standard	OCT	OCT	FFA for classic and mixed ICG angiography for occult and polyps OCT for PED
Outcomes	Accuracy of diagnostic tests including sensitivity, specificity, positive likelihood ratios and negative likelihood ratios		

Diagnostic cross-sectional evidence was considered to be the highest quality evidence available to answer this question, and studies were excluded if they did not provide sufficient data to be able to construct a 2x2 table to evaluate diagnostic accuracy. Papers were also excluded if they:

- were not published in the English language
- did not report diagnostic accuracy outcomes
- were abstracts, conference proceedings, guideline, report, narrative reviews

7.2.1.1 Description of included studies

A systematic search identified 9,859 references. The references were screened on their titles and abstracts and 175 references were ordered for full text review. A total of 15 studies were included in the final review. There were 2 systematic reviews identified in the search but there was no new evidence added to the evidence. For the list of excluded studies with reasons, see Appendix F. An update search carried out near the end of guideline development identified 2 further studies.

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A brief summary of included studies was provided in Table 25. References of included studies are listed in Appendix I.

Table 25 Summary of included studies

Study	Study population	Diagnostic test	Reference test	Outcome
Cachulo L et al. 2011	Patients with neovascular AMD in the non-study eye and early AMD in the study eye at risk of developing CNV (n=62 people)	Indocyanine green angiography (ICG); Fundus autofluorescence; OCT; Imagining and retinal leakage analysis	FFA	The reliability and relative value of different clinical methodologies used to identify AMD disease progression
Cheung et al. 2015	Patients represented with untreated AMD or polypoidal choroidal vasculopathy (n=230 people)	ICG (modified criteria in detecting polypoidal choroidal vasculopathy)		The comparison of diagnostic accuracy between a single sign of “subretinal focal hyperfluorescences” on IGA and a modified criteria
Cheung et al 2016	Patients with typical AMD or polypoidal choroidal vasculopathy (n=86 eyes)	OCT-A	ICG	Agreement between OCT-A and ICGA in characterising PCV
De Carlo,T.E. et al. 2015	Patients with choroidal neovascularisation (n=61 people)	OCT-A	FFA	The sensitivity and specificity of detection choroidal neovascularisation using OCT-A
De Salvo et al. 2014	Patients have 1 or more pigment epithelial detachment (PEDs) in at least 1 eye (n=44 people)	Spectral-Domain OCT (SD-OCT)	ICG	The accuracy of spectral-domain OCT in detecting idiopathic polypoidal choroidal vasculopathy (PCV)
Do D V et al. 2012	Patients had neovascular AMD in 1 eye (the non-study eye) (n=89 people)	OCT	FFA	The sensitivity of time domain OCT in detecting conversion to neovascular AMD in eyes at high risk of choroidal neovascularisation
Gong et al 2016	Patients with maculopathy (n=53 people, 86 eyes)	OCT-A	FFA	The accuracy of OCT-A for the diagnosis of late AMD (wet active)
Maberley et al. 2005	Patients were referred by general ophthalmologists with a diagnosis of AMD (n=74 eyes)	Fundus photograph	FFA	The diagnostic accuracy of colour fundus photographs for identifying patients with potentially treatable neovascular AMD
Mathew R et al. 2014	Patients initiated on ranibizumab	SD-OCT	FFA	The sensitivity and specificity of SD-OCT

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Study	Study population	Diagnostic test	Reference test	Outcome
	therapy for neovascular AMD (n=130 people)			in the determination of CNV subtypes in neovascular AMD
Mokwa N et al. 2013	Patients with early, intermediate or later AMD as well as control cases who with no sign of AMD (n=66 people, 120 eyes)	Spectral-Domain OCT (SD-OCT) FFA Fundus photographs	Fundus photographs (AMD) FFA (CNV)	The comparison of diagnostic accuracy between FP, FFA and SDOCT in detecting AMD and CNV.
Lim et al. 2002	Patients had diagnosis of AMD (n=17 people)	Fundus photograph (digital)	Fundus photograph (film)	The comparison of diagnostic accuracy between non-mydriatic digitised images and 35mm slide images for detecting AMD
Padnick-Silver L et al. 2012	Patients with bilateral AMD, who had developed unilateral exudative changes (n=79 people)	OCT	FFA	The diagnostic accuracy of OCT to detect early choroidal neovascularisation in AMD
Pirbhai A et al. 2004	Patients were seen in the AMD screening clinic at the Ivey Eye institute in London (n=118 people, 236 eyes)	Fundus photograph	Clinical assessment (including review of FFAs)	The comparison of diagnostic accuracy between fundus photographs and clinical assessment in identifying exudative AMD
Sallet G et al. 1996	Patients with AMD presenting with pigment epithelial detachment without classic CNV on FFA (n=52 people, 58 eyes)	ICG	FFA	The diagnostic accuracy of ICG for the detection of choroidal neovascularisation
Sandhu S and Talks 2005	Patients with suspected choroidal neovascularisation (n=118 people, 131 eyes)	OCT	FFA	The diagnostic accuracy of OCT with/without colour fundus photograph in predicting patients with suspected CNV
Talks et al. 2007	Patients were referred with wet AMD (n=111 people)	OCT	FFA/ ICG	The diagnostic accuracy of OCT for new AMD
Wilde et al. 2015	Patients over 50 years of age that were referred for suspected neovascular AMD (n=411 people, 822 eyes)	SD-OCT	FFA	The diagnostic accuracy of spectral-domain OCT for neovascular AMD

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7.2.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD. A total of 3,163 unique references was retrieved, of which 1 was included for this question. This review question was not prioritised for health economic modelling.

Mowatt et al. (2014) evaluated the cost effectiveness of a range of organisational models for diagnosing and monitoring wet AMD. Diagnostic strategies used fundus fluorescein angiography (FFA), optical coherence tomography (OCT), visual acuity (VA) and slit-lamp biomicroscopy (SLB), interpreted by ophthalmologists. Monitoring strategies were: ophthalmologist interpretation of either OCT alone or VA with SLB and OCT, and nurse- or technician-led OCT and VA with referral to an ophthalmologist for positive or unclear assessments. The third monitoring strategy was included to represent a 'virtual clinic'.

A Markov model was developed, with active/inactive and treated/untreated disease health states, five underlying VA-related states, and a dead state, for the treatment of AMD in one eye. A lifetime horizon was used, with costs and QALYs discounted at 3.5%. Diagnostic accuracy inputs were from a systematic review and expert opinion. Treatment was monthly ranibizumab, with effectiveness derived from the MARINA (Rosenfeld et al., 2006), CATT (Martin et al., 2012) and IVAN (Chakravarthy et al., 2012) studies. Health state utilities were obtained from Brown et al. (2000, 2007). Unit costs were from routine NHS/PSS sources.

The least costly organisational model is diagnosis using FFA followed by nurse or technician-led monitoring (Table 26). Diagnosis based on FFA only, followed by ophthalmologist-led monitoring has higher total expected QALYs. However, the strategy is also associated with additional costs, with an incremental cost per QALY gained (ICER) of nearly £50,000. All other strategies were dominated (both more expensive total costs and less total QALYs) by at least 1 other option. At a threshold of £20,000 per QALY, FFA and nurse- or technician-led monitoring has a 57.4% chance of being the optimal organisational model. The next most cost-effective option, FFA and ophthalmologist monitoring, has a 21.8% probability of being optimal at the same threshold.

Table 26: Mowatt et al. (2014) – base-case model results

	Absolute		Incremental		
Strategy	**Cost (£)**	**Effects (QALYs)**	**Cost (£)**	**Effects (QALYs)**	**ICER (£/QALY)**
FFA & Nurse/technician	39,769	10.473	-	-	-
Ophthalmologist & Nurse/technician	39,790	10.472	21	-0.001	Dominated
OCT & Nurse/technician	41,607	10.465	1838	-0.008	Dominated
FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	Dominated
OCT & Ophthalmologist	47,131	10.567	2482	-0.008	Dominated
FFA & OCT	62,759	10.449	18,110	-0.126	Dominated
Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	Dominated
OCT & OCT	67,421	10.442	22,772	-0.133	Dominated

NB: Incremental values compared to last non-dominated treatment option

Fundus photography was not explicitly included in the analysis by Mowatt et al. It is considered to be a quick procedure that can be conducted at a routine ophthalmology outpatient clinic visit, such that the resource impact of conducting fundus photography is likely to be small. The relevant NHS reference cost (2014–15), for digital retinal photography, is £116.99.

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7.2.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

7.2.3.1 Diagnostic tools for diagnosing early AMD

7.2.3.1.1 Confirming early AMD

Very low-quality evidence from 1 study of 17 people (33 eyes) shows that signs of drusen found on digital fundus imaging raise the probability that early AMD would be detected on film fundus imaging to a **very large** degree; however, at a 95% confidence level, data are also consistent with a **small** increase in probability.

Low-quality evidence from 1 study of 66 people (120 eyes) shows that the signs of greater than 10 small (≤63micrometres) hard drusen and pigmentary changes or at least 1 intermediate (64-124 micrometres) or large (≥125micrometres) drusen inside the 6mm ETDRS grid found on OCT raises the probability that AMD would be detected on fundus photograph to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **large** increase in probability.

Very low-quality evidence from 1 study of 66 people (120 eyes) shows that the signs of greater than 10 small (≤63micrometres) hard drusen and pigmentary changes or at least 1 intermediate (64-124 micrometres) or large (≥125micrometres) drusen inside the 6mm ETDRS grid found on FFA raises the probability that AMD would be detected on fundus photograph to a **large** degree.

7.2.3.1.2 Excluding early AMD

Very low-quality evidence from 1 study of 17 people (33 eyes) shows the absence of drusen found on digital fundus imaging decreases the probability that early AMD would be detected on film fundus imaging to a **small** degree; however, at a 95% confidence level, data are also consistent with a **large** decrease or **small** increase in probability.

Low-quality evidence from 1 study of 66 people (120 eyes) shows that the absence of signs of greater than 10 small (≤63micrometres) hard drusen and pigmentary changes or at least 1 intermediate (64-124 micrometres) or large (≥125micrometres) drusen inside the 6mm ETDRS grid found on OCT decreases the probability that AMD would be detected on fundus photograph to a **large** degree; however, at a 95% confidence level, data are also consistent with a **very large** or **moderate** decrease in probability.

Very low-quality evidence from 1 study of 66 people (120 eyes) shows that the absence of signs of AMD with greater than 10 small (≤63micrometres) hard drusen and pigmentary changes or at least 1 intermediate (64-124 micrometres) or large (≥125micrometres) drusen inside the 6mm ETDRS grid found on FFA decreases the probability that AMD would be detected on fundus photograph to a **large** degree; at a 95% confidence level, data are also consistent with a **very large** decrease in probability.

7.2.3.2 Diagnostic tools for diagnosing geographic atrophy

7.2.3.2.1 Confirming dry AMD

Low-quality evidence from 1 study of 118 people (223 eyes) shows that the signs of dry AMD found on fundus photography raises the probability that dry AMD would be detected by clinical assessment to a **large** degree.

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7.2.3.2.2 Excluding dry AMD

Very low-quality evidence from 1 study of 118 people (223 eyes) shows that the absence of signs of dry AMD found on fundus photography decreases the probability that dry AMD would be detected by clinical assessment to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small** decrease in probability.

7.2.3.3 Diagnostic tools for diagnosing late AMD (wet active)

7.2.3.3.1 Confirming late AMD (wet active)/choroidal neovascularisation

Low-quality evidence from 4 retrospective studies of 759 people (854 eyes) shows that the signs of choroidal neovascularisation found on OCT raises the probability that late AMD (wet active) would be detected by FFA to a **large** degree; however, at a 95% confidence level, data are also consistent with a **moderate or very large** increase in probability.

Very-low quality evidence from 3 prospective studies of 282 people (295 eyes) shows that shows that the signs of choroidal neovascularisation found on OCT raises the probability that late AMD (wet active) would be detected by FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small or large** increase in probability.

Low-quality evidence from 1 study of 24 people (30 eyes) shows that the signs of choroidal neovascularisation found on OCT-A raises the probability that late AMD (wet active) would be detected by FFA to a **large** degree; however, at a 95% confidence level, data are also consistent with a **small** or **very large** increase in probability.

Moderate-quality evidence from 1 study of 53 people (86 eyes) shows that the signs of late AMD (wet active) found on OCT-A raises the probability that late AMD (wet active) would be detected by FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **large** increase in probability.

Moderate-quality evidence from 1 prospective study of 40 people (74 eyes) shows that the signs of late AMD (wet active) found on fundus photography raises the probability that late AMD (wet active) would be detected by FFA to a **large** degree; however, at a 95% confidence level, data are also consistent with a **moderate** or **very large** increase in probability.

Low-quality evidence from 1 retrospective study of 66 people (120 eyes) shows that the signs of late AMD (wet active) found on fundus photography raises the probability that late AMD (wet active) would be detected by FFA to a **very large** degree.

Moderate-quality evidence from 1 study of 40 people (74 eyes) shows that the signs of late AMD (wet active) found on fundus photography raises the probability that late AMD (wet active) would be detected by FFA combined with clinical information to a **large** degree; however, at a 95% confidence level, data are also consistent with a **moderate** increase in probability.

Moderate-quality evidence from 1 study of 118 people (223 eyes) shows that the signs of late AMD (wet active) found on fundus photography raises the probability that late AMD (wet active) would be detected by clinical assessment to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **large** increase in probability.

Very-low quality evidence from 1 study of 17 people (33 eyes) shows that the signs of late AMD (wet active) found on digital fundus imaging raises the probability that late AMD (wet active) would be detected on film fundus imaging to a **large** degree; however, at a 95% confidence level, data are also consistent with a **very large** increase or small decrease in probability.

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Low-quality evidence from 1 study of 52 people (58 eyes) shows that the signs of late AMD (wet active) found on fundus autofluorescence raises the probability that late AMD (wet active) would be detected by FFA to a **very large** degree; however, at a 95% confidence level, data are also consistent with a **moderate** increase in probability.

Very-low quality evidence from 2 studies of 104 people (110 eyes) shows that the signs of choroidal neovascularisation found on indocyanine green angiography (ICG) raises the probability that late AMD (wet active) would be detected by FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small** or **large** increase in probability.

7.2.3.3.2 Excluding late AMD (wet active)

Low-quality evidence from 4 retrospective studies of 759 people (854 eyes) shows that the absence of signs of choroidal neovascularisation found on OCT decreases the probability that late AMD (wet active) would be detected by FFA to a **very large** degree; however, at a 95% confidence level, data are also consistent with a **moderate** decrease in probability.

Very-low quality evidence from 3 prospective studies of 282 people (295 eyes) shows that the absence of signs of choroidal neovascularisation found on OCT decrease the probability that late AMD (wet active) would be detected by FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small** or **very large** decrease in probability.

Low-quality evidence from 1 study of 24 people (30 eyes) shows that the absence of signs of choroidal neovascularisation found on OCT-A decreases the probability that late AMD (wet active) would be detected by FFA to a **small** degree; however, at a 95% confidence level, data are also consistent with a **moderate** decrease or **small** increase in probability.

Moderate-quality of evidence from 1 study of 53 people (86 eyes) shows that the absence of signs of late AMD (wet active) found on OCT-A decreases the probability that late AMD (wet active) would be detected by FFA to a small degree; however, at a 95% confidence level, data are also consistent with a moderate decrease or small increase in probability.

Moderate-quality evidence from 1 prospective study of 40 people (74 eyes) shows that the absence of signs of late AMD (wet active) found on fundus photography decreases the probability that late AMD (wet active) would be detected by FFA to **large** degree; however, at a 95% confidence level, data are also consistent with a **moderate** decrease in probability.

Low-quality evidence from 1 retrospective study of 66 people (120 eyes) shows that the absence of signs of late AMD (wet active) found on fundus photography decreases the probability that late AMD (wet active) would be detected by FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **large** decrease in probability.

Moderate-quality evidence from 1 study of 40 people (74 eyes) shows that the absence of signs of late AMD (wet active) found on fundus photography decreases the probability that late AMD (wet active) would be detected by FFA combined with clinical information to a **very large** degree; however, at a 95% confidence level, data are also consistent with a **moderate** decrease in probability.

Moderate-quality evidence from 1 study of 118 people (223 eyes) shows that the absence of signs of late AMD (wet active) found on fundus photography decreases the probability that late AMD (wet active) would be detected by clinical assessment to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **large** decrease in probability.

Very-low quality evidence from 1 study of 17 people (33 eyes) shows that the absence of signs of late AMD (wet active) found on digital fundus imaging decreases the probability that

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late AMD (wet active) would be detected on film fundus imaging to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small** decrease in probability.

Low-quality evidence from 1 study of 52 people (58 eyes) shows that the absence of signs of late AMD (wet active) found on fundus autofluorescence decreases the probability that late AMD (wet active) would be detected by FFA to a **large** degree; however, at a 95% confidence level, data are also consistent with a **very large** or **moderate** decrease in probability.

Very-low quality evidence from 2 studies of 104 people (110 eyes) shows that the absence of signs of choroidal neovascularisation found on ICG decreases the probability that late AMD (wet active) would be detected by FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small** decrease in probability.

7.2.3.4 Diagnostic tools for diagnosing polypoidal choroidal vasculopathy

7.2.3.4.1 Confirming polypoidal choroidal vasculopathy (PCV)

Low-quality evidence from 1 study of 44 people (51 eyes) shows that the signs of PCV found on OCT raises the probability that PCV would be detected by ICG to a **very large** degree; however, at a 95% confidence level, data are also consistent with a **small** increase in probability.

Low-quality evidence from 1 study of 86 eyes shows that the signs of PCV found on OCT-A raises the probability that PCV would be detected by ICG to a **moderate** degree.

Low-quality evidence from 1 study of 230 people (241 eyes) shows that the signs of PCV found on flash fundus camera-based ICG raises the probability that PCV would be detected by confocal scanning laser ophthalmoscope-based ICG to a **large** degree; however, at a 95% confidence level, data are also consistent with a **moderate or very large** increase in probability.

Moderate-quality evidence from 1 study of 118 people (223 eyes) shows that the signs of PCV found on fundus photography raises the probability that PCV would be detected by clinical assessment to a **large** degree; however, at a 95% confidence level, data are also consistent with a **moderate** increase in probability.

7.2.3.4.2 Excluding polypoidal choroidal vasculopathy (PCV)

Low-quality evidence from 1 study of 44 people (51 eyes) shows that the absence of signs of PCV found on OCT decreases the probability that PCV would be detected by ICG to a **very large** degree; however, at a 95% confidence level, data are also consistent with a **moderate** decrease in probability.

Low-quality evidence from 1 study of 86 eyes shows that the absence of signs of PCV found on OCT-A decreases the probability that PCV would be detected by ICG to a **slight** degree.

Low-quality evidence from 1 study of 230 people (241 eyes) shows that the absence of signs of PCV found on flash fundus camera-based ICG decreases the probability that PCV would be detected by confocal scanning laser ophthalmoscope-based ICG to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **large** decrease in probability.

Moderate-quality evidence from 1 study of 118 people (223 eyes) shows that the absence of signs of PCV found on fundus photography decreases the probability that PCV would be detected by clinical assessment to a **large** degree; however, at a 95% confidence level, data are also consistent with a **very large** or **moderate** decrease in probability.

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7.2.3.5 Diagnostic tools for diagnosing pigment epithelial detachment

7.2.3.5.1 Confirming pigment epithelial detachment

Low-quality evidence from 1 study of 118 people (223 eyes) shows that the signs of pigment epithelial detachment (PED) found fundus photography raises the probability that PED would be detected by clinical assessment to a **large** degree; however, at a 95% confidence level, data are also consistent with a **moderate or very large** increase in probability.

Very low-quality evidence from 1 study of 17 people (33 eyes) shows that the signs of PED found digital fundus imaging raises the probability that PED would be detected by film fundus imaging to a **very large** degree; however, at a 95% confidence level, data are also consistent with a **small** increase in probability.

7.2.3.5.2 Excluding pigment epithelial detachment

Low-quality evidence from 1 study of 118 people (223 eyes) shows that the absence of signs of pigment epithelial detachment (PED) found fundus photography decreases the probability that PED would be detected by clinical assessment to a **small** degree; however, at a 95% confidence level, data are also consistent with a **moderate** decrease in probability.

Very low-quality evidence from 1 study of 17 people (33 eyes) shows that the absence of signs of PED found digital fundus imaging decreases the probability that PED would be detected by film fundus imaging to a **small** degree; however, at a 95% confidence level, data are also consistent with a **moderate** decrease or a **small** increase in probability.

7.2.3.6 Health economic evidence

One directly applicable single-eye cost–utility analysis with potentially serious limitations suggests that a strategy of FFA diagnosis and subsequent nurse-led monitoring dominates (is less costly and generates more QALYs than) all other strategies, except those with ophthalmologist-led monitoring, which have ICERs in excess of £47,000 per QALY gained. At a threshold of £20,000 per QALY, FFA and nurse-led monitoring has a 57.4% chance of being the optimal strategy.

7.2.4 Evidence to recommendations

Relative value of different outcomes	The guideline committee agreed that diagnostic accuracy data (expressed as likelihood ratios and/or sensitivity and specificity) provide the critical outcomes to inform recommendations on tools to assess and confirm diagnosis of AMD. The committee agreed that the included studies captured the diagnostic tools that are commonly used in NHS practice; however, none of these diagnostic tests is optimally accurate – that is, no test is good enough to be used on its own to confirm a diagnosis of AMD, and differentiate different types of AMD, in all cases (as different tests are better at picking up different pathological features). The committee noted that the diagnosis of any AMD is commonly made based on a combination of clinical examination and diagnostic tools. In clinical practice, the current gold standard for diagnosis of early AMD is based on a person's symptoms combined with clinical examination, which may begin in the community (for example, slit-lamp biomicroscopy by an optometrist). While OCT is often used alongside clinical examination to detect fluid swelling of the retina in people's eyes, and thereby raise the suspicion of neovascular AMD, current practice is to use FFA to confirm the diagnosis and inform treatment options.
Trade-off between benefits and harms	Regarding the diagnostic accuracy of the included diagnostic tools, the committee considered that, in instances of a true positive, accurate detection of people with AMD enabled referral to

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appropriate services and care which, in turn, results in an increased possibility of maintaining or improving visual acuity through prompt initiation of treatment. In instances of true negatives, reassurance and continued monitoring by healthcare professionals in appropriate settings or services would be considered appropriate practice.

The committee discussed the consequences of a false negative including an increased possibility of developing a treatable late AMD (wet active) that is not diagnosed soon enough and thereby resulting in an avoidable deterioration in the individuals' visual function and quality of life. The consequences of numerous false positives could include inappropriate use of expensive treatments, overloaded retinal clinics, needlessly distressed patients, increased waiting times and poor monitoring of existing patients with late AMD (wet active). Further, the consequences of an overloaded retinal clinic could be delayed treatment for those with confirmed late AMD (wet active).

Committee members used their clinical experience and expertise to consider the potential consequences for both patients and services associated with different diagnosis strategies. The committee agreed by consensus that clinical examination, including slit lamp biomicroscopy, should be used as the first-line diagnostic strategy when people present with any signs or symptoms of AMD.

Early AMD

The committee noted that only 3 studies examined the diagnostic accuracy of retinal imaging findings in detecting early AMD, with the specificity ranging from 50% to 92%, and there was no evidence that the use of tests such as fundus photography, OCT and FFA provided meaningful improvements in the diagnostic accuracy of early stage of AMD. Consequently, the committee agreed that those with early AMD but no apparent symptoms should be observed/monitored using services that are available in the community rather than being referred to hospital eye services for diagnostic tests such as OCT or FFA.

Late AMD

<u>Late AMD (wet active)</u>

The committee discussed and agreed that the primary benefit of OCT is that it is a non-invasive procedure, whilst FFA involves dye injection, and patients often report feelings of nausea, a general unpleasant feeling or skin rash following the injection. In some rare instances, people may experience an acute allergic reaction to the dye (anaphylaxis), which may even be fatal, though there are very few reports of this happening.

The included evidence confirmed the committee's expectation that, when compared with FFA, OCT has excellent sensitivity for the diagnosis of late AMD (wet active) – that is, it misses very few cases (false-negative diagnoses) – but it is insufficiently specific to be used as a single test – that is, it produces an excess of false-positive findings. In particular, the committee noted that the largest, most recent, UK-based study to compare OCT with FFA (Wilde et al., 2015) found only one false-negative diagnosis (a sensitivity of over 99%), but was subject to a false-positive rate of around 1-in-5 (specificity of 81%). The committee agreed that these findings provided good validation of the current common practice of using OCT as a non-invasive first-line investigation, to rule out cases that do not have late AMD (wet active), and identify those that require FFA to confirm a positive diagnosis.

The committee also noted that the inclusion criteria of RCTs of antiangiogenic therapies for late AMD (wet active) invariably required neovascularisation to be demonstrated on FFA; therefore, it was

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	sensible that access to those treatments in the NHS should reflect this requirement. Bringing these considerations together, the committee recommended that, if the patient is symptomatic, or late AMD (wet active) cannot be excluded, OCT should be undertaken to identify retinal features of AMD such as drusen, fluid, and retinal disruption. Then, if late AMD (wet active) cannot be excluded after the OCT, FFA should be used to confirm the diagnosis. Polypoidal choroidal vasculopathy(PCV) The committee discussed ICG as a diagnostic tool, noting that it has become more widely available, and that it is most commonly used for identifying polypoidal choroidal vasculopathy (PCV; 'polyps'), which is a subtype of late AMD (wet active). Like FFA, it is an invasive procedure that involves systemic injection of dye; however, the committee's experience is that fewer adverse reactions tend to be reported compared with FFA. ICG dye is more expensive than fluorescein. In addition, the committee indicated that ICG, in some practices, has not just been used to diagnose PCV but also to help guide treatment with the use of ICG-guided therapy for PCV. However, the committee also noted that there are currently no clinically-proven treatments that target PCV in particular (see sections 10.3 and 10.4). Therefore, the committee suggested that the evidence it had reviewed did not support the routine use of ICG angiography throughout the NHS. However, the committee expressed the view that PCV may well be amenable to targeted therapy in future. Therefore, it is important that the NHS should maintain the capacity to offer and interpret ICGs, and more research efforts are needed to establish the diagnostic accuracy of the technique. To this end, the committee agreed a research recommendation specifying the ideal form of such investigations. OCT-A Three small studies provided low- to moderate-quality evidence on the accuracy of OCT-A, suggesting that it is no better than OCT for detecting late AMD (wet) and lacks sensitivity when compared with FFA or ICG. However, the committee was mindful that some clinicians are rapidly gaining experience with this relatively new technology and that, as a non-invasive approach that has the potential to reduce the need for FFA and/or ICG, it would be desirable to recommend more research into its accuracy. Late AMD (dry) Currently there is no treatment for people with late AMD (dry), but the committee noted that people with late AMD (dry) may also develop late AMD (wet active). Therefore, if new visual symptoms develop, it would be appropriate to consider referring people to hospital eye services to further investigation, and a re-examination of their diagnosis.
Consideration of health benefits and resource use	The committee considered that the modelled cohort in the included CUA had some characteristics that are not representative of the group's clinical experience. In particular, the committee considered 6/24 as an upper bound for presenting VA as an unrealistic assumption, given that many patients will present with greater loss of vision. The expert assumption that 10% of patients will receive FFA was also considered to be conservative and, although the committee were unable to provide a precise alternative figure, it was agreed that this would underestimate the total cost of FFA. The model assumes that all patients who are diagnosed with late AMD (wet active) will receive monthly treatment with ranibizumab; the effectiveness data for this treatment strategy is modelled from the MARINA trial which the committee emphasised only included patients with occult

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	neovascularisation and may therefore underestimate the true effectiveness in this cohort. The committee considered that inclusion of the results from ANCHOR (which included patients with classic neovascularisation) and IVAN (year 2 results now published) would provide a better estimate of anti-VEGF treatment effectiveness. The committee also considered that the cost of treatment in the model did not reflect the patient access scheme pricing for ranibizumab, and that the model could have considered alternative treatment costs scenario analyses in addition to the extreme £50 scenario. The parameterised diagnostic accuracy of OCT was also considered to be a likely underestimate of the current state-of-the-art as image resolution has improved considerably in the time since the studies included in the authors' systematic review were published. On examining the diagnostic accuracy parameters, the committee agreed it was a weakness of the model that a systematic review was undertaken to establish sensitivity and specificity ranges for OCT, but that the 'Ophthalmologist' diagnostic strategy, which includes OCT, is based entirely on expert opinion. Based on this in addition to the assumption of perfect information for FFA, the committee felt that the model could be systematically biased against OCT. The committee also agreed that important differences between the invasiveness of FFA and OCT had not been accounted for in the model (see 'trade-off between benefit and harms', above). Although the cost and QALY differences incurred may be small when averaged out over the cohort if the model incorporated these adverse events, the committee noted that the incremental analysis suggests predominantly small differences in disaggregated costs and QALYs between strategies, and that the inclusion of FFA's potential harms could therefore change the model results to be more favourable to strategies containing OCT. Although the committee understood that the model is based on a cohort of patients entering secondary care with a clinical suspicion of late AMD (wet active), it agreed that a recommendation of FFA testing for all patients with suspected late AMD (wet active) would have a significant resource impact on hospital eye-clinics and that the health economic model did not provide compelling evidence to alter that view. For this reason, and because of the concerns outlined above, the committee agreed that the correct role for FFA was to confirm a diagnosis of late AMD (wet active) in cases where neovascular disease cannot be ruled out by OCT.
Quality of evidence	The committee considered that the studies in this review were of poor quality. There are 3 main limitations of the evidence. Firstly, a number of studies were relatively old (up to 10 years), in the context of extremely rapid technological improvement. For instance, 1 study compared digitised fundus imaging with film imaging using fundus photography, whilst film imaging is no longer used in clinical practice. Therefore this evidence added little value to the review. Also some data reported in earlier OCT studies may not accurately reflect the true sensitivity and specificity of current OCT tests. Secondly, all the evidence presented in the review included people who were already under hospital care, and there was no evidence on diagnostic tools for those people who present with suspected AMD before they are referred to secondary care. Therefore, there is a gap in the evidence to identify the accuracy of diagnostic tools applied in this population. Thirdly, included studies examined the accuracy of diagnostic tools against a range of different standard references, and none of studies for detecting early AMD and geographic atrophy used the standard reference (OCT) proposed in original review protocol. Therefore a lack of consistency of comparison between index tests and comparators made it difficult to draw robust conclusions about diagnostic accuracy.

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	The committee discussed the difficulty of obtaining high-quality evidence for diagnostic tools, and several factors that may affect quality of evidence. Firstly, the diagnosis itself bears a lot of uncertainties as discussed earlier. In practice, a final diagnosis is arrived at by clinicians based on clinical assessment and multiple relevant investigations; this process is difficult to replicate in a research setting, in which a single determination of each participant's 'true' status is required. Secondly, published diagnostic studies tend to be relatively small series comprising data collected by research hospitals, and the much more extensive data held by reading centres tend not to be available for research for commercial reasons. The committee discussed that only 2 small studies reported the accuracy of OCT angiography, which is a recently developed, non-invasive imaging technique that may be valuable in confirming a diagnosis of late AMD (wet active) without the use of intravenous dye. Against FFA as a reference standard, these studies reported sensitivity of 50% and 86.5%, which is worse than for conventional OCT. Nevertheless, the committee noted that these were early results from small studies, and agreed that further diagnostic studies of OCT angiography will be valuable to assess its accuracy for diagnosing AMD.
Other considerations	The committee discussed the lack of evidence for the diagnostic accuracy of investigations for early AMD and geographic atrophy. This was understandable since retinal imaging were not often used to make a diagnosis. This may echo the committee's early comments about the study populations in the included evidence. Therefore it would be unlikely to find such a study from which diagnostic accuracy outcomes could be derived using a study population in the community setting.

7.2.5 Recommendations

6. Early AMD

6.1. Confirm a diagnosis of early AMD using slit-lamp biomicrosopic fundus examination alone.

7. Late AMD (dry)

7.1. Confirm a diagnosis of late AMD (dry) using slit-lamp biomicrosopic fundus examination.

8. Late AMD (wet active)

8.1. Offer optical coherence tomography (OCT) to people with suspected late AMD (wet active).

8.2. Do not offer fundus fluorescein angiography (FFA) to people with suspected late AMD (wet active) if clinical examination and OCT exclude neovascularisation.

8.3. Offer FFA to people with suspected late AMD (wet active) to confirm the diagnosis if OCT does not exclude neovascular disease.

7.2.6 Research recommendations

3. What is the diagnostic accuracy of indocyanine green angiography (ICG) for diagnosing people with subtypes of AMD (in particular, polypoidal choroidal

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vasculopathy [PCV], a form of late AMD [wet active])? What is the impact of ICG on consequent treatment for PCV?

Why this is important

Indocyanine green (ICG) has been used for ophthalmic angiography. It is similar to fundus fluorescein angiography (FFA) in that it involves the systemic injection of dye to image patterns of blood flow in the eye. Reports of the use of ICG indicate fewer adverse reactions compared with FFA based on clinicians' experience. This imaging tool is considered to be particularly useful for identifying a subtype of late AMD, named as polypoidal choroidal vasculopathy (PCV), and in some cases, it also has been used to help guide treatment with the application of ICG-guided therapy for PCV. However, there is a lack of evidence on the diagnostic accuracy of ICG, and this makes it difficult to recommend the routine use of ICG angiography as part of both the diagnostic and therapeutic processes. There is therefore the need for studies looking at diagnostic accuracy and the application of ICG as an imaging guide for identifying and treating PCV. The optimal study design for this question would be a cohort or cross-sectional study of people diagnosed with PCV.

4. **What is diagnostic accuracy of OCT-A for diagnosing people with late AMD (wet active), compared with FFA as the reference standard?**

Why this is important

A new, non-invasive imaging technique, OCT angiography (OCT-A) is becoming available in clinical practice. Only 3 small studies were found reporting the diagnostic accuracy of OCT-A, and the committee were unable to make any recommendations based on the outcomes from these. A well conducted cohort or cross-sectional study of people presenting with neovascular AMD that uses fundus fluorescein angiography as its reference standard would provide valuable data on the accuracy of OCT-A for detecting neovascular AMD.

5. **What is the diagnostic accuracy of OCT to exclude a diagnosis of late AMD (wet active) when offered in primary care?**

Why this is important

In answering questions on diagnostic tools and referral pathways, the committee used their clinical experience and expertise to consider the potential consequences for both patients and services associated with different diagnosis strategies. The committee was aware that OCT is becoming increasingly available in community optometry settings, and it is plausible that this will improve referrals (by providing strongly suggestive evidence of late AMD (wet active) while minimising false-positive cases). However, no evidence was found that investigates whether the usefulness of OCT as a 'rule out' test in secondary care translates to the primary care setting. Therefore, further research is required to investigate the impact of the use of OCT in optometric practice on the referral rate and accuracy of late AMD (wet active) diagnosis. The optimal study design would be a cross-sectional diagnostic study. It will be important to ensure that all participants receive reference-standard diagnosis in secondary care, regardless of whether the index test indicates referral (in order to quantify the potential risk of false-negative findings).

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8 Referral and treatment pathways

This chapter considers the impact of different organisational models, referral pathways, approaches to triage and diagnosis, and optimal models for ongoing treatment and follow up on outcomes for people with suspected or confirmed AMD. AMD damages central vision in either or both eyes. Onset can be rapid or gradual; so ensuring that patients know when to self-refer is an important aspect of any referral pathway. Self-referral advice needs to be consistent and clear to avoid patients delaying seeking specialist advice, as AMD is not a painful condition and symptoms may not initially be apparent. This is coupled with the fact that patients presenting with wet AMD can deteriorate rapidly, meaning that any delay in diagnosis and treatment for people at the early stages of the disease may lead to a worsening of outcomes over the longer term.

An optometrist or GP will typically be the first point of contact for a patient experiencing the early symptoms of wet AMD, and ensuring that symptoms are rapidly identified and referred onwards by primary care clinicians in a timely way to receive treatment is an important aspect for consideration.

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8.1 Organisational models for AMD diagnosis and management

Review questions:

- How do different organisational models and referral pathways for triage, diagnosis, ongoing treatment and follow up influence outcomes for people with suspected AMD (for example correct diagnosis, errors in diagnosis, delays in diagnosis, process outcomes)?
- How do different organisational models for ongoing treatment and follow up influence outcomes for people with diagnosed late AMD (wet active) (for example disease progression, time to treatment, non-attendance)?
- How soon should people with late AMD (wet active) be diagnosed and treated after becoming symptomatic?

8.1.1 Expert witnesses

To support the committee's consideration of the evidence for organisational models and referral pathways expert witnesses from the Association of British Dispensing Opticians (ABDO) – Dr Scott Mackie and Mr Barry Duncan were invited to present to the committee on the role of dispensing opticians in the diagnosis, referral and management of AMD. A paper summarising the evidence presented is provided as Appendix M.

8.1.2 Evidence review

The aim of this review was to establish what models of service organisation are most effective for the triage, diagnosis, treatment and follow up of people with suspected or confirmed late AMD (wet active). The review focused on identifying studies that fulfilled the conditions specified in Table 27. For full details of the review protocol please see Appendix C.

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Table 27: PICO table – organisational models and referral pathways for people with suspected AMD

Population	Adults (18 years and older) suspected of AMD
Interventions	• Telemedicine and virtual retinal clinics • Triage through fast track clinics • Triage through optometrist services • Two stop and one stop models of care. • Direct referral from GP, Optometrist or emergency services to retinal clinic • Alternative referral pathways: including Optometrist to GP to retinal clinic, referral to the general hospital eye services
Comparator	Any of the above
Outcomes	• Clinical outcomes (visual acuity (LogMAR), disease stage progression) (critical) • Safety and adverse events (important) • Error in diagnosis (important) • Time to diagnosis/treatment/follow up (important) • Number of people seen (i.e. number of people being referred) (important) • Patient satisfaction • Appointment attendance and non-attendance (important) • Resource use and costs (critical)

Table 28: PICO table – organisational models for ongoing treatment and follow up of people with late AMD (wet active)

Population	Adults (18 years and older) diagnosed with neovascular AMD
Interventions	• Telemedicine and virtual retinal clinics • Triage through fast track clinics • Triage through optometrist services • Two stop and one stop models of care. • Optometrist/optician provision of treatment • Optometrist/optician provision of follow up • Optometrist/optician provision of monitoring • Specialist nurse/technician provided injections • Direct referral from GP, Optometrist or emergency services to retinal clinic • Community based ophthalmology care • Alternative referral pathways: including Optometrist to GP to retinal clinic, referral to the general hospital eye services • Treatment delay
Comparator	Any of the above
Outcomes	• Clinical outcomes (visual acuity (LogMAR), disease stage progression) (critical) • Safety and adverse events (important) • Error in diagnosis (important) • Time to treatment/follow up (important) • Number of people seen (important) • Patient satisfaction • Appointment attendance and non-attendance (important) • Resource use and costs (critical)

Table 29: PICO table – optimal time for diagnosing and treating people with late AMD (wet active)

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Population	Adults (18 years and older) diagnosed with neovascular AMD
Interventions	• Telemedicine and virtual retinal clinics • Triage through fast track clinics • Triage through optometrist services • Two stop and one stop models of care. • Optometrist/optician provision of treatment • Optometrist/optician provision of follow up • Optometrist/optician provision of monitoring • Specialist nurse/technician provided injections • Direct referral from GP, Optometrist or emergency services to retinal clinic • Community based ophthalmology care • Alternative referral pathways: including Optometrist to GP to retinal clinic, referral to the general hospital eye services • Treatment delay
Comparator	Any of the above
Outcomes	• Clinical outcomes (visual acuity (LogMAR), disease stage progression) (critical) • Safety and adverse events (important) • Time to diagnosis/treatment/follow up (critical) • Number of people being referral (important) • Patient satisfaction • Appointment attendance and non-attendance (important) • Resource use and costs (critical)

Primary studies (RCTs) and systematic reviews were included if they assessed or compared different models of care. As there was not a sufficient number of RCTs identified through the search, non-RCT evidence from observational studies (including non-comparative studies) was included. These are initially rated as low quality and the quality of the evidence for each outcome was downgraded or not from this point. Papers were excluded if they:

- were not published in the English language
- were abstracts, conference proceedings, guideline/health technology assessment report, narrative reviews and diagnostic studies

8.1.2.1 Description of included studies

A systematic search identified 4,067 references. The references were screened on their titles and abstracts and 88 references were ordered for full-text review (87 identified through the initial search, and 1 relevant trial identified and added following scrutiny of the reference lists from the included studies). Following review of full-text papers, a total of 19 studies were included in the review. Included studies were relevant to the accuracy of identification of people with AMD, models of care or service delivery (telecommunication network, tele-ophthalmology, etc.), and the association between visual acuity and time delay (symptoms, diagnosis and treatment). For the list of excluded studies with reasons, see Appendix F. An update search carried out near the end of guideline development identified 3 further studies including 1 systematic review of non-physician delivered intravitreal injection service.

A brief summary of included studies is provided in Table 30. References of included studies are listed in Appendix I.

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Table 30: Summary of included studies

Study	Design	Population	Intervention and Comparison	Outcome
Arias (2009) Delay in treating age-related macular degeneration in Spain is associated with progressive vision loss [Spain]	Retrospective cohort	People with untreated subfoveal neovascular AMD (n=100 people)	Treatment delay (Different times from referral to treatment and changes in visual acuity from diagnosis to treatment)	Visual acuity
Azzolini (2013) A teleconsultation network improves the efficacy of anti-VEGF therapy in retinal diseases [Italy]	Prospective cohort	People with AMD (n=678)	Teleconsultation network vs usual care	Visual acuity and time between first visit and onset treatment
Chasan (2014) Effect of a teleretinal screening program on eye care use and resources [USA]	Retrospective cohort	People underwent diabetic teleretinal screening in the community-based clinic (n=1,935)	Teleretinal screening, diagnosis made through teleretinal screening and face-to-face visits	Number of people being referred and number of people attended ophthalmologic examinations; accuracy of teleretinal screening in detecting AMD
Dobbelsteyn (2015) What percentage of patients presenting for routine eye examinations require referral for secondary care? A study of referrals from optometrists to ophthalmologists [Canada]	Retrospective cohort	People presented for routine eye examinations, were found to have pathology results in referrals to ophthalmologists (n=23,330 people)	Community-based routine eye examination, referrals for symptomatic and asymptomatic patients	Number of people with or without symptoms being identified for eye conditions.
Engman (2011) Administration of repeat intravitreal anti-VEGF drugs by retina specialists in an injection-only clinic for patients with exudative AMD: patient acceptance and safety [USA]	Chart review	People received anti-VEGF injections (n=110 people, 115 eyes)	Intravitreal injections of ant-VEFG by retina specialist : interrupted vs un-interrupted injections	Acceptance and safety of repeated intravitreal injections (uninterrupted vs interrupted injection cycles)
Ghazala (2013) Improving treatment provision of Wet AMD with intravitreal ranibizumab [UK]	Before–after audit study	People attending the AMD clinic and people with AMD being followed up (up to 162 people)	Improvement in service provision (including additional staff and facilities): before and after improvement in service provision	Visual acuity

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Study	Design	Population	Intervention and Comparison	Outcome
Goudie (2014) Ophthalmic digital image transfer: benefits to triage, patient care and resource [Scotland]	Retrospective cohort	People being referred to hospital eye service (n=358 referrals)	Electronic referrals (with images attached) vs electronic referrals (without images attached)	Number of people being referred
Li (2015) Prospective evaluation of teleophthalmology in screening and recurrence monitoring of neovascular age-related macular degeneration: a randomised clinical trial [Canada]	RCT	People with suspected and/or confirmed neovascular AMD (up to 106 people)	Telemedicine network ophthalmology vs routine care	Time from being referred to diagnostic image and/or treatment
Lim (2012) Delay to treatment and visual outcomes in patients treated with anti-vascular endothelial growth factor for age-related macular degeneration [Australia]	Case series	People diagnosed with subfoveal CNV secondary to AMD (n=185 people, 185 eyes)	Treatment delay (Different times from referral to treatment and changes in visual acuity from diagnosis to treatment)	Visual acuity
Markun (2015) The Chronic Care for Wet Age Related Macular Degeneration (CHARMED) Study: A Randomised Controlled Trial [Switzerland]	RCT	People with wet AMD (n=169 people, 190 eyes)	Chronic Care Model (delivery by trained chronic care coaches, reminder systems, structured follow-up empowering patients in self-monitoring and giving decision-support) vs usual care	Best corrected visual acuity (primary care)
Muen (2011) Quality of optometry referrals to neovascular age-related macular degeneration clinic: a prospective study [UK]	Prospective cohort	Patients being referred by optometrists to ophthalmologists (n=54 referrals)	Referrals (a rapid access referral form, RARF), AMD diagnosis made by optometrists and ophthalmologists	The overall agreement on AMD diagnosis made by optometrists and ophthalmologists
Muether (2011) Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity [Germany]	Non-randomised trial	People with neovascular AMD (n=90 people)	Treatment delay (Different times from referral to treatment and changes in visual acuity from diagnosis to treatment)	Visual acuity

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Study	Design	Population	Intervention and Comparison	Outcome
Muether (2013) Long-term effects of ranibizumab treatment delay in neovascular age-related macular degeneration [Germany]	Non-randomised trial	People with primary diagnosis of exudative AMD (n=102 people)	Treatment delay (Different times from referral to treatment and changes in visual acuity from diagnosis to treatment)	Visual acuity
Oliver-Fernandez (2005) Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration [Canada]	Case series	People with AMD (n=38 people)	Treatment delay (Different times from referral to treatment and changes in visual acuity from diagnosis to treatment)	Visual acuity
Rauch (2012) Time to first treatment: The significance of early treatment of exudative age-related macular degeneration [Austria]	Case series	People with new-onset CNV (n=45 people)	Treatment delay (Different times from referral to treatment and changes in visual acuity from diagnosis to treatment)	Visual acuity
Rasul (2016) Non-physician delivered intravitreal injection service is feasible and safe-a systematic review.	Systematic review	People receiving intravitreal injections (n=5 studies included	Non-physician intravitreal injections therapy	Prevalence of adverse events; Patient satisfaction
Rasmussen (2015) Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration [Demark]	Case series	People receiving anti-VEGF treatment for neovascular AMD (n=1,099 people, 1185 eyes)	Treatment delay [Time to treatment (13.5 days) Time to treatment (5.8 days)]	Visual acuity
Real (2013) Accessibility as a conditioning factor in treatment for exudative age-related macular degeneration [Argentina]	Case series	People treated for neovascular AMD with ranibizumab or bevacizumab (n=78 people, 96 eyes)	Treatment delay (Different times from referral to treatment and changes in visual acuity from diagnosis to treatment)	Waiting time and changes in visual acuity
Reeves (2016) Effectiveness of community versus hospital eye service follow-up for patients with neovascular age-related macular degeneration (ECHoES): a virtual non-inferiority trial [UK]	Virtual RCT	Optometrist and ophthalmologists (n=155 people)	Vignettes created from clinical and image repository of a clinical trial vs reference standard agreed by 3 medical retinal experts	Correct classification of the activation status of neovascular AMD lesion

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Study	Design	Population	Intervention and Comparison	Outcome
Takahashi (2015) Relationship between visual prognosis and delay of intravitreal injection of ranibizumab when treating age-related macular degeneration [Japan]	Cohort study	People received PRN ranibizumab monotherapy (n=50 people, 50 eyes)	Treatment delay (Different time delay to injection, ranging from 0 to 56 days)	Visual acuity
Tschuor (2013) Optimising assessment intervals improves visual outcomes in ranibizumab-treated age-related neovascular degeneration: using the stability phase as a benchmark [UK]	Prospective cohort	People with neovascular AMD receiving ranibizumab (n=62 people, 72 eyes)	Community clinic follow-up (monthly) vs hospital follow-up (8-weekly)	Visual acuity

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8.1.3 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD. A total of 3,163 unique references was retrieved, of which 1 was included for this question. This review question was not prioritised for health economic modelling.

The study included for this review question has been described in Section 7.2.2 (Mowatt et al. 2014). The cost–utility analysis evaluated a range of organisational models for diagnosing and monitoring wet AMD. A more detailed description of the study is provided in Appendix J.

8.1.4 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

8.1.4.1 Diagnostic agreement between optometrists and ophthalmologists

Two studies were included that reported diagnostic agreement between optometrist and ophthalmologist:

- A crude agreement of 57.4% (95%CI 44.2 to 70.6%; n=54) in identifying history of reduction of vision, distortion and central scotoma amongst referred patients (very low-quality evidence). 37% (95%CI 24.1 to 50.0%; n=54) of people with exudative AMD were correctly diagnosed by an optometrist (very low-quality evidence)
- Ophthalmologists were less likely to correctly classify a vignette[6] as reactivated compared with optometrists (RR 0.93 [95%CI 0.88 to 0.97]; 1 virtual RCT with 994 images) but they were more likely to correctly classify a vignette as quiescent or suspicious compared with optometrists (RR 1.09 [95%CI 1.06 to 1.11]; 1 virtual RCT with 1,022 images) (moderate-quality evidence)

8.1.4.2 Number of patients being seen

Three studies were included that reported the number of patients who were seen and then diagnosed with AMD:

- 2.7% (95%CI 1.7 to 3.7%) of asymptomatic people and 5.1% (95%CI 4.3 to 6.0%) of symptomatic people being referred following routine eye examinations were diagnosed with AMD (1 study with 4,076 participants; very low-quality evidence).
- 24% (95%CI 22.1 to 25.9%) of people screened through teleretinal screening programme were referred to the eye clinic for an ophthalmic examination. Of those referred, 13% (95%CI 9.85 to 15.95%) were diagnosed with AMD (1 study with 1,935 participants; very low-quality evidence).
- Electronic referrals attached with images were less likely to result in a hospital appointment compared with electronic referrals without attached images (RR 0.73 [95%CI 0.67 to 0.79]) (1 study with 1,152 participants; very low-quality evidence).

8.1.4.3 Anti-VEGF injection administration

Two studies were included that provided outcomes for anti-VEGF injection administration:

[6] The vignette consisted of a brief clinical summary that provided a patient's age, gender, cardiovascular health and smoking status; two sets of images comprising colour fundus and radial pattern spectral domain OCT from two separate visits. The two sets of images were termed baseline and index, with the former from a visit when the lesion was quiescent and the latter from a visit when the lesion could have been either quiescent or reactivated.

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- 76.5% (134 out of 175) anti-VEFG injection cycles were uninterrupted and 41 injections cycles were interrupted for possible adverse events (visual change, symptoms of infection, evaluated intra-ocular pressure) (n=110 patients; very low-quality of evidence).
- One systematic review reported 5 studies (DaCosta 2014, Hasler 2015, Michelotti 2014, Simcock 2014 and Varma 2013) with a total of 31,303 injections having been performed by 16 nurses. The prevalence of endophthalmitis after injections was 0 to 0.40%, and patient satisfaction was high (62–97%; low-quality evidence). These data were taken directly from the systematic review, rather than the included primary studies.

8.1.4.4 Visual acuity

Four studies reported visual acuity of people who received different models of care: a) hospital vs community eye clinic follow-up for people treated with late AMD (wet active); b) chronic model of care (delivery by trained chronic care coaches, using reminder systems, performing structured follow-up empowering patients in self-monitoring and giving decision-support); c) service provision improvement (staff and treatment capacity) for people with late AMD (wet active)

- Very low-quality evidence showed that people's visual acuity was more likely to improve if they were visiting a community eye clinic compared with visiting a hospital (RR for gain of 15 ETDRS letters 9.00 [95%CI 1.18 to 68.92]), but mean visual acuity could not be differentiated between hospital and community clinics (MD +1.2 ETDRS letters [95%CI -4.00 to 6.40]; 1 RCT of 72 eyes).
- Low-quality evidence could not differentiate visual acuity between a chronic model of care and usual care at 12-month follow-up (MD -4.80 ETDRS letters [95%CI -11.31 to 1.71]; 1 RCT of 169 people).
- Very low-quality evidence showed that people receiving ranibizumab treatment were more likely to show improved vision after the service increased capacity for late AMD (wet active) than before (RR 3.53 [95%CI 1.05 to 11.85]; 1 before–after study of 113 people).

8.1.4.5 Diagnosis and/or treatment time interval

Three studies reported the time intervals between referral and diagnosis and/or treatment observed with different models of care: a) teleophthalmology; b) teleconsultation network; c) service provision improvement (staff and treatment capacity) for people with late AMD (wet active)

- There was no difference in the time from referral to diagnosis/treatment between people with suspected late AMD (wet active) receiving teleophthalmology and routine screening (diagnostic imaging in the form of FFA and OCT and being assessed by the retinal specialists), but people with confirmed AMD who received teleophthalmogy monitoring experienced a longer time interval between recurrence of AMD[7] and further treatment than those receiving routine monitoring at 12-month follow up (MD 13.5 days [95%CI 9.0 to 18.2]; 1 RCT of 63 people; low- to moderate-quality evidence).
- People who participated in a teleconsultation network waited less time from their first visit to treatment compared with people who received usual care (MD -23.20 [95%CI -23.66 to -22.74]; 1 prospective cohort study of 360 people; very low-quality evidence).
- People with late AMD were more likely to be seen within 1 week of referral after the service increased capacity for late AMD (wet active) compared with before (RR 2.14 [95%CI 1.33 to 3.45];1 before–after study of 113 people; very low-quality evidence).

8.1.4.6 Vision-related quality of life (NEI-VFQ-25)

One study was included that provided outcomes for vision-related quality of life:

[7] Patients who were previously treated for neovascular AMD, and did not have evidence of disease activity at the time of enrolment

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- There was no difference in vision-related quality of life between people with late AMD (wet active) receiving a chronic model of care compared with usual care at 12-month follow-up (MD 2.10 on NEI-VFQ-25 [95%CI -0.96 to 5.16]; 1 RCT of 169 people) (low-quality of evidence).

8.1.4.7 Association between time interval (diagnosis/treatment) and visual acuity

Nine studies were included that provided outcomes for association between time interval and visual acuity:

- People lost an average of 5.89 ETDRS letters for every 65 days waiting to treatment over a 2 to 4 year study period (very low-quality evidence).
- A loss of 1.79 letters ETDRS visual acuity during waiting between confirmed need for treatment and subsequent commencing of treatment (average 23.5 days) (MD=-1.79 [95%CI -3.71 to 0.13] (very low-quality evidence).
- Visual acuity declined by approximately 1 letter for every 3 days between initial diagnosis and treatment (logMAR coefficient = 0.00674 [95%CI 0.003 to 0.010]) (very low-quality evidence).
- People who had a loss of more than 1 line (5 ETDRS letters) waited longer for treatment when their AMD recurred than those without vision loss of more than line 1 line (MD 32.0 days [95%CI 10.05 to 53.93]) (very low-quality evidence).

8.1.4.8 Health economic evidence

One directly applicable study with potentially serious limitations suggests that, assuming QALYs are valued at less than £50,000 each, an organisational model of diagnosis by FFA followed by nurse- or technician-led monitoring represents the optimal balance of costs and benefits compared with alternative models using OCT and combined VA, OCT and SLB testing.

8.1.5 Evidence to recommendations

Relative value of different outcomes	The committee acknowledged that, although it would be ideal to provide recommendations on the basis of well conducted trials that demonstrated the long-term effects – particularly visual acuity – associated with different models of care, this was an unrealistic expectation (see 'Quality of evidence', below). Therefore, the committee agreed that it should draw such inferences as it could from the outcomes presented in the included evidence. These outcomes comprised visual acuity, diagnosis/treatment time delay, number of referrals and diagnosis agreement between optometrist and ophthalmologists. As regards appropriate referrals for late AMD (wet active), the committee agreed that it is critical to minimise false negatives, which may have irreversibly harmful consequences for the person. In contrast, although false-positive referrals have implications for the efficiency of the system (and, by implication, the quality of care it provides to all people with AMD – see 'Trade-off between benefits and harms', below), they do not have immediately dire consequences. In other words, ophthalmologists would rather see cases they didn't need to than miss cases they would have been able to treat.
Trade-off between benefits and harms	**Models of referral** <u>Teleophthalmology – digital imaging</u> The committee discussed the evidence relevant to teleophthalmology in referring and monitoring people with AMD. The committee noted that attaching digital images with electronic referrals meant that patients could be prioritised and treated at the appropriate hospital specialist clinic, reducing unnecessary hospital appointments by 27% (Goudie

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2014). The committee agreed that, if inappropriate referrals could be reduced, this would be help to concentrate resources for those in true need of specialist management. However, from the evidence presented, it is not clear whether the people whose initial referrals did not proceed to specialist care, following review of digital imaging, included false-negative cases that should really have been seen in hospital. The committee agreed that, before considering if the reported reduction in appointments was a real benefit, it would be necessary to establish the number of false negatives who were not given appointments.

The committee noted that this evidence was based on the Scottish healthcare system where e-referrals have been made widely available following a change to the model of optometric funding. This had been explained by members of the committee and by the expert witnesses from the Association of British Dispensing Opticians. In England, a move to the Scottish model of funding is not anticipated, so it is unlikely that dedicated e-referral infrastructure will be available in short or medium term.

Nevertheless, the committee agreed that referrals with digital images do have the potential to improve the efficiency and quality of referrals and, with advances in technology, the committee considered that there is the scope for attaching digital images when referring people with suspected AMD (even when there is no dedicated mechanism for doing so).

In the experience of committee members, the usefulness of digital images in ophthalmology largely depends on quality of imaging, which enables an accurate diagnosis to be made. However, current evidence on the diagnostic accuracy of digital images is limited and more robust evidence is needed to establish the role of digital images in correctly diagnosing AMD. The committee agreed a research recommendation reflecting this priority.

<u>Teleophthalmology – impact on time to diagnosis and/or treatment</u>

Included evidence demonstrated both benefits and harms of teleophthalmology. One study (Azzolini et al., 2013) showed a positive impact on the time interval between a patient's first visit and treatment initiation, which was shortened by 23 days amongst those who received care in a teleconsultation network. Another study (Lin et al., 2015) reported that teleophthalmology had little impact on the time interval from referral to diagnosis and treatment initiation, and led to a longer wait time between recurrence of neovascular AMD and treatment (MD 13.5 days, 95%CI 9.0 to 18.2). The committee noted that the traditional follow-up model allowed for same-day treatment following face-to-face consultation with ophthalmologists, but such quick access to treatment was unlikely when people were monitored through teleophthalmology. Therefore the committee discussed the possibility that teleophthalmology could result in a treatment delay for patients when compared with face-to-face consultations. Given the mixed effect of teleophthalmology on diagnosis/treatment time interval, the committee agreed that it did not have sufficient evidence to be able to recommend its use.

<u>Role of optometrists</u>

The committee noted that there was a lack of evidence on one-stop or two-stop models of care, and also little evidence on optometrist provision of treatment, follow-up and monitoring for people with AMD. Acknowledging the role of optometrists in the referral pathway, the committee discussed the evidence evaluating the quality and accuracy of diagnoses of late AMD (wet) made by optometrists and ophthalmologists. Evidence from the EChoES trial (Reeves et al., 2016), a virtual trial based on vignettes, showed that optometrists were non-inferior to ophthalmologists with respect to their ability to correctly identify neovascular lesions (RR 1.01, 95%CI 0.99 to 1.04). The trial found that, compared with ophthalmologists, optometrists were more

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likely to classify a vignette as a reactivated lesion but less likely to classify a lesion as quiescent or suspicious. Optometrists' tendency to classify a lesion as reactivated may be in line with their roles in the community, examining and referring any people suspected of having pathological presentation to minimise the risk of false-negative diagnosis.

The committee discussed the finding of Muen et al. (2011) that a high proportion of people being referred by optometrists to a rapid access programme for people with suspected late AMD (wet active) did not ultimately receive that diagnosis when reviewed by macular specialists (63%). People who do not have neovascular AMD being seen unnecessarily at the macular clinic may increase hospital workloads, but the committee considered that optometrists have an obligation to refer people with suspected neovascular changes so patients do not miss out on potential beneficial treatment. In addition, people with AMD vary in their visual symptoms and disease progression based on the different forms of AMD. The committee agreed that, although visual symptoms might not provide enough information on their own to warrant a referral, a timely referral can potentially minimise vision loss, and maximise the possible treatment benefit. Similarly, the committee agreed that a lack of symptoms should not preclude referral, particularly when neovascular AMD is still suspected. As such, the committee emphasised the importance of an urgent referral to a retinal unit once people with suspected late AMD (wet) present to optometrists or GPs, and recommended that this should be offered to minimise any diagnosis delay irrespective of the presentation of visual symptoms.

Referral routes

The committee agreed that there were different referral and re-referral pathways in use in different parts of the country, and that there was no evidence to suggest particular pathways are more effective than others. However, it agreed it was important that local areas should have clear pathways in place, covering all aspects of referral, discharge and re-referral. The committee also agreed it was appropriate to specify that direct referral is the preferred method, as it is obvious that removing unnecessary barriers to referral will lead to the shortest delays in both appointment and treatment.

Late AMD (wet active) – time from presentation to treatment

The committee noted that included evidence demonstrated a clear association between visual loss and time delay in diagnosis and treatment for people with AMD. In some studies, the rate of loss was as rapid as 1 ETDRS letter every 3 days. Evidence from the included RCTs in section 10.1 was also considered. This suggests that eyes with late AMD (wet active) that were randomised to placebo anti-VEGF or sham PDT lost approximately 15 ETDRS letters over 1 year's follow-up. The committee interpreted this evidence as providing a clear mandate for the swiftest possible patient journey from suspicion to treatment of late AMD (wet active).

The committee identified 3 linked intervals (initial presentation to referral, referral to diagnosis, and diagnosis to treatment) that comprise the initial referral pathway. The committee noted that delay at any of these junctures could have an important impact on people's visual changeThis could be broken down into 2 components

- For presentation to referral, the committee agreed that there was not usually any reason why referral could not be made on the same day as disease is suspected; accordingly, it recommended that people should usually be referred within 1 working day. The committee explored a concern that this might be interpreted as a significant intensification of current practice, and lead to healthcare professionals taking drastic steps that are not necessary (e.g. attempting to contact ophthalmologists in person in every case, or sending people to

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emergency departments). To guard against this misinterpretation, a qualification was added emphasising that emergency referral is not necessary.

- For time from referral to diagnosis and diagnosis to treatment, the committee was mindful that current guidelines from the Royal College of Ophthalmologists state that patients should be treated preferably within 2 weeks of detection of a treatable lesion. In its original discussion, the committee concluded that this target should be seen as aspirational, and expressed the view that it may not be possible in all hospital eye services to provide treatment within 2 weeks. For this reason, the draft of this guideline on which stakeholder comments were solicited specified that the total period from referral to diagnosis and diagnosis to treatment should not exceed 21 days. However, stakeholder feedback from providers and commissioners unanimously suggested that this had been unnecessarily cautious, and a target of 14 days should be achievable in all centres. The committee took this as evidence that its previous concerns about the achievability of a shorter target had been unfounded. Therefore, the committee was happy to revise its guidance to specify a 14-day target, in the knowledge that a shorter delay would maximise chances of preserving vision.

Early AMD and late AMD (dry)

For those with early AMD and late AMD (dry), the committee considered that referral to hospital service should be avoided since there is no treatment available. However, the committee was mindful that certification of sight impairment can only be undertaken by hospital eye services and, in many areas, people access low-vision services (see section 9.2) via the hospital. Therefore, additional qualifications were made, emphasising that people with untreatable disease should be referred if either of these is necessary. In addition, the committee considered that, where professionals in primary care are aware that research into new treatments for late AMD (dry) is ongoing locally in secondary care, this would be another reason for referral.

Anti-VEGF injection

Anti-VEGF is commonly offered as first-line treatment for people with late AMD (wet active). Current marketing authorisations for both ranibizumab and aflibercept state that injections must be administered by a qualified ophthalmologist or physician experienced in intravitreal injections. The committee discussed the evidence from an audit study (Simcock et al., 2014) evaluating the safety of a nurse-practitioner delivered injection service for treating late AMD (wet active) with ranibizumab. This study reported very low rates of complications that, based on their experience, the committee noted was comparable or superior to that achieved by medical consultants. From the patients' perspective, the lay members of the committee stated that the injection experience can vary based on delivery by different clinicians. The committee expressed the view that improved injection technique is likely to be achieved by healthcare professionals who deliver such injections more often. This could be expected to lead to reduced pain for people receiving injections, along with a lower rate of adverse events. Therefore, the committee emphasised that the qualifications of the professional providing injections are less important than their training and experience in delivering intraocular injections. Consequently, it recommended that any trained clinician with experience in intravitreal injection should be able to deliver anti-VEGF treatment. However, it emphasised that, in instances where the person delivering treatment is not medically qualified, it will be necessary to ensure that treatment takes place in a setting where medical cover is available in the event that any ophthalmological or medical complications occur.

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Trade-off between net health benefits and resource use	The committee acknowledged that there was little health economic evidence relevant to these review questions overall. The committee did review economic evidence from 1 study evaluating the cost effectiveness of alternative models of diagnosis and treatment (Mowatt et al., 2014). The committee acknowledged that it was appropriate to compare the relative effects of the different monitoring strategies for this review question, given that the diagnosis aspect was covered elsewhere (see section 7.2), and because one of the modelled monitoring strategies represented an approach of particular relevance to the review question on ongoing monitoring of patients – a virtual clinic (using nurses and technicians as first point of contact). The benefits of this approach are the reduced staff cost that would be associated with monitoring visits in the majority of cases, with only positive or uncertain assessments requiring the input of an ophthalmologist (and therefore becoming potentially more costly). The committee noted that this strategy appeared to be cost effective, and that this was consistent with their own clinical experience of the competence of trained non-ophthalmologist staff in this area.
Quality of evidence	The committee agreed that the overall quality of the evidence was low. Only 3 RCTs were identified, evaluating teleophthalmology (Li et al. 2015), diagnosis agreement between optometrist and ophthalmologist (Reeves et al. 2016) and people's visual improvement by the chronic care model (Markin et al., 2015). The quality of evidence from the 3 randomised trials ranged from very low to moderate. Since there was insufficient evidence from RCTs, observational studies including case series were also included in the review. These study designs were likely to introduce biases (most notably selection bias) to the evidence. The committee agreed that it was difficult to assess the reported accuracy in detecting neovascular lesion between optometrists and ophthalmologists because of the reference standard used in the study. Since there was no established reference standard when assessing diagnosis agreement, this study used a reference standard based on the judgement of 3 medical retina experts reading 288 vignettes. Results could vary if a different reference standard was used. This review did not identify any direct evidence on how soon people with neovascular AMD should be diagnosed and treated after becoming symptomatic. Although evidence that confirmed visual loss is linked with delays to diagnosis and/or treatment, the committee noted that there was no evidence that supported the effectiveness of any particular model of care/services in reducing any of the time intervals throughout the referral pathway, and the subsequent influence on people' visual acuity and quality of life. Therefore, the committee agreed to make a research recommendation on the long-term effectiveness of different organisational models on referral, diagnosis and treatment.
Other considerations	**Strength of recommendations** The committee was unanimous that, though it had seen no high-quality, directly relevant evidence, it was still important to make unambiguous recommendations, in this area. The committee felt comfortable doing this, as it took the view that its guidance would codify current practice, rather than impose new imperatives on the service (see above). Moreover, the nature of the topic area makes it difficult to make weak recommendations that remain coherent: for instance, it would not make sense to ask first-line healthcare professionals to 'consider' referring people with suspected late AMD (wet active) to a specialist, when the evidence is at least clear that people whose treatment is delayed risk a significant, irreversible decline in visual acuity. One possible exception came in the recommendation that specifies that hospital eye services should commence treatment for confirmed late AMD (wet active) within 14 days of the initial referral. However, the committee, reassured by comments stakeholders had made during consultation on the draft

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	guideline (see above), agreed that all retinal units should be able to achieve this goal without significant diversion of resources. When it came to providing guidance about referral pathways, the committee agreed that it had no strong evidence to mandate any particular approach; however, it could specify the general principles that should be agreed by commissioners and providers in each locality, without the need to impose a particular structure on every service.

8.1.6 Recommendations

9. **Make an urgent referral for people with suspected late AMD (wet active) to a macula service, whether or not they report any visual impairment. The referral should normally be made within 1 working day but does not need emergency referral.**

10. **Do not refer people with asymptomatic early AMD to hospital eye services for further diagnostic tests.**

11. **Refer people with late AMD (dry) to hospital eye services only:**
    - for certification of sight impairment **or**
    - if this is how people access low-vision services in the local pathway (see recommendation 18) **or**
    - if they develop new visual symptoms that may suggest late AMD (wet active) **or**
    - if it would enable them to participate in research into new treatments for late AMD (dry).

12. **For eyes with confirmed late AMD (wet active) for which antiangiogenic treatment is recommended (see recommendations 21–30), offer treatment as soon as possible (within 14 days of referral to the macula service).**

13. **Ensure intraocular injections are given by suitably trained healthcare professionals, for example:**
    - medical specialists, such as ophthalmologists
    - nurse practitioners, optometrists and technicians with experience in giving intraocular injections.

If the injection is delivered by someone who is not medically qualified, ensure that cover is in place to manage any ophthalmological or medical complications.

14. **Commissioners and providers should agree a clear local pathway for people with AMD, which should cover:**
    - referral from primary to secondary care, with direct referral preferred
    - discharge from secondary to primary care, covering ongoing management and re-referral when necessary

8.1.7 Research recommendations

6. **What is the diagnostic accuracy of providing an electronic image with the initial referral of people with suspected late AMD (wet active)?**

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Why this is important

With the development of technology in ophthalmologic examination, digital images are becoming a key part of the diagnostic process. In the Scottish health service, attaching digital images with electronic referrals has become common practice, allowing for patients to be prioritised and treated at the appropriate hospital specialist clinic, thus avoiding unnecessary hospital appointments. Although such e-referral infrastructure is unlikely to be available in England in the short or medium term, the committee considered there is scope for attaching digital images when referring people with suspected neovascular AMD. Additionally the usefulness of digital images in ophthalmology largely depends on quality of imaging, which enables an accurate diagnosis to be made. To date, there is no evidence on the diagnostic accuracy of digital images. Therefore, evidence is needed to fill this gap in the gap in evidence base, and to establish the role of digital images in correctly diagnosing AMD.

7. What is the long-term effectiveness, in terms of patient-relevant outcomes including visual acuity and quality of life, of different models of care that aim to reduce time from initial presentation to referral, diagnosis, and treatment?

Why this is important

There is robust evidence showing that visual loss is linked with delays in diagnosis and/or treatment. However, there is a lack of evidence evaluating the impact of any particular model of care/services in reducing any of the time intervals throughout the referral and treatment process, or the subsequent influence of different models of care on peoples' visual acuity and quality of life. A well conducted trial would, therefore, provide evidence to assess the long-term effectiveness of different organisational models on referral, diagnosis and treatment for people with late AMD (wet active).

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9 Non-pharmacological management

AMD is common eye disease and a leading cause of vision loss among older adults. It is a progressive condition. People can progress from early to late stages of AMD, and the change of vision symptoms through the progression has an impact on an individuals' vision and their ability to carry out activities of daily living. Not all visual symptoms related to AMD can be improved by pharmacological interventions. Non-pharmacological interventions such as psychological support and low vision rehabilitation are provided to help people with AMD to acquire skills and confidence to help them cope with the visual loss that they are experiencing, so as to improve their independence and wellbeing.

As a supportive approach, people with AMD may be offered psychological interventions such as cognitive behavioural therapy, self-management and problem solving treatment to help them deal with emotional change and improve their mental wellbeing. They may also be referred to a low vision clinic or community low vision service to assess their specific vision-related needs; for instance whether the person needs to be registered using the certificates of vision impairment. In practice, delivery of these non-pharmacological interventions is not always assured by conventional clinical consultations. Furthermore, some supporting services are not consistently provided or resourced in the NHS, and rehabilitation is delivered by a variety of service models but with wide variations in these services being provided. This chapter aims to address the effectiveness of non-pharmacological interventions including psychological interventions and supporting services including low vision services, and also to identify benefits and risks of these interventions to optimise visual performances of people with AMD and maintain their confidence and quality of life.

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9.1 Psychological therapies

Review question:

- What is the effectiveness of psychological therapies for AMD?

9.1.1 Evidence review

The aim of this review was to estimate the effectiveness of psychological therapies to manage the mental wellbeing of people with AMD. The review focused on identifying studies that fulfilled the conditions specified in Table 31. For full details of the review protocol see Appendix C.

Table 31: PICO table – psychological therapies

Population	Adults (18 years and older) with AMD
Intervention	Comparative trials of psychological and psychosocial interventions: • CBT (cognitive behavioural therapy including computerised CBT), mindfulness • Self-management • Problem solving treatment • Peer support • Befriending services (formalised, volunteer) • Sight loss counselling
Comparator	Usual care or being on a waiting list for psychological therapy (deferred treatment).
Outcomes	Clinical outcomes: • Anxiety and depression • Patient satisfaction Functional capacity, participation, independence and ability to carry out activities of daily living. Health related quality of life Impact on carers Safety and adverse events (including suicide and parasuicide) Resource use and costs

Randomised controlled trials (RCTs), non-randomised controlled trials, comparative cohort studies and systematic reviews of RCTs, non-randomised controlled trials and comparative cohort studies were included if they evaluated psychological or psychosocial interventions. Papers were excluded if they:

- were not published in the English language.
- were abstracts, conference proceedings, narrative reviews, case-studies, diagnostic studies or non-comparative studies.

9.1.1.1 Description of included studies

A systematic search and a hand search of the reference lists of systematic reviews identified 1,461 references. The references were screened on their titles and abstracts and 25 references were ordered for full-text screening.

Of these, 18 studies were excluded as they did not meet the eligibility criteria for this review. Common reasons for exclusion included study design (e.g. non-systematic review, trial protocol or conference abstract), or not reporting any outcomes of interest. A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

In total 7 articles were included. The studies made the following comparisons:

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- Problem solving treatment vs delayed treatment
- Problem solving therapy vs supportive therapy
- Psychosocial intervention programme vs usual care
- Self-management vs delayed treatment
- Behavioural activation and low vision rehabilitation (LVR) vs supportive therapy and LVR.

The intervention studies found in this review presented outcomes for depression, anxiety, patient satisfaction, functional capacity, independence and ability to carry out activities of daily living, health and vision related quality of life. However, no studies reported outcomes for impact on carers, safety and adverse events, or resource use and costs.

A brief summary of included studies is provided in Table 32. References of included studies are listed in Appendix I.

Table 32 Included studies for psychological therapies

Study [country]	Study sample	Interventions and comparators	Outcomes reported
Birk (2004) [Germany]	Bilateral AMD VA in better eye < 20/70 (n=22 people)	Psychosocial intervention programme vs usual care	Positive and negative affect schedule (PANAS) score Geriatric depression scale (GDS) score Activities of Daily Living (ADL) score Perceived autonomy Active problem orientation
Brody (2002), [USA]	AMD and visual acuity of 20/60 or worse in the better eye and 20/100 or worse in the other eye with habitual correction (n=214 people)	Self-management vs waiting list	Profile of Mood States (POMS) National Eye Institute-vision functioning questionnaire-25 (NEI-VFQ-25) AMD self-efficacy score GDS score Duke Social Support Index-11 Life orientation scale
Brody (2005) [USA]	AMD and visual acuity of 20/60 or worse in the better eye and 20/100 or worse in the other eye with habitual correction (n=214 people)	Self-management vs waiting list	POMS NEI-VFQ-25 AMD self-efficacy score GDS score Duke Social Support Index-11 Life orientation scale
Brody (2006) [USA]	AMD and visual acuity of 20/60 or worse in the better eye and 20/100 or worse in the other eye with habitual correction (n=32 people)	Self-management vs waiting list	POMS NEI-VFQ-25 AMD self-efficacy score GDS score Duke Social Support Index-11 Life orientation scale
Rovner (2007) [USA]	Neovascular AMD in one eye diagnosed within the preceding 6 months, by FFA	Problem solving treatment vs usual care	Depression incident Hamilton Depression rating score No. of lost activities

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Study [country]	Study sample	Interventions and comparators	Outcomes reported
	Pre-existing AMD in the fellow eye. (n=206 people)		NEI VFQ-17
Rovner (2013) [USA]	Bilateral AMD (neovascular and/or geographic atrophy); visual acuity between 20/70 and 20/400; moderate difficulty in at least one valued vision-function goal (n=241 people)	Problem solving therapy vs supportive therapy	Targeted visual function NEI-VFQ QoL Activities inventory Control strategies
Rovner (2014) [USA]	Bilateral AMD (either neovascular disease or geographic atrophy); BCVA <20/70 in the better seeing eye; >5 antiangiogenic injections if the better eye had neovascular disease, or no injections in the previous 3 months; moderate difficulty performing a valued vision-dependent activity; subthreshold depressive symptoms, (n=188 people)	Behavioural activation and low vision rehabilitation (LVR) vs supportive therapy and LVR	Depression incident

9.1.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. No references were identified as being relevant to this review question. Health economic modelling was not prioritised for this review question.

9.1.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

9.1.3.1 Problem solving treatment versus usual care

Low-quality evidence from 1 RCT of 206 people found fewer activities were lost in people offered problem solving treatment versus usual care, but could not differentiate levels of depression or visual function during 6-month study follow-up.

9.1.3.2 Problem solving treatment versus supportive therapy

Very low- to low-quality evidence from 1 RCT of 141 people found worse levels of selective primary control in people offered problem solving treatment versus supportive therapy, but could not differentiate visual function, numbers of activities lost, quality of life or other aspects of control strategies apart from selective primary control.

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9.1.3.3 Psychosocial intervention versus usual care

Very low- to low-quality evidence from 1 RCT of up to 22 people found better levels of depression, negative affect and activities of daily living in people offered a psychosocial intervention programme versus usual care, but could not differentiate positive affect, perceived autonomy or problem orientation.

9.1.3.4 Self-management versus waiting list

Low- to moderate-quality evidence from 1 RCT of 214 people found better levels of mood, self-efficacy and visual function in people offered self-management versus a waiting list control.

Low- to moderate-quality evidence from 1 RCT of 66 people found better levels of mood, self-efficacy and visual function in people with depression at baseline offered self-management versus a waiting list control, but could not differentiate levels of depression, social support or life orientation.

Low-quality evidence from 1 RCT of 162 people could not differentiate levels of mood, self-efficacy or visual function in people without depression at baseline offered self-management or a waiting list control.

9.1.3.5 Health economic evidence

No cost–utility analyses were identified that were relevant to psychological therapies.

9.1.4 Evidence to recommendations

Relative value of different outcomes	The committee agreed the 2 most important considerations when evaluating the efficacy of psychological and psychosocial interventions for people with AMD were whether they can prevent the onset of depression (and improve mental and emotional wellbeing), and whether they are useful for the treatment of people with depression. The committee considered the most important outcomes to be incident depression (as defined by DSM-IV), the geriatric depression scale (GDS), the Hamilton depression rating score, and the NEI-VFQ visual function score. Secondary outcomes considered to be relevant but less important included activities of daily living scores (ADL), active problem orientation scores, the profile of moods score (POMS), positive and negative affect (PANAS), social support and activities inventories.
Trade-off between benefits and harms	The committee considered that, should these therapies be found to be effective, referral in an appropriate cohort of patients could result in a decreased risk of depression, anxiety and long-term mental illness. Appropriate interventions could also help a patient develop greater resilience and improve emotional wellbeing which would be reflected in an enhanced quality of life. The committee discussed the possibility of any psychological or psychosocial intervention causing harm rather than good, but no evidence suggested this would be likely. The committee agreed that, whilst some interventions (problem solving treatment, psychosocial interventions and self-management) showed positive results in some outcome domains, these effects were not consistent, and were often around or below the defined minimal important differences for these outcomes, where they were available. The evidence suggested the effects of these interventions were greatest in people diagnosed with depression at baseline, with no significant effects found in people without depression at baseline.

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	The psychosocial and psychological interventions in the trials were usually multicomponent, including a number of therapeutic elements (CBT, peer support, counselling, information, exercise therapy and rehabilitative equipment) and it was thus difficult to distinguish which of these components was producing the positive effect, if any. The committee agreed that the evidence was only able to demonstrate that psychosocial therapies may be beneficial in those with diagnosed depression. NICE has published guidance for depression in adults with a chronic physical health problem and this guidance reflects the evidence found here. The committee therefore made a recommendation to cross-refer to this guidance that was also designed to raise awareness of the risk of depression in people with AMD. The committee agreed that the evidence presented did not justify the use of preventative psychological interventions for people not diagnosed with depression, and therefore no recommendation was made for this group. However, the evidence in this group was characterised by wide, inconclusive confidence intervals; accordingly, it was considered a case of 'absence of evidence of benefit' rather than 'evidence of absence of benefit'.
Trade-off between net health benefits and resource use	No health economic evidence was found and this review question was not prioritised for health economic modelling. The committee considered the resource implications inherent in referring a greater number of people with AMD for psychological and psychosocial therapies. However, as the only recommendation was a cross-referral to existing NICE guidance, the committee was confident that the management recommended has been shown to be effective and cost effective.
Quality of evidence	The committee considered the general quality of studies reported in this review to be low. It specified that many of the studies had not adjusted for the measurement of multiple outcomes, and as a result a study that had measured many outcomes or sub-outcomes may find a significant result by chance. Some studies had not used validated outcomes leading to uncertainty as to the importance of some reported outcomes (for example, number of lost activities at follow up). One non-randomised study (Birk et al) had a low number of participants which led to uncertainty regarding its findings that a psychosocial intervention programme could significantly reduce the PANAS negative affect score, GDS score, and activities of daily living score. It also found no significant effect on the PANAS positive affect score, perceived autonomy score and active problem orientation score. This study had not adjusted for multiple measurements. There was no subgroup analysis for those with depression diagnosed at baseline. As such the committee focused on the larger, better-conducted randomised controlled trials included in this review.
Other considerations	The committee discussed the exclusion of studies that included qualitative outcomes. The decision to focus on quantitative evidence that was more robust and could be analysed in a more meaningful way was agreed to be a valid approach since many aspects of a patient's experience, opinions and feelings would still be reported in the quantitative results. These results included quality of life measures, support indexes, self-efficacy scales, and mood scores. The committee noted that there was a lack of evidence in this area, especially to support the findings that there was no preventative effect of psychological therapies for depression in AMD. The committee agreed there was a need for evidence to demonstrate the benefits of emotional support strategies in people with AMD, not just those with diagnosed depression in the general population (the committee considered that a person's wellbeing would have been allowed to deteriorate too far if depression had progressed to mental

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	illness). As such a research recommendation was drafted to assess the effectiveness and cost-effectiveness of these interventions in people with AMD but no diagnosis of depression.

9.1.5 Recommendations

15. **Be aware that people with AMD are at an increased risk of depression. Identify and manage the depression according to the NICE guideline on** depression in adults with a chronic physical health problem.

9.1.6 Research recommendations

8. **What is the effectiveness and cost effectiveness of psychological therapies for the prevention of depression in people with AMD?**

Why this is important

Whilst very low-quality evidence was found looking at the effectiveness of psychological interventions in reducing levels of depression in people with AMD and depression at baseline, no evidence was identified for a preventative effect of psychological interventions for people with AMD but without depression at baseline, where it is believed there may be a positive effect. If pre-emptive referral to these services is going to be justified for the purpose of preventing depression in people with AMD but not depression at baseline, well-conducted RCTs comparing psychological therapies to standard (or usual) care alone are needed, and would fill an important gap in the evidence base around the efficacy of psychological interventions for preventing depression in people with AMD.

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9.2 The effectiveness of support strategies for people with visual impairment and AMD

Review question:

- What is the effectiveness of support strategies for people with visual impairment and AMD (for example reablement services and strategies for optimising existing visual performance)?

9.2.1 Evidence review

The aim of this review was to establish the risks and benefits of support strategies for people with visual loss and AMD.

The review focussed on identifying studies that fulfilled the conditions specified in table below. For full details of the review protocol please see appendix C.

Table 33: PICO table – support strategies for people with impairment and AMD

Population	Adults (18 years and older) with AMD and vision impairment
Interventions	• Low vision services including: • Sensory impairment team (including rehabilitation officers, sight loss advisor, ECLO) or low vision services at home, in the community or in secondary care. • Orientation and mobility programmes • Magnifiers, optical devices and low vision aids. • Daily living aids or assistive technologies
Comparator	Usual care (or waiting list)

Outcomes	• Clinical outcomes (critical):
	  ○ anxiety and depression
	  ○ patient satisfaction
	• Functional capacity, participation, independence and ability to carry out activities of daily living (important)
	• Health related quality of life (important)
	• Impact on carers
	• Safety and adverse events
	• Resource use and costs (critical)

Randomised controlled trials (RCTs) and systematic review of RCTs were included if they compared interventions for supporting AMD people with standard (usual) care. Papers were excluded if they:

- were not published in the English language
- were abstracts, conference proceedings, narrative reviews, case-studies, diagnostic studies, non-comparative studies

9.2.1.1 Description of included studies

A systematic search identified 2,968 references. The references were screened on their titles and abstracts and 56 references were ordered for full-text review. Following review of full-text papers, a total of 6 studies was included in the review, plus an additional 2 RCTs identified through hand searches. Included studies were relevant to the effectiveness of support strategies for people with AMD. A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

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A brief summary of included studies is provided in Table 33. References of included studies are listed in Appendix I.

Table 34: Summary of included studies

Study [Country]	Population	Intervention	Comparator	Outcome
Cheong (2005) [Australia]	People with low vision due to AMD (n=25 people)	Reading practice (home training) before the stand magnifiers prescription	People with no reading practice	Reading rate
Eklund (2004) [Sweden]	People with AMD living at home (n=229 people)	Group-based health education programme led by occupational therapist	Individual programme (1 hour session at the clinic followed up by telephone contact within 2-4 weeks)	Perceived security in the performance of daily occupations
Eklund (2008) [Sweden]	People with AMD living at home (n=229 people)	Group-based health promotion programme led by occupational therapist	Individual standard programme in the low vision clinic	Activities of daily living and self-reported health problems
Parodi (2004) [Italy]	People with advanced AMD (n=28 people)	Prismatic correction	No prismatic correction	Visual acuity
Smith (2005) [UK]	People with AMD (n=225 people)	Custom or standard prism spectacles	Spectacles without prism	Visual acuity, reading rate, quality of life (NEI-VFQ-25), Melbourne low-vision ADL index
Reeves (2004) [UK]	People with AMD (n=226 people)	Enhanced low vision rehabilitation (conventional low vision rehabilitation plus home visits by a rehabilitation office or a community worker)	Conventional low vision rehabilitation by hospital eye service	Vision specific Quality of life; general health; self-reported restriction in everyday activities
Vukicevic 2009 [Australia]	People with AMD (n=48 people)	Eccentric viewing training	No eccentric viewing training	Melbourne low-vision ADL index; visual acuity
Vukicevic 2005 [Australia]	People with AMD (n=58 people)	Eccentric viewing training; magnifier; a combination of eccentric viewing and magnifier	Non-intervention	Melbourne low-vision ADL index

9.2.1 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. No references were identified as being relevant to

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this review question. Health economic modelling was not prioritised for this review question. However, the use of low vision rehabilitation services has been included in the economic model developed for the pharmacological management topic. The unit cost of these support services were therefore identified. Annual use of low vision aids and low vision rehabilitation services are estimated to cost £214.69 and £323.30 per service user, respectively (Meads et al, 2003; PSSRU 2009 & 2016).

9.2.2 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

9.2.2.1 Activities of daily living

Very low-quality evidence reported people receiving a group-based health promotion programme were more likely to be independent in performing daily activities including cleaning, shopping, transportation and cooking compared with those receiving a standard programme at the low-vision clinic at 28 months' follow-up (RR 1.78 [95%CI 1.03 to 3.08]; 1 study of 131 people).

Moderate-quality evidence could not differentiate between people in intervention groups (enhanced low-vision rehabilitation, prism spectacles) and those in control groups in performing activities of daily living and self-rated restriction in everyday activities (2 studies of 419 people).

Moderate-quality evidence reported people receiving eccentric viewing training were more likely to improve performance of activities of daily living compared with those without training following an 8-week study period (MD 6.25 [95%CI 3.72 to 8.78]; 1 study of 48 people).

9.2.2.2 Perceived security in the performance of daily activities

Low-quality evidence reported people receiving a group-based health education programme felt more secure in performing daily occupations at 28 months' follow-up compared with those who received a standard individual low-vision programme (MD 0.42 [95%CI 0.19 to 0.65]; 1 study of 131 people).

9.2.2.3 Visual acuity

Very low-quality evidence could not differentiate visual acuity (proportion worse than 6/60) between people who received a group-based health promotion programme and those who received a standard individual programme at the low-vision clinic at 28 months' follow-up (RR 0.97 [95%CI 0.52 to 1.83]; 1 study of 131 people).

Evidence for spectacle prism correction was contradictory:

- 1 study found that people receiving prism correction achieved substantially better distance vision than those without prism correction following a 360-day study period (MD -0.40 logMAR [95%CI -0.52 to -0.28]; 1 study of 28 people; moderate-quality evidence).
- 1 study found that there is no difference in visual acuity between people with prism correction and those without prism correction at 3 months' follow-up (MD -0.02 logMAR [95%CI 0.07 to 0.03]; 1 study of 225 people; high-quality evidence).

Moderate-quality evidence reported people receiving eccentric viewing training read 19 letters more than those without training following an 8-week study period (MD [near acuity] -0.38 logMAR [95%CI -0.47 to -0.29]; 1 study of 48 people).

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9.2.2.4 Vision-related quality of life

Moderate-quality evidence could not differentiate vision-related quality of life between people in the intervention groups (enhanced low-vision rehabilitation, prism spectacles) and those in the control groups (2 studies of 419 people).

9.2.2.5 General health

Very low-quality evidence reported people receiving a group-based health promotion programme were less likely to rate their general health as 'bad' at 28 months' follow-up, compared with those who received a standard individual programme at the low-vision clinic (RR 0.56, [95%CI 0.31 to 0.98], 1 study of 131).

Moderate-quality evidence showed people receiving an enhanced low-vision rehabilitation programme reported worse physical health (SF-36) compared with those receiving conventional low-vision rehabilitation (MD -6.05 [95%CI -10.2 to -1.91]; 1 study of 124 people), but could not demonstrate a meaningful difference between enhanced and conventional rehabilitation in mental health (SF-36; MD -4.04 [95%CI -7.44 to -0.65]; 1 study of 124 people).

9.2.2.6 Reading performance

Moderate-quality evidence could not differentiate reading rate between enhanced low-vision rehabilitation and conventional rehabilitation at 3 months' follow-up (MD 6.5 words per minute [95%CI -7.84, 20.84], 1 study of 225 people).

9.2.2.7 Health economic evidence

No cost–utility analyses were identified that were relevant to support strategies for people with visual impairment and AMD.

9.2.3 Evidence to recommendations

Relative value of different outcomes	The committee agreed that the most important considerations when evaluating the effectiveness of support strategies for people with AMD were: 1. whether they promote individuals' independent living (and improve vision-related quality of life), 2. whether they are useful for improving vision. Therefore, the committee considered activities of daily living (ADL) score and visual acuity to be the most important outcomes. Other outcomes, including vision-related quality of life, self-assessed general health and reading performance were deemed to be relevant but less important.
Trade-off between benefits and harms	Evidence across a range of interventions was presented. The committee suggested that, in its experience, prism spectacles and health education/promotion programmes were not commonly used in current UK practice. For example, a Swedish study (Eklund 2008) reported that a group-based health promotion programme was effective at improving people's performance in everyday activities, but there is no similar programme available in the NHS. It was further noted that a group-based programme might not be suitable or appropriate for everyone (some people may prefer one-to-one support rather than joining a group). Evidence from 2 studies (Parodi et al., 2004 and Smith et al., 2005) examined the effectiveness of prism spectacles on the visual acuity of people with AMD but, similarly, prism spectacles are not widely prescribed to people with AMD in the UK. In addition, the committee noted that the study results were not consistent. Parodi et al. reported

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that people receiving prism correction could read 20 letters more than those without prism correction after 1 year of study follow-up, but Smith et al.'s UK study reported no difference in visual acuity between treatment and control groups. The committee indicated that the 20 letters of visual acuity difference reported in Parodi et al. (2004) was based on a small study sample (n=28) and the outcome appeared to be much higher than expected. The study also reported a continued improvement in visual acuity across the study period, which the committee agreed was not plausible (visual improvement would be expected shortly after prism correction and would be maintained at this level of improvement over time). The committee agreed that the results from Smith et al. (2005) were much closer to what would be expected in practice. Therefore, the committee agreed that no recommendation could be made on the use of prism spectacles due to their limited use in low-vision services and a lack of a certainty about any benefits they confer.

The committee discussed eccentric viewing training as a support strategy to optimise the peripheral vision of people with AMD, and agreed that the benefit presented in the included studies was plausible. However, such training is not appropriate for everyone, and in particular is only suitable for those with bilateral AMD. The committee noted that the evidence showed that people who had eccentric viewing training could read approximately 19 letters more than those without training, and that such a difference was observed after an 8-week study period (Vukicevic 2009). The committee considered that 8 weeks was a relatively short follow-up period to achieve the observed treatment benefit, though it agreed that such an effect was possible, especially in a trial setting. Hence, the committee made a recommendation to consider eccentric viewing training for those with bilateral central vision loss so as to maximise the use of their peripheral vision.

Evidence from a UK study (Reeves 2005) showed that enhanced models of low-vision rehabilitation were no more effective than conventional low-vision rehabilitation provided by a healthcare eye service. Both of the enhanced models of low-vision rehabilitation reviewed in the evidence included the elements of conventional rehabilitation services, supplemented by home visits from either a trained rehabilitation officer or a community care worker. The committee acknowledged that the evidence presented included studies comparing different models of low vision services; however, in committee members' experience, the main components outlined in the conventional rehabilitation model did not reflect typical low-vision rehabilitation provided in everyday clinical practice in the UK, as many components were not routinely available or provided in practice. The conventional rehabilitation model reported in the trial was more comprehensive than what is generally currently available in the UK.

Therefore, the comparison made between enhanced and conventional low-vision rehabilitation did not provide robust evidence with which to estimate any potential treatment effect. It would be more valuable to be able to quantify the benefits of improving current provision to a level commensurate with 'conventional rehabilitation' in the trial.

The committee emphasised that people with vision loss due to AMD should be referred to low-vision services to obtain the necessary support, but that wide variation exists in service provision across the UK, and a lack of low-vision services in many parts of the country means that not all people with AMD are able to obtain support. The committee agreed that the evidence presented could not demonstrate the beneficial effect of low-vision services, but committee members indicated that they were aware of a number of published studies reporting the effectiveness of low-vision services (i.e. improved quality of life) in people with low vision; however, none of those studies

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	exclusively included people with AMD, or they were not designed as randomised trials and had therefore been excluded from the evidence base. Having reviewed the included evidence, the committee agreed that the evidence was not sufficiently robust to make a strong recommendation for low vision services. However based on committee members' experience of the benefits of the support provided, and the evidence available from non-AMD populations (Binns et al., 2012), it agreed to recommend that the provision of such services should be considered for people with AMD when they experience vision problems. Due to the conflict between the committee's understanding of the benefits of low-vision services and the lack of any high-quality evidence to substantiate this, the committee agreed that more research would be useful to understand the impact of improving low-vision services specifically on people with AMD and made a research recommendation to this effect. Two Swedish studies (Eklund 2004 and Eklund 2008) reported on group-based programmes led by occupational therapists, and the committee noted that both studies showed beneficial effects through improvements in independent living and perceived security in performing daily activities. Although such a group programme is not currently available on the NHS, the committee agreed that a group-based intervention should be considered as an approach when delivering low-vision services to people with AMD. This was reflected in the recommendation on low-vision service provision.
Trade-off between net health benefits and resource use	No health economic evidence was found and this review question was not prioritised for health economic modelling. The committee discussed a scenario in which people with AMD are not referred to the low-vision service until their vision has declined substantially, consequently restricting potential treatments, including many that might have been available with a timely referral. The committee considered that such a delayed referral could have potential resource implications by missing the chance to provide effective treatment. The committee agreed that the timely referral of people in the early stages of AMD to a low-vision service as soon as vision problems occur would constitute a good use of resources, and enable people with AMD to obtain appropriate support to optimise their vision. The committee discussed the potential resource implications of low-vision services. It noted that there is a lack of low-vision services in many parts of the country, and therefore recommending low-vision service would be an important service-level change in many areas. The committee was aware that the outcomes presented for low-vision services were of low quality and therefore agreed by consensus, based on group-members' experience and extrapolation from evidence of generic low-vision services of which they were aware, to recommend that low-vision services should be considered for people with AMD when vision problems occur. The provision of low-vision services for some people is a common component of the costs accounted for in economic evaluations of anti-VEGFs, including the de novo economic modelling undertaken for this guideline (see section 10.1). Here, the unit cost for a person accessing a low-vision rehabilitation service was estimated to be £323.30 per year (Meads et al. 2003). This is a relatively low cost resource; for example, the unit cost of OCT examination is £115.52 (NHS reference costs 2014–15), and a number of OCTs will be performed annually as part of the routine monitoring of people with AMD. Based on its unit cost, low-vision rehabilitation services would only be required to make modest QALY gains in order to be considered cost-effective (e.g. 0.015 QALYs gained in 1 year at a cost

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	of £306.23 would have an ICER of £20,000). The committee was confident that such services have at least this magnitude of impact. The committee noted that, although group-based programmes are not available on the NHS (such as those described by Eklund [2004] and Eklund [2008]), there is currently some provision of such services by the voluntary sector. The committee was aware that having the NHS provide such group-based intervention services, rather than voluntary sector provision, would potentially have public resource implications.
Quality of evidence	The committee considered the general quality of evidence reported in this review to be low. It specified that high dropout rates (Eklund 2004 and Eklund 2008) and small sample sizes (Parodi 2004) were 2 of the main factors affecting the quality of evidence. In addition, the committee noted that some study outcomes (e.g. general health) were difficult to interpret and potentially counterintuitive. For example, 1 study (Reeves 2004) reported that people receiving enhanced low-vision rehabilitation (home visits from a rehabilitation officer) reported worse physical and mental health than those who received conventional rehabilitation. The committee suggested that a possible explanation for this unexpected finding was that the enhanced programme could potentially improve people's confidence, enabling them to discuss their health problems more openly. Four studies (Reeves 2004, Smith 2005, Eklund 2008 and Vukicevic 2009) reported activities of daily living scores, and used 3 different types of instruments to measure the treatment effect. Although these instruments had been validated, clinically important differences were not defined or reported in the studies, leading to uncertainty about the interpretation of the estimated effect. The committee also discussed the control groups in some included studies, noting that they were not representative of current UK practice (for example, the availability of the service provided). The committee further noted that standard care was not always a 'true' intervention-free arm (i.e. participants in the non-intervention group in Vukicevic 2009 received support but no rehabilitation advice). The committee therefore agreed that the true extent of observed effects in the trials is difficult to establish.
Other considerations	The committee was mindful that, currently, eccentric viewing training is not commonly available in the NHS, and agreed that the evidence of its effectiveness was not strong enough to underpin a strong recommendation that would mandate its routine provision throughout the system. However, the committee was aware that some voluntary groups provide skills training for people with visual impairment that includes the technique. Therefore, it concluded that a weaker ('consider') recommendation would encourage healthcare professionals to refer appropriate patients to NHS services, where they exist, and, where they do not, signpost those patients to other sources of training that may be available. The committee noted that people with AMD often have significant comorbidities. Since no evidence was identified suggesting these should be managed differently in people with AMD to the general population, the committee agreed the appropriate way to address this was to cross-reference to the nice guideline on assessment and management of multimorbidity.

9.2.4 Recommendations

16. **Be aware that many people with AMD have other significant comorbidities. For guidance on optimising care for adults with multiple long-term conditions, see the NICE guideline on multimorbidity.**

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17. **Offer certification of visual impairment to all people with AMD as soon as they become eligible, even if they are still receiving active treatment.**

18. **Consider referring people with AMD causing visual impairment to low-vision services.**

19. **Consider a group-based rehabilitation programme in addition to a low-vision service to promote independent living for people with AMD.**

20. **Consider eccentric viewing training for people with central vision loss in both eyes.**

9.2.5 Research recommendations

9. What is the impact of optimising low vision services on people with AMD?

Why this is important

The committee noted that, there are published studies reporting the effectiveness of low-vision services (for instance improved quality of life), but these studies either did not exclusively include people with AMD, or were not designed as randomised trials. The lack of robust evidence base makes it difficult to make a strong recommendation for low-vision services. Well conducted trials should evaluate the effectiveness of low vision services on people with AMD, and should include outcome measures such as visual acuity, functional performance of daily activities, as well as vision and health-related quality of life to enable the results to be used to assess the impact of low vision service on people being referred for the service.

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10 Pharmacological management

Treatment of late AMD (wet active) was transformed by the introduction of anti-vascular endothelial growth factor (VEGF) agents in the mid-2000s. Before the introduction of anti-VEGFs, the only treatment available for neovascular AMD was photodynamic therapy or focal argon laser. These treatments were only suitable for a subset of patients and the clinical benefits were small with a reduction in the rate of visual loss and no improvement in vision. By contrast, anti-VEGF agents are suitable for all subtypes of late AMD (wet active) and on average improve vision, at least in the first 2 years after starting therapy. However, the delivery of anti-VEGF agents required a new way of working for ophthalmology units with frequent (monthly) review and intra-ocular injection procedures in a large group of patients who had not had any treatment before. This has necessitated setting up new services, with new personnel, equipment and space in most ophthalmology units across the country.

The original clinical trials showing anti-VEGF treatment was effective in late AMD (wet active) opened the door to this new treatment but left many questions unanswered, such as what vision range this treatment was effective for, when can treatment be discontinued, and is it worthwhile switching from one agent to another. Evidence relating to some of these questions has now accumulated. Given the burden of monthly eye injections to the patients and to hospital eye services a key question is what is the ideal treatment regimen which minimises visits and treatments, maximises cost effectiveness whilst maintaining clinical effectiveness?

There is also uncertainty around which eye(s) of a person with late AMD (wet active) should receive treatment. In practice AMD invariably affects both eyes, and a person with late AMD (wet active) in 1 eye may have a fellow eye with better or worse vision which may or may not require similar treatment immediately or at a later stage. These complexities affect the quality of life for a person with AMD as well as directly influencing cost-effectiveness of treatment. Most existing models of AMD simulate treatment in 1 eye only – usually, this is (implicitly or explicitly) assumed to be the person's better-seeing eye – and those that have adopted a 2-eye structure have not assessed the incremental cost effectiveness of treatment strategies targeting better- and/or worse-seeing eyes.

There are currently licensed treatments for wet AMD and a treatment (bevacizumab) which has been used to treat AMD despite not having a marketing authorisation for such use. It is clear that, without authorisation in the product's SPC, the use of bevacizumab in AMD is off-label. The MHRA view is that the dividing of prepared vials of bevacizumab into smaller doses for intraocular use also makes it unlicensed. Doctors are required by the GMC to use licensed medications where available. Moreover, the UK government has previously decided that it will not disregard drug licensing purely to save money on drug costs (see parliamentary written question 227588). However, intraocular bevacizumab is widely used in many other countries, and many UK authorities, including the Royal College of Ophthalmologists, have called for it to be made available for NHS practice, in view of the substantial cost savings that would be engendered.

NICE has previously performed technology appraisals, which are incorporated in this guideline, on the licensed anti-VEGF agents. These recommend aflibercept and ranibizumab for late AMD (wet active), and commissioners in England and Wales are bound to fund them as a result. For this guideline, the committee has considered the published evidence on clinical effectiveness and cost effectiveness of all treatments for late AMD (wet active), regardless of license status.

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10.1 Antiangiogenic therapies and frequency of administration

Review questions:

- What is the effectiveness of different antiangiogenic therapies (including photodynamic therapy) for the treatment of late AMD (wet active)?
- What is the effectiveness of different frequencies of administration of antiangiogenic therapies for the treatment of late AMD (wet active)?

10.1.1 Evidence review

This review was a collaboration between the NICE Internal Clinical Guidelines Team and the Cochrane Eyes and Vision Group. For consistency with the rest of the guideline, some analyses have been adapted from those in the published Cochrane reviews, and therefore results may not be identical to those reported in the Cochrane reviews. In particular, outcomes reported as odds ratios in the Cochrane reviews have been converted to relative risks.

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Table 35: PICO table – antiangiogenic therapies for people with late AMD (wet active)

Population	Adults (18 years and older) diagnosed with late AMD (wet active, treatment naïve)
Interventions	Comparative trials of: • Aflibercept • Bevacizumab • Ranibizumab • Photodynamic therapy • Placebo • No treatment
Comparator	Any of the above
Outcomes	Clinical outcomes: • Visual acuity (LogMAR) • Safety and adverse events • Functional capacity, participation, independence and ability to carry out activities of daily living. • Health related quality of life • Impact on carers • Resource use and costs

Table 36: PICO table – treatment frequency for antiangiogenic therapies for people with late AMD (wet active)

Population	Adults (18 years and older) diagnosed with late AMD (wet active)
Interventions	Different frequencies of administration for: • Aflibercept • Bevacizumab • Ranibizumab • Photodynamic therapy For example: • Ranibizumab – treat-and-extend, PRN • Aflibercept- dosing as described in SPC • Bevacizumab - dosing as described in trial evidence Other frequencies of administration found in trial evidence.
Comparator	Any of the above
Outcomes	Clinical outcomes: • Visual acuity (LogMAR) • Safety and adverse events • Functional capacity, participation, independence and ability to carry out activities of daily living. • Health related quality of life • Impact on carers • Resource use and costs

Randomised controlled trials (RCTs) and systematic reviews of RCTs were included if they compared antiangiogenic therapies (including photodynamic therapy) or different frequencies of administration. Papers were excluded if they:

- were not published in the English language
- reported non-randomised or cohort studies

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- were abstracts, conference proceedings, narrative reviews, case-studies, non-comparative studies

10.1.1.1 Description of included studies-effectiveness of antiangiogenic therapies and treatment frequency

The search undertaken by the Cochrane group identified 360 references on photodynamic therapy (PDT) for AMD up to 2005, and 4 studies met the study inclusion criteria and were included in the review. We also conducted an additional update search on PDT, identifying 326 references from which 1 study comparing PDT and anti-vascular endothelial growth factor treatment for neovascular AMD was included in the review.

The search undertaken by the Cochrane group identified 5,249 references on anti-vascular endothelial growth factor (anti-VEGF) treatment for neovascular AMD up to 2015, and 12 studies on bevacizumab and/or ranibizumab met the study inclusion criteria and were included in the review. The Cochrane group also searched through databases for aflibercept for neovascular AMD, identified 9,961 references up to 2015. Two studies met the inclusion criteria and were included in the review. An update search carried out near the end of guideline development identified 2 further studies including: one RCT (Schauwvlieghe 2016) compared the effectiveness of bevacizumab and ranibizumab treatment and one study (Vogel 2016) compared vision-related function between people who received aflibercept and ranibizumab injection.

The search undertaken by the Cochrane group was conducted on treatment schedules for treating neovascular AMD up to 2016, and 727 references were identified. Thirteen[8] studies met the inclusion criteria and were included in the review. An update search carried out near the end of guideline development identified 2 further studies. Of these, one RCT (Eldem 2015) examined visual acuity between patients treated with either a PRN regimen, requiring routine monitoring to inform treatment decisions, or a PRN-and-extend regimen, where the interval between monitoring appointments could be extended by the clinician. Another RCT (Chan 2015) compared visual outcomes between people receiving 0.5 or 2 mg ranibizumab PRN or monthly injections. Some studies, like this one, used dosages that are not currently licensed, however these also included licensed dosages (2 mg aflibercept, 0.5 mg ranibizumab) and were included in the evidence. A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

1 newly published RCT (TREND; Silva et al., 2017) was added to the evidence base when it was highlighted by a stakeholder during consultation on the draft guideline. This large, multicentre trial compares treat-and-extend administration of ranibizumab with monthly administration of ranibizumab. Although the publication of this study postdated the search dates for the guideline, it was judged to be of sufficient importance to include without updating searches.

A brief summary of included studies is provided in Tables 37–39. References of included studies are listed in Appendix I.

Table 37: Photodynamic therapy vs control

Study	Population	Intervention	Comparator	Outcome
TAP 1999	People with subfoveal CNV lesions caused by AMD (n=609 people)	Photodynamic therapy following verteporfin injection	Photodynamic therapy following intravenous 5% dextrose	Visual acuity at 12 and 24 months

[8] Original 12 studies included. EXCITE study was added after reviewing the evidence (Cochrane review excluded the study due to the eligibility of comparison doses)

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Study	Population	Intervention	Comparator	Outcome
VIM 2005	People with minimally classic CNV due to AMD (n=117 people)	Photodynamic therapy following verteporfin injection	Photodynamic therapy following intravenous 5% dextrose	Visual acuity at 12 and 24 months
VIO 2007	People with occult but no classic CNV due to AMD (n=364 people)	Photodynamic therapy (verteporfin)	Placebo (5% dextrose in water for injection)	Loss of fewer than 15 letters
VIP 2001	People with subfoveal CNV cause by AMD (n=339 people)	Photodynamic therapy following verteporfin injection	Photodynamic therapy following intravenous 5% dextrose	Visual acuity

Table 38: Anti-vascular endothelial growth factor for late AMD (wet active)

Study	Population	Intervention	Comparator	Outcome
Bevacizumab vs control				
ABC 2010	People with CNV lesion in study eye due to AMD (n=131 people)	Bevacizumab	Standard treatment (including pegaptanib, verteporfin PDT, sham injection)	Proportion of people gaining 15 letter or more at 1 year
Sacu 2009	People with late AMD (wet active) (n=28 people)	Bevacizumab	Verteporfin PDT plus intravitreal triamcinolone	Change in mean visual acuity
Ranibizumab vs control				
ANCHOR 2006	People with CNV due to AMD (n=423 people)	Ranibizumab	Sham injection	Proportion of people losing fewer than 15 letter at 12 months
MARINA 2006	People with active primary or recurrent subfoveal lesions with CNV secondary to AMD (n=716 people)	Ranibizumab	Sham injection	Proportion of people losing fewer than 15 letter at 12 months
PIER 2008	People with primary or recurrent subfoveal CNV secondary to AMD(n=184 people)	Ranibizumab	Sham injection	Changes in VA at 1 year
LAPTOP 2013	People with treatment naïve PCV (n=93 people)	Ranibizumab	Photodynamic therapy (verteporfin)	Proportion of people losing of more than 0.2logMAR at 24 weeks
Bevacizumab vs ranibizumab				
Biswas 2011	People with presence of subfoveal or juxtafoveal CNV (n=120 people)	Bevacizumab	Ranibizumab	Changes in BCVA

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CATT 2011	People with untreated active CNV due to AMD (n=1,208 people)	Bevacizumab	Ranibizumab	Change in visual acuity
GEFAL 2013	People with active foveal neovascular AMD (n=501 people)	Bevacizumab	Ranibizumab	Change in BCVA at 1 year
IVAN 2013	People with untreated neovascular AMD (n=628 people)	Bevacizumab	Ranibizumab	Change in BCVA at 2 years
LUCAS 2015	People with untreated active neovascular AMD in study eye (n=441 people)	Bevacizumab	Ranibizumab	Change in BCVA at 2 years
MANTA 2013	People with active primary or recurrent subfoveal lesion with CNV (n=321 people)	Bevacizumab	Ranibizumab	Change in BCVA at 1 year
Schauwvlieghe 2016	People with primary or recurrent sub- or juxtafoveal CNV due to AMD (n=327 people)	Bevacizumab	Ranibizumab	Change in BCVA at 1 year
Subramanian 2010	People with presence of symptomatic CNV (n=28 people)	Bevacizumab	Ranibizumab	Visual acuity
Aflibercept vs Ranibizumab				
VIEW 1	People diagnosed with neovascular AMD in the study eye (n=1,217 people)	Aflibercept	Ranibizumab	Proportion of people maintaining vision at week 52
VIEW 2	People diagnosed with neovascular AMD in the study eye (n=1,240 people)	Aflibercept	Ranibizumab	Proportion of people maintaining vision at week 52
Yuzawa 2015	People diagnosed with neovascular AMD in the study eye (VIEW 1 and VIEW2) (n=2,419 people)	Aflibercept	Ranibizumab	NEI-VFQ score

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Table 39: Effectiveness of treatment schedules of antiangiogenic therapies for the treatment of late AMD (wet active)

Study	Population	Intervention	Comparisons	Outcome
Bevacizumab				
Barikian 2015	People with subfoveal choroidal neovascular membrane (CNV) attributable to AMD (n=90 people)	Bevacizumab	1 injection, PRN; Every 2 weeks for 3 injections, PRN; Every 4 week for 3 injections, PRN	Visual acuity improvement
BeMOc 2013	People were treatment-naive with active subfoveal choroidal neovascularisation of minimally classic or occult type, secondary to AMD (n=100 people)	Bevacizumab	PRN Every 4 weeks for 3 injections, then PRN	Proportion with visual stability, defined as less than or equal to loss of 15 letters from baseline
El-Mollagyess 2012	People with subfoveal choroidal neovascularization (CNV) attributable to AMD (n=120 people)	Bevacizumab	PRN Every 4 to 6 weeks	Visual acuity improvement
GMAN 2015	People with a diagnosis of neovascular AMD (n=331 people)	Bevacizumab	3 monthly loading, then PRN; 3 monthly loading, then every 12 weeks (routine treatment)	Mean visual acuity
Lushchyk 2013	People with untreated active choroidal neovascularization due to ARMD; presence of active leakage to establish active choroidal neovascularization defined as a leakage (n=191 people)	Bevacizumab	Every 4 weeks; Every 6 weeks; Every 8 weeks	Visual acuity
NATTB 2012	People with untreated active choroidal neovascularization (n=185 people_	Bevacizumab	Every 6 weeks for 8 injections; Every 6 weeks for the first 3 injections, then every 12 weeks for 2 injections	Mean change in visual acuity
Ranibizumab				
Chan 2015	People being treated for vascularised pigment epithelial detachment due to AMD (n=36 people)	Ranibizumab	0.5mg monthly for 12 months; 0.5mg monthly for 4 months followed by PRN; 2.0mg monthly for 12 months; 2.0mg monthly for 4 months followed by PRN	Proportion of people gain 15 letter or more

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EXCITE 2010	People with subfoveal CNV secondary to AMD, with predominantly classic, minimally classic, or occult (with no classic component) lesions (n=353 people)	Ranibizumab	3 initial monthly injections followed by 0.3/0.5mg quarterly; 0.3 mg monthly	Visual acuity
Eldem 2015	People with CNV due to AMD (treatment naïve) (n=93 people)	Ranibizumab	PRN & extend (PRN with variable follow-up of up to 8 weeks, depending on disease activity) PRN	Mean change in VA; proportion of people gain or loss 15 letters or more
HARBOR 2013	People with active subfoveal lesions with classic CNV, some classic CNV component, or purely occult CNV (n=1,098 people)	Ranibizumab	0.5mg monthly; 2mg monthly	Mean visual acuity change
TREND	People with treatment-naive neovascular AMD (n=650 people)	Ranibizumab	Monthly for 2 months, then treat-an-extend; Monthly for 1 year	Visual acuity changes
TREX-AMD 2015	People were treatment-naïve choroidal neovascularization secondary to exudative AMD (n=60 people)	Ranibizumab	Monthly for 3 months, then treat-an-extend; Monthly for 2 years	Visual acuity changes
Bevacizumab vs ranibizumab				
CATT 2011	People with untreated active CNV due to AMD (n=1,208 people)	Bevacizumab Ranibizumab	PRN Every 4 weeks for first year, then re-randomisation to injections PRN or every 4 weeks	Visual acuity changes
IVAN 2012	People with any component of the neovascular lesion (CNV, blood, serous pigment epithelial detachment, elevated blocked fluorescence (n=628 people)	Bevacizumab Ranibizumab	1.25mg monthly; 1.25mg monthly for 3 months, then PRN; 0.5mg monthly; 0.5mg monthly for 3 months, then PRN	
Aflibercept				
CLEAR-IT2 2011	People had a diagnosis of subfoveal CNV secondary to wet AMD (n=159 people)	Aflibercept	0.5/2mg every 4 weeks; 0.5/2/4mg every 12 weeks	Visual acuity change; proportion of people with a gain of 15 or more letters, proportion of

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				people with a loss of 15 or more letters
VIEW 2012	People diagnosed with neovascular AMD (n=2,457 people)	Aflibercept ranibizumab	0.5/2mg every 4 week 2mg every 8 weeks for initial 3, then every 4 weeks injections 0.5mg every 4 weeks	

10.1.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. From these, 77 references were retrieved for full-text review, of which 22 studies were included. NICE technology appraisals evaluating the use of anti-VEGF therapies and/or PDT were also reviewed in order to identify any cost–utility evidence not captured in peer-reviewed journals.

10.1.2.1 Review of included cost–utility analyses

Detailed reviews of all included studies can be found in Appendix J; a brief summary is provided here.

Of the 22 studies identified, 17 provided cost-effectiveness evidence regarding the use of anti-VEGF therapies. Three studies were country adaptations of an analysis by Colquitt et al. (2008) that provided the same conclusions as the original study. To avoid placing undue weight on one analysis, the 3 adaptations are not included in the evidence review. Two NICE technology appraisal submissions were identified with cost–utility analyses relevant to these review questions. These are TA 155 (ranibizumab and pegaptanib for the treatment of AMD) and TA 294 (aflibercept for treating wet age‑related macular degeneration). Extensive detail of the health economic analysis is available for the latter of these.

Nine studies included a bevacizumab treatment arm, and in each case bevacizumab was found to have an ICER of less than £20,000 per QALY gained (Dakin et al. 2014; Elshout et al. 2014; Fletcher et al. 2008; Hurley et al. 2008; Patel et al. 2012; Raftery et al. 2007; Stein et al. 2014; Vottonen & Kankaanpää, 2016; Wu et al. 2016). This was typically attributed to a similar level of effectiveness compared with alternative anti-VEGF therapies and a substantially lower treatment cost. In the 5 analyses that compared aflibercept with ranibizumab, without a bevacizumab arm, 3 reported aflibercept as having an ICER of less than £20,000 per QALY (Panchmatia et al. 2016; TA 294; Yanagi et al. 2016). The remaining 2 studies found ranibizumab to have an ICER of less than £20,000 per QALY (Claxton et al. 2016; Ghosh et al. 2016). Where studies were funded by the manufacturer of an intervention, the results went in favour of the manufacturer-funded intervention.

Five of the 22 studies identified included PDT as an intervention, but no anti-VEGF therapy as a comparator (Grieve et al. 2009; Hopley et al 2004; Meads et al. 2003; Meads & Moore 2001; Smith 2004). In each case, PDT was compared with providing no active treatment. These studies are generally older than the anti-VEGF evidence base, published before the advent of anti-VEGF therapy. Only 1 study determined that PDT was associated with an ICER below £30,000 per QALY gained compared with providing no active treatment. A NICE technology appraisal for PDT (TA 68) was also reviewed, though a thorough review of the methodology was not possible. In the 5 studies that compared PDT or BSC with at least 1 anti-VEGF therapy, 4 identified treatment with an anti-VEGF was dominant or had an ICER

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below £30,000 or dominant (Colquitt et al. 2008; Elshout et al. 2014; Hurley et al. 2008; Wu et al. 2016).

10.1.2.2 Health economic analysis

No directly applicable studies with only minor limitations were found that covered all the comparators for this guideline. A new economic analysis was therefore undertaken. A full description of the health economic model can be found in Appendix J; a summary is presented here. The model was developed in line with the NICE reference case (NICE, 2012) and Guidelines Manual (NICE, 2014).

A single health economic model structure was developed to simultaneously address review questions 12 (antiangiogenic agents), 18 (treatment frequencies), 10 (upper acuity threshold for initiation) and 25 (lower acuity threshold for initiation) It has been shown that modelling interdependent decisions such as these in a single pathway is conceptually and analytically superior to the alternative of 'piecewise' analysis (see Tappenden et al. 2012, 2013).

10.1.2.2.1 Methods

A patient-level Markov ('microsimulation') model was developed, with a cycle length of 1 year and a lifetime horizon. Unlike many existing cost–utility models, the new model is a '2-eye' model, in which the treatment and visual acuity of both eyes are modelled simultaneously and independently.

Each eye in the model is in 1 of 6 health states defined by 15-ETDRS-letter ranges of best-corrected visual acuity (VA), so there a total of 36 unique VA states across 2 eyes. Alongside these VA states are another 6 treatment states, defined by where each eye is in the treatment pathway. All patients are assumed to enter the model with late AMD (wet active) present in at least 1 eye. The fellow eye of patients who present with unilateral disease will start the model without late AMD (wet active), but this can develop over time, at a rate of 42% over 3 years (Zarranz-Ventura et al. 2014). At any given time, a living patient in the model is simultaneously situated in 2 VA states, 1 for each eye, and 2 treatment states, 1 for each eye (Figure 1). Mortality is modelled using National Life Tables for England and Wales (2013–15), increased by hazard ratios of 1.23 or 1.54 in people with some or severe visual impairment, respectively (Christ et al., 2008).

The VA of an eye can change due to treatment and due to progression of disease. Transition probabilities are derived from a network meta-analysis (NMA) which uses the standardised mean change in VA reported in clinical trials. By using a mean VA change treatment effect obtained from the NMA for each treatment, and assuming it to be normally distributed, it is possible to estimate the probability that an eye gains any given number of letters. Previous Markov models have typically assumed that an eye must gain 15 or more letters to move up or down by one 15-letter health state. Departing from this, the new model assumes that, on average, an eye is in the middle of its 15-letter VA health state, meaning the probability of moving up (or down) by 1 health state is in fact the probability of gaining (or losing) between 7.5 and 22.5 letters. Similarly, the probability of moving up or down by 2 health states is equal to the probability of gaining (or losing) more than 22.5 letters. A simulation exercise was undertaken to confirm that this is more accurate than previous modelling assumptions.

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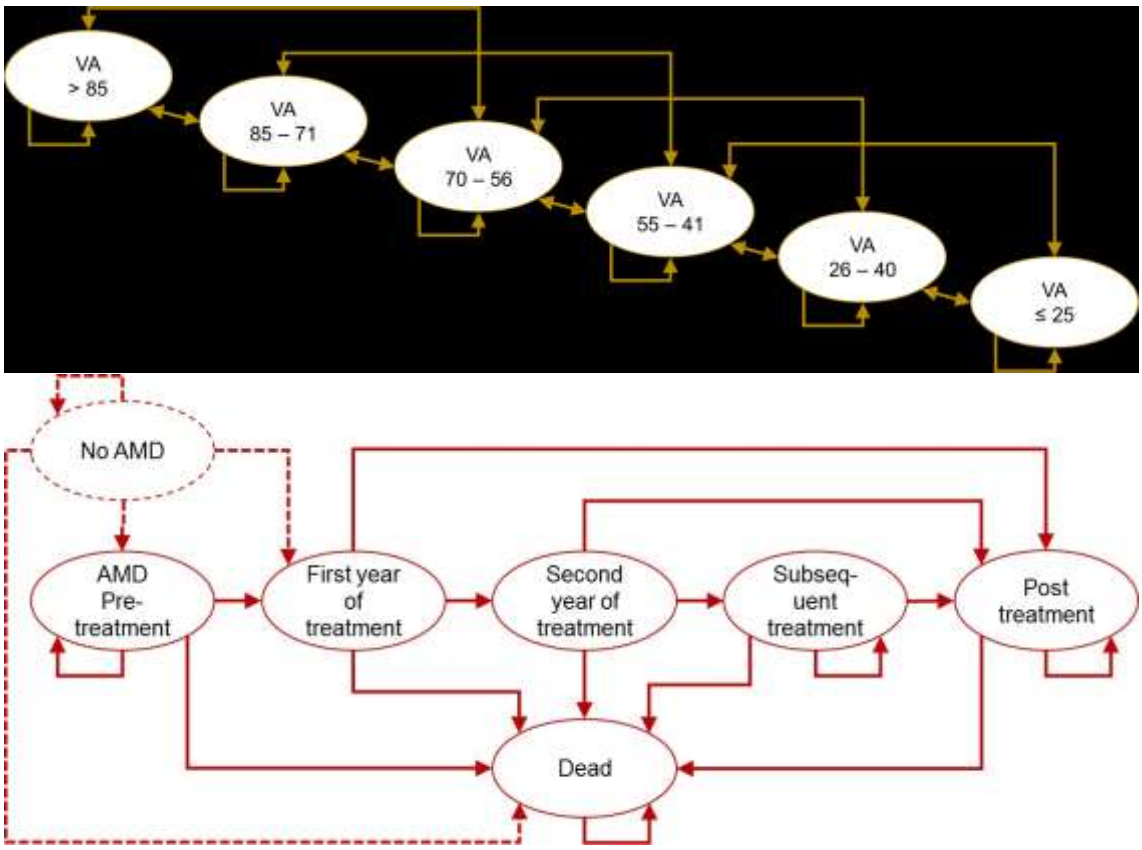

Note: Dashed lines indicate health states and transitions that only a fellow eye with no AMD can experience.

Figure 1: Schematic of health economic model

Interventions

Comparators included in the model are comprehensive treatment strategies, made up of several components. The first is the choice of treatment; therapies included are aflibercept (2.0 mg), bevacizumab (1.25 mg), ranibizumab (0.5 mg), verteporfin plus photodynamic therapy (PDT), and 'no active treatment'. This choice is made alongside a choice of treatment frequency (or dosing regimen), such as 1-monthly, 2-monthly, or PRN (treat as needed), and decision rules about which eyes should be treated. Four decision rules relate to the extending the VA range in which eyes are eligible for treatment (or not), while 2 relate to restricting treatment to better-seeing eyes only (or not). The different combinations of these aspects multiply to produce 161 unique treatment strategies.

Some regimens included in the model have little or no evidence of effectiveness (for example, 2-monthly bevacizumab). However, both components of this regimen – the agent, bevacizumab, and the protocol, 2-monthly injections – are themselves well connected within the network. An effect size attributable to bevacizumab and an effect size attributable to routine, 2-monthly injections, can therefore be combined to produce an estimate of the effectiveness of the regimen. The 'PRN-and-extend' treatment protocol (PRNX) is not included in our base-case analysis, however, as it is connected to the NMA only by a single trial with a small sample. The limited evidence base means our NMA predicts PRNX to be superior to routine monthly treatment, which is not consistent with the expected dose–response relationship. Therefore, 137 unique treatment strategies were considered suitable for comparison in our base-case analysis, and 'PRN-and-extend' regimens were explored in scenario analyses.

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Baseline data

The model requires baseline age and gender data, which were obtained from a large, observational UK AMD database (Tufail et al., 2014). The mean age of these patients was 79.7 years (range: 55–101), and 36.6% of the sample was male.

Baseline VA data were also required, to inform the starting distribution of eyes. No published data were identified to inform this. Instead, through guideline committee members, data were obtained data from two UK patient samples (Royal Liverpool and Broadgreen University Hospitals Trust and Sheffield Teaching Hospitals NHS Foundation Trust).

Effectiveness data

A network meta-analysis was conducted to inform the relative effectiveness of different interventions. The key effectiveness outcomes were standardised mean differences in VA at 1 and 2 years, obtained from the randomised clinical trial evidence. The synthesis model produced a relative effectiveness coefficient for the drug used, the dosing regimen used, and whether or not an initial treatment loading phase was used. A baseline synthesis was undertaken for the reference treatment, monthly ranibizumab. The mean change treatment effects are assumed to be normally distributed with a common standard deviation.

Year 1 transition probabilities are weighted by baseline VA using observational UK data (Buckle et al. 2016). The data show that a mean treatment effect should be weighted in favour of eyes with worse baseline VA, which have greater potential to improve, and against eyes with better baseline VA, which have greater potential to decline. Beyond year 2, long-term VA change is anchored to that observed in third-year follow-up evidence of treatment with PRN ranibizumab in the UK (-2.5 letters per year; Tufail et al., 2014). This reference change is subject to the relative treatment effects for year 1 to year 2, with the exception that the effect of an initial loading phase is assumed to cease in the long term. Long-term injection frequency is also anchored to ranibizumab PRN from the same UK data (3.7 injections per year), with discontinuous regimens (e.g. TREX) varying from this based on an indirect comparison of 2-year RCTs. Long-term injections on continuous regimens (e.g. monthly injections) are assumed to require the planned number of injections for that regimen (e.g. 12 per year), adjusted to reflect sub-perfect adherence shown in the UK IVAN trial (91% adherence).

Treatment discontinuation of each treatment is informed by another NMA using 1-year discontinuation rates from the trial data. The resulting 1-year rates are assumed to remain constant beyond year 1. Eyes that discontinue treatment are assumed to experience VA change associated with sham injections (no active treatment).

Resource use and costs

Treatment administration is assumed to occur at NHS hospital outpatient clinics. The number of injections required in year 1 and year 2 was obtained from those clinical trials that reported such data. For those regimens with no such data, the number of injections was estimated using the data for other treatments. The number of injections is assumed to remain constant in treated eyes beyond year 2 (Tufail et al., 2014; Gillies et al., 2015). Monitoring occurs at every treatment appointment by an OCT examination. PRN ranibizumab and PRN bevacizumab incur additional OCT appointments, to account for those at which treatment is not required (Tufail et al., 2014).

Resources required to treat severe adverse events associated with anti-VEGF treatment are included in the model (cataracts, endophthalmitis and retinal detachment). Non-ocular events (gastrointestinal disorders and stroke), and events associated with PDT specifically, are also captured. Similar to many previous cost–utility analyses, resources associated with the management and consequences of profound vision loss are included (Meads et al. 2003).

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All unit costs were measured from an NHS and PSS perspective (NICE Guidelines Manual 2014) and, where necessary, inflated to 2014–15 prices (Curtis 2015).

Utilities

Utility associated with VA was modelled used the regression analysis resulting from a UK time trade-off study using simulation contact lenses (Czoski-Murray et al. 2009). A scaling factor of 0.3 was applied to this, as per previous models (TA 294; TA 346), to inform the relative impact on utility of VA change in a person's worse-seeing eye compared with their better-seeing eye. A scenario analysis using health state utilities derived from the widely-used Brown et al. (2000) study is also included in the model.

Adverse event decrements are included from a combination of published sources and guideline committee advice. Previous CUAs invariably assume that all uncomplicated intravitreal injections have no disutility for the patient. Both clinical and patient members of the guideline committee agreed that this does not reflect their experience. Therefore, a proportion of simulated patients (50% in the base case) experience disutility reflecting injection-related anxiety and/or pain; in the absence of direct evidence, this was assumed to be equivalent to a 100% utility loss for 1 day.

Model outcomes

Total and incremental cost and QALY outcomes are combined to produces ICERs associated with each treatment strategy. Net health benefits (NHB), evaluated at opportunity costs for 1 QALY of £20,000 and £30,000, were also calculated. NHB can be interpreted as the net balance of the QALYs gained by a strategy – for example, by the AMD patient receiving treatment – and the QALYs foregone by not using those resources elsewhere in the health care system. A positive NHB indicates that the strategy achieves more QALYs than could be achieved by using the required resources (costs) on alternative options within the NHS. A negative NHB indicates the opposite of this: funding the strategy provides fewer QALYs than could be achieved by using those resources on other things. NHB values for different strategies can be directly compared, and the strategy with the highest NHB provides the best use of resources (or the best net health outcome for the system).

Base-case results are based on 2,000,000 individual patient simulations. The first set of results contains all possible comprehensive strategies across 2 tables – one showing NHB results, one showing ICER results for non-dominated strategies. Two further sets of ICER results are also presented, the first of which excludes bevacizumab strategies. This restriction reflects that bevacizumab is not currently licensed for the treatment of AMD, and as such, it might be considered useful to inform decision-making. However, there has been extensive clinical research into the use of bevacizumab as a treatment for AMD, and the guideline committee advised that there are circumstances where it is currently used in the NHS and elsewhere.

The second additional set of ICER results includes only those strategies with treatment regimens that are included on product labels. This further restriction reflects that a number of our treatment strategies have been simulated, despite not being used in practice or, in some cases, in clinical trials. However, the guideline committee felt that an analysis comparing regimens listed on the product labels would be valuable.

Probabilistic sensitivity analyses were run to capture second-order, parameter uncertainty, using 5,000 simulations of 20,000 individuals. One-way sensitivity analyses were run for key variables and scenarios using 200,000 individuals.

10.1.2.2.2 Cost–utility results

In its base case, the model predicts, as expected, that routine monthly injections provide the most benefit overall, and 3-monthly injections provide the least. Though not included in the

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base-case results, PRNX regimens provides even more QALYs than continuous monthly injections, in contrast to the expected dose-response relationship. On average, a patient receives more injections in total when treated with aflibercept than with ranibizumab, due to the higher discontinuation rate associated with ranibizumab. Treatment with ranibizumab leads to more injections in total than bevacizumab, as bevacizumab has the highest discontinuation rate of the 3 interventions.

The base-case NHB results (Table 40), at an opportunity cost of £20,000 per QALY, show the following strategy to be optimal: **bevacizumab**, injected **every 2 months**, regardless of whether an eye is the **better or worse-seeing eye**, and **including eyes with VA better than 6/12**. This produces the highest NHB, generating 3.652 QALYs per patient for the healthcare system as a whole. Treating eyes every 3 months with bevacizumab, rather than every 2, produces less overall NHB, and also fewer QALYs to the person being treated (4.231 vs. 4.337), reflecting the improved clinical outcomes gained from providing more frequent injections. Bevacizumab delivered every 2 months also produces the largest NHB if the opportunity cost of a QALY forgone is £30,000.

At an opportunity cost of £20,000 per QALY, only 52 of the 137 base-case active treatment strategies provide a higher NHB value than providing AMD patients with no treatment. This means they produce net health outcomes to the NHS that are better than offering no active AMD treatment, taking into account both the health benefits to AMD patients and the costs involved, which could alternatively have been used elsewhere in the system. Of the 52, 48 involve treatment with bevacizumab. The remaining 4 strategies that produce better net health outcomes than providing no treatment involve treatment with ranibizumab, but only for better-seeing eyes. Here, treating worse-seeing eyes achieves only small health gains (or even health losses) relative to the additional costs. All 4 of the ranibizumab strategies that are superior to providing no treatment involve the lowest intensity treatment level modelled (3-month intervals between injections). Unlike bevacizumab, 3-monthly regimens produce higher NHB than 2-monthly regimens for ranibizumab, due to the large incremental costs associated with more frequent injections. It should be noted, however, that this base-case analysis evaluated aflibercept and ranibizumab at their stated list prices (both are available to the NHS at the confidential lower price).

All other (85) active treatment strategies provide worse net health outcomes to the NHS than providing no active treatment to late AMD (wet active) patients (when treatments are evaluated at their list prices). This means that, although the AMD patient will experience more QALYs if they are treated, the resources spent to do so would provide more QALYs if used in alternative ways elsewhere in the NHS. If the opportunity cost of 1 QALY is increased to £30,000, 16 ranibizumab strategies and 2 aflibercept (all low intensity) produce a higher NHB than offering no active treatment. However, even here, no PDT strategies would be considered to be cost-effective compared with providing no treatment..

Table 40: Base-case deterministic cost–utility results – all strategies – top 10 highest NHB plus selected others (at list prices)

Strategy Treatment | Regimen | Eyes to treat | VA range to treat	Total		NHB [a]		
	Costs	QALYs	£20K/QALY	Rank at £20K (out of 137)	£30K/QALY
Beva | 2mo | Treat any eye | including VA >6/12	£13,688	4.337	3.652	1	3.880
Beva | 2mo | Treat only BSEs | at any VA level	£11,355	4.215	3.647	2	3.837
Beva | 2mo | Treat any eye | at any VA level	£13,846	4.337	3.645	3	3.876
Beva | 2mo | Treat only BSEs | including VA >6/12	£11,437	4.211	3.639	4	3.830
Beva | 2mo | Treat only BSEs | including VA <6/96	£10,403	4.130	3.610	5	3.783

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Strategy Treatment | Regimen | Eyes to treat | VA range to treat	Total		NHB [a]		
	Costs	QALYs	£20K/QALY	Rank at £20K (out of 137)	£30K/QALY
Beva | 3mo | Treat any eye | including VA >6/12	£12,524	4.231	3.604	6	3.813
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,510	4.126	3.601	7	3.776
Beva | 3mo | Treat only BSEs | at any VA level	£10,843	4.143	3.601	8	3.781
Beva | 3mo | Treat any eye | at any VA level	£12,623	4.230	3.599	9	3.809
Beva | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	£13,516	4.274	3.598	10	3.823
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Rani | 3mo | Treat only BSEs | including VA <6/96	£15,752	4.082	3.294	49	3.557
---	---	---	---	---	---
No active treatment	£11,936	3.842	3.245	53	3.444
---	---	---	---	---	---
PDT | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£16,240	3.921	3.109	66	3.379
---	---	---	---	---	---
Aflib | 2mo->PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	£22,182	4.201	3.092	69	3.461

(a) NHB (net health benefit) represents the total QALYs achieved by the health care system by pursuing a given strategy, at a given opportunity cost per 1 QALY (here, £20,000). The NHB represents the QALYs gained by the direct beneficiaries of treatment (e.g. patients, carers) minus the QALYs foregone by not using those resources elsewhere in the system (assuming that for every £20,000 spent, 1 QALY is being foregone from potentially using those resources for other things).

Key: 2mo/3mo, 2/3-month treatment intervals; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; Current practice VA range, 6/12 to 6/96; NHB, net health benefit; QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

As shown by Table 40, when treating both better- and worse-seeing eyes, treating according to current VA thresholds provides higher NHB than extending treatment to people with baseline VA worse than 6/96, if 2 strategies are otherwise identical. Similarly, extending treatment only to people with good baseline VA (better than 6/12) provides higher NHB than extending treatment to all levels of VA, all else equal. This implies that extending treatment eligibility to eyes with presenting VA worse than 6/96 is *never* superior to the equivalent strategy without doing so, when both better and worse-seeing eyes are potentially eligible for treatment. This is not necessarily true of strategies that are restricted to treating better-seeing eyes only, however. A person's better-seeing eye does not typically have VA of 6/96 or worse at presentation; however, if it does, then treating that eye has the potential to substantially improve the person's visual function (with plenty of room for its VA to improve). VA in a person's better-seeing eye has a bigger impact on quality of life than VA in the worse-seeing eye, therefore the impact on simulated patients' quality of life is much greater in this scenario.

All treatments included

Given that strategies extending treatment to eyes with severe impairment are not optimal unless a better-seeing eye-only approach is adopted, our fully incremental results exclude strategies that extend treatment to eyes with presenting VA of less than 6/96. We include only strategies using current practice VA thresholds or extending this to treat people presenting with VA better than 6/12. Table 41 shows the results of a fully incremental analysis, including ICERs, for all resulting non-dominated base-case strategies. The

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interpretation of these results is ultimately the same as the NHB results: treatment with 2-monthly bevacizumab, including eyes with VA better than 6/12, is cost effective at both £20,000 and £30,000 per QALY thresholds.

Results are shown in order of increasing total costs, such that each strategy is always compared with the next-highest cost alternative. Sham injections are dominated and therefore do not appear in the results table; they are not the lowest-cost strategy overall, due to costs associated with low vision. The first non-dominated strategy – the lowest cost strategy – is treating only better-seeing eyes with bevacizumab every 3 months. Compared with this, providing 2-monthly treatment has an ICER of £3,458 per QALY gained. Extending treatment to better-seeing eyes with presenting VA above 6/12 is associated with an ICER of £10,955 with 2-monthly injections. Treating better and worse-seeing eyes with 2-monthly bevacizumab, including eyes with presenting VA above 6/12, produces an ICER of £17,895, which is the highest ICER that remains under £20,000. Using a regimen of a loading dose phase followed by PRN injections generates 0.108 additional QALYs at an extra cost of £3,707, with an ICER of £34,405. The only ranibizumab and aflibercept strategies that feature among the non-dominated strategies produce the most QALYs, but do so with high incremental costs, leading to ICERs ranging from of £470,000 to £580,000 per QALY gained (when evaluated at their list prices).

Table 41: Base-case deterministic cost–utility results – all treatments included – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes to treat | VA range to treat	Total		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,313	4.069			
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,510	4.126	£197	0.057	£3,458
Beva | 2mo | Treat only BSEs | including VA >6/12	£11,437	4.211	£927	0.085	£10,955
Beva | 2mo | Treat any eye | including VA >6/12	£13,688	4.337	£2,251	0.126	£17,895
Beva | Load+PRN | Treat any eye | including VA >6/12	£17,395	4.445	£3,707	0.108	£34,405
Rani | Load+PRN | Treat any eye | including VA >6/12	£32,023	4.476	£14,627	0.031	£470,559
Aflib | 2mo->PRN | Treat any eye | including VA >6/12	£37,979	4.488	£5,956	0.012	£483,462
Aflib | 1mo | Treat any eye | including VA >6/12	£85,243	4.569	£47,264	0.081	£584,215

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; Load+PRN, loading phase followed by treatment as needed; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Probabilistic sensitivity analysis (PSA) was performed with 5,000 unique sets of parameters drawn and each used for 20,000 patient simulations per strategy. Strategies that extend treatment eligibility to include eyes with visual acuity worse than 6/96 were not included in the PSA. The results, presented as cost-effectiveness acceptability curves (CEACs), present the probability that each strategy is optimal for a given value of 1 QALY (e.g. £20–30,000). The CEAC when all strategies are included suggests that the optimal strategy from the deterministic results – 2-monthly bevacizumab, with treatment of worse-seeing eyes permitted, and including eyes with VA better than 6/12 – has the highest probability of being cost-effective, when 1 QALY is valued at £17,000 or higher (Figure 2). At QALY values of £20,000 and £30,000, its likelihood of being optimal is 30.6% and 34.8% respectively. However, bevacizumab delivered by some regimen is almost certain to be cost-effective.

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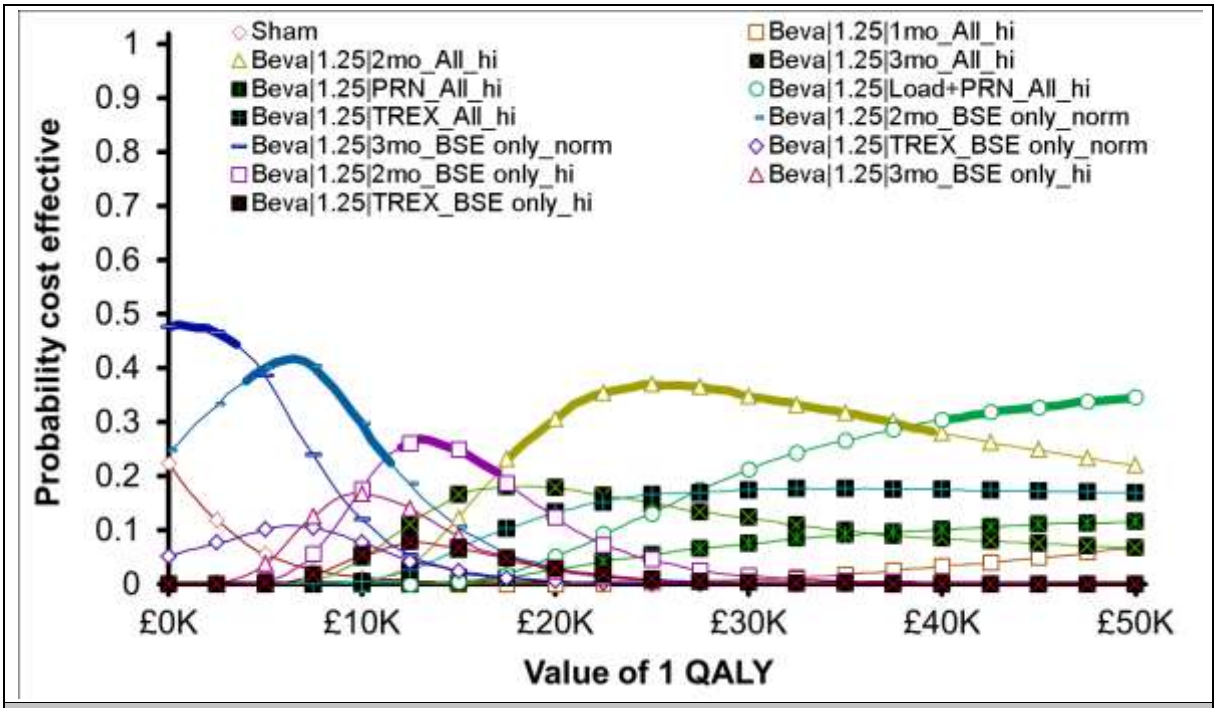

CEAC key displays all strategies that have a ≥5% probability of being cost-effective at any point along the 'value of 1 QALY' range shown. Other strategies are not shown in the key for diagram simplicity.

Bold line shows the strategy providing the highest expected NHB.

Key: 2/3mo, 2/3-monthly treatment intervals; Aflib|2.0, aflibercept; All, better and worse-seeing eyes are eligible for treatment; Beva|1.25, bevacizumab; BSE, better-seeing eyes only; hi, extend treatment eligibility to include VA >6/12; Load+PRN, 3-month loading phase followed by treatment as needed; norm, eyes are eligible for treatment in the current practice VA range (6/12 to 6/96); PRN, treatment as needed; Rani|0.5, ranibizumab.

Figure 2: Cost-effectiveness acceptability curve – all treatments included – list prices

Bevacizumab omitted

Table 42 shows the results of a fully incremental analysis for all non-dominated, non-bevacizumab base-case strategies, with aflibercept and ranibizumab again evaluated at their list prices. Only 1 intervention produces an ICER of less than £20,000 per QALY – ranibizumab injections every 3 months, for better seeing-eyes only, without extending the current VA thresholds (£15,967 per QALY gained compared with doing nothing). Extending treatment to people with VA above 6/12 has an ICER of £27,521 per extra QALY. Removing the restriction of treating better-seeing eyes only has an ICER of £52,478. Treating eyes more frequently than once every 3 months is never cost effective unless bevacizumab is used, as shown in Table 41.

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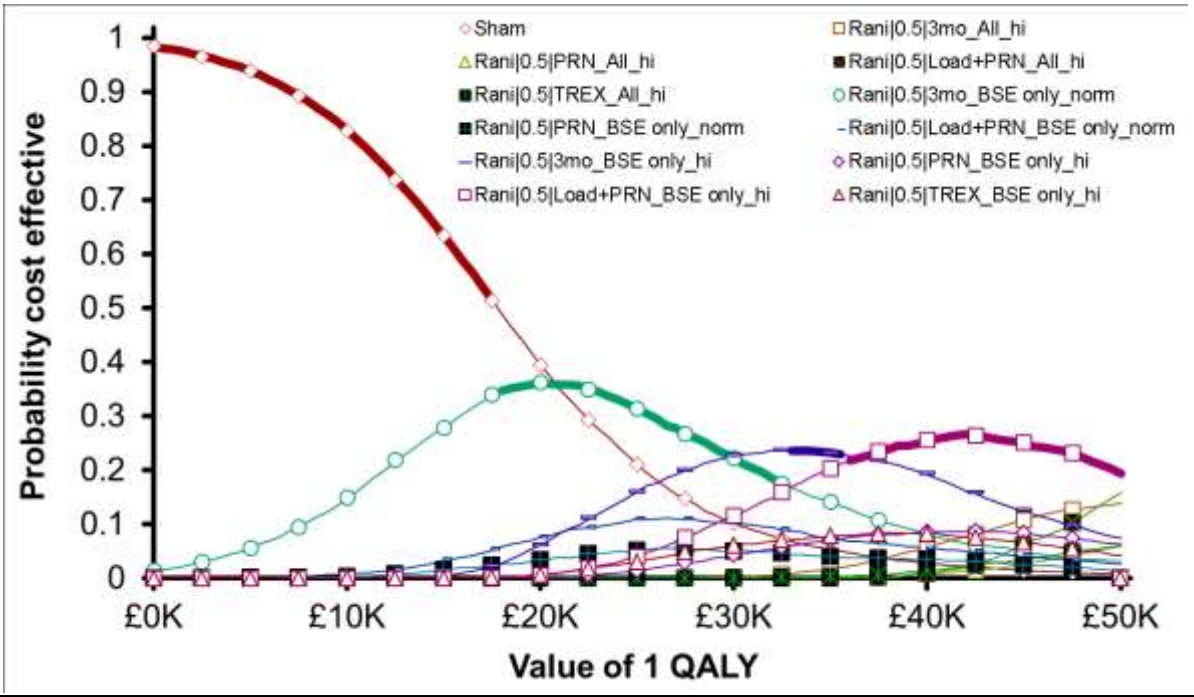
Table 42: Base-case deterministic cost–utility results – excluding bevacizumab – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes to treat | VA range to treat	Total		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
No treatment	£11,936	3.842			
Rani | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£15,698	4.078	£3,761	0.236	£15,967
Rani | 3mo | Treat only BSEs | including VA >6/12	£17,808	4.154	£2,110	0.077	£27,521
Rani | Load+PRN | Treat only BSEs | including VA >6/12	£22,752	4.299	£4,945	0.144	£34,226
Rani | Load+PRN | Treat any eye | including VA >6/12	£32,023	4.476	£9,270	0.177	£52,478
Aflib | 2mo->PRN | Treat any eye | including VA >6/12	£37,979	4.488	£5,956	0.012	£483,462
Aflib | 1mo | Treat any eye | including VA >6/12	£85,243	4.569	£47,264	0.081	£584,215

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; Aflib, aflibercept; BSE, better-seeing eyes; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

When bevacizumab strategies are excluded from the PSA, results suggest that, at a QALY value of £20,000, no active treatment is likely to be cost-effective. Here, providing no treatment is 39.5% likely to be the optimal strategy (Figure 3). Ranibizumab used to treat only better-seeing eyes at 3-month intervals has a 36.2% probability of being cost effective at this point, with bevacizumab excluded from the decision space. At a QALY value of £30,000, this ranibizumab strategy extended to treat eye with VA better than 6/12 has a probability of being cost effective of 22.6%. Permitting ranibizumab for the treatment of WSEs as well as BSEs does not have the highest likelihood of being optimal at any QALY value up to £50,000.



CEAC key displays all strategies that have a ≥5% probability of being cost-effective at any point along the 'value of 1 QALY' range shown. Other strategies are not shown in the key for diagram simplicity.

Bold line shows the strategy providing the highest expected NHB.

Key: 2/3mo, 2/3-monthly treatment intervals; 2mo->PRN, 2-monthly treatment intervals for 1 year then treatment as needed; Aflib\|2.0, aflibercept; All, better and worse-seeing eyes are eligible for treatment; Beva\|1.25, bevacizumab; BSE, better-seeing eyes only; hi, extend treatment eligibility to include VA >6/12; Load+PRN, 3-month loading phase followed by treatment as needed; norm, eyes are eligible for treatment in the current practice VA range (6/12 to 6/96); PRN, treatment as needed; Rani\|0.5, ranibizumab.

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Figure 3: Cost-effectiveness acceptability curve – excluding bevacizumab – list prices

Product label regimens only

Table 43 shows the results of a fully incremental analysis for all non-dominated strategies, with only those treatment regimens included on the product labels. The exception to this is treat-and-extend aflibercept, which was included in the model as TREX from treatment initiation, whereas its label suggests that a TREX protocol should only be followed after 1 year of regular injections. The present analysis includes strategies that are commonly used in practice: aflibercept (2 mg), delivered via a loading phase then every 2 months for 1 year, then as needed (PRN); ranibizumab (0.5 mg) delivered via loading phase then PRN; monthly ranibizumab; and ranibizumab TREX. PDT and 'no treatment' are also included.

No strategies produce an ICER of less than £20,000 per QALY. As such, at an opportunity cost of £20,000 per 1 QALY, the model predicts that no regimens listed on product labels are cost effective compared with providing no active treatment for late AMD (wet active). This implies that providing active treatment would cause a net health loss to the wider system. This is consistent with Table 41 and Table 42, in which no product label regimens feature among the optimal strategies overall. The lowest non-dominated ICER is £21,572 per QALY gained, associated with ranibizumab (loading phase then PRN), and used to the treat better-seeing eyes only, according to current practice VA thresholds. The lowest ICER for strategies without the better-seeing eyes only restriction is £52,478, also using ranibizumab PRN. Aflibercept given as per the VIEW trial regimen produces the most QALYs, with an ICER in excess of £480,000 per QALY gained. Even when compared with only product label regimens, PDT is not a cost effective use of resources.

Table 43: Base-case deterministic cost–utility results – product label regimens only – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes to treat | VA range to treat	Total		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
No treatment	£11,936	3.842			
Rani | Load+PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	£19,575	4.196	£7,639	0.354	£21,572
Rani | Load+PRN | Treat only BSEs | including VA >6/12	£22,752	4.299	£3,177	0.103	£30,965
Rani | Load+PRN | Treat any eye | including VA >6/12	£32,023	4.476	£9,270	0.177	£52,478
Aflib | 2mo->PRN | Treat any eye | including VA >6/12	£37,979	4.488	£5,956	0.012	£483,462

Key: 1mo, 1-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; BSE, better-seeing eyes; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

The PSA was also evaluated using a heavily restricted set of possible strategies, that included only regimens on product labels, excluded PDT, excluded 'no treatment', and had worse-seeing eyes as eligible for treatment. This analysis is therefore the most reflective of treatment options used in current practice. The resulting CEAC suggests that ranibizumab, given as a loading dose followed by injections as needed, is likely to be cost-effective across the range of QALY values shown, compared with aflibercept (Figure 4). Extending treatment to eyes with visual acuity better than 6/12 becomes the strategy most likely to optimal beyond £16,000 per QALY. However, it is important to note that these results were obtained using the list prices of aflibercept and ranibizumab, both of which are made available to the NHS at a confidential discount agreed in a patient access scheme (PAS). Results using the PAS prices are discussed at the end of this section.

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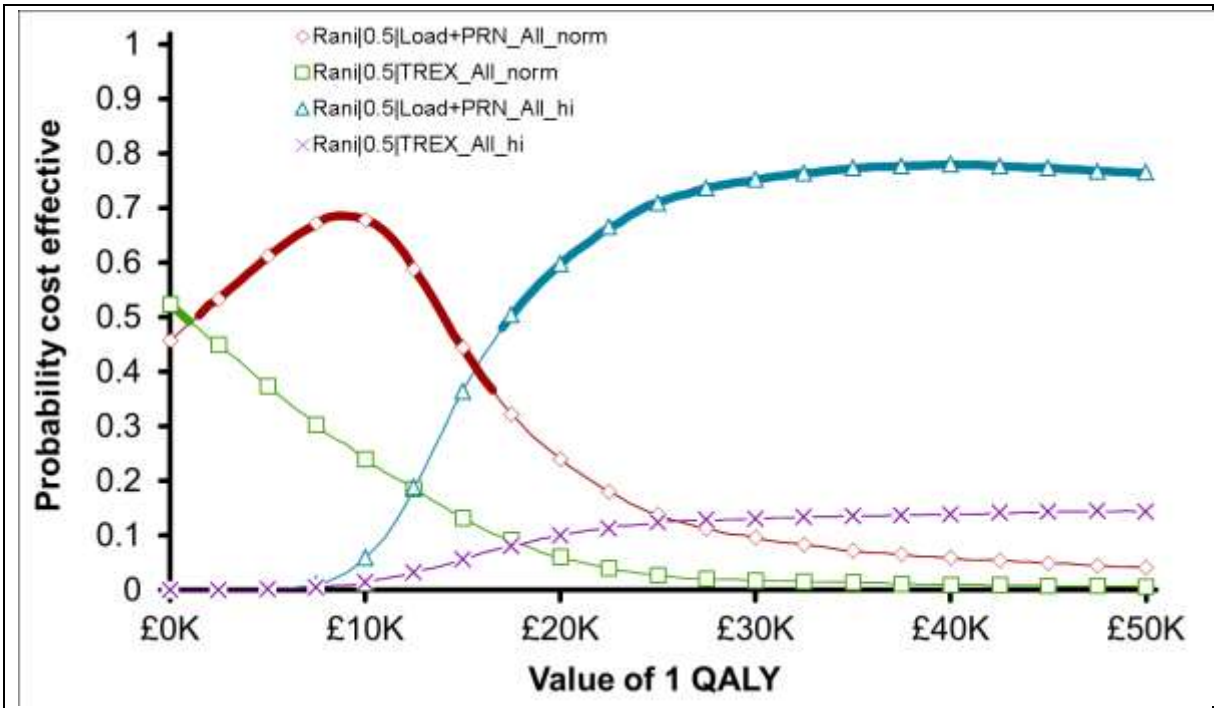

CEAC key displays all strategies that have a ≥5% probability of being cost-effective at any point along the 'value of 1 QALY' range shown. Other strategies are not shown in the key for diagram simplicity.

Bold line shows the strategy providing the highest expected NHB.

Key: 2mo->PRN, 2-monthly treatment intervals for 1 year then treatment as needed; Aflib|2.0, aflibercept; All, better and worse-seeing eyes are eligible for treatment; hi, extend treatment eligibility to include VA >6/12; Load+PRN, 3-month loading phase followed by treatment as needed; norm, eyes are eligible for treatment in the current practice VA range (6/12 to 6/96); Rani|0.5, ranibizumab.

Figure 4: Cost-effectiveness acceptability curve – product label regimens – list prices

One-way sensitivity analysis and scenario analysis

One-way sensitivity analyses (OSA) and scenario analyses were conducted to evaluate the sensitivity of cost–utility results to variation of individual input parameters between sensible upper and lower bounds and to alternative modelling assumptions. The outcome for OSA results was NHB evaluated at a value of £20,000 per 1 QALY. Both OSA and scenario analysis results suggest that the deterministic finding of bevacizumab being cost effective is robust.

Three-monthly treatment intervals become superior to 2-monthly intervals if a substantial proportion of treatment is provided during day-case admissions, rather than outpatient appointments; if the price of an aliquoted dose of bevacizumab is much higher than the model estimate; and if the treatment effect of more frequent treatment is reduced. When aflibercept, given every 2 months for 1 year then as needed, was compared with ranibizumab, given via a loading phase then as needed, at their list prices, the OSA showed that the option producing the highest NHB (ranibizumab) was generally robust to model parameters being varied within plausible ranges, though this is not the case when evaluated at their confidential, lower prices (discussed in the next sub-section). All other results suggest that base-case findings are largely robust to univariate parameter variation.

Patient access scheme price analysis

As noted above, both aflibercept and ranibizumab are subject to confidential pricing, such that the price paid by the NHS is lower than the published list prices. All exact results from the new analysis presented in this guideline used the list prices in order to protect the confidentiality of the discounted prices. However, results evaluated at the lower prices were

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presented to the guideline committee as evidence, as these are the most relevant for decision-making. In these results, the base-case optimal strategy (2-monthly bevacizumab in all eyes, including those with VA better than 6/12) continues to produce the highest NHB. Strategies that use aflibercept or ranibizumab continue to produce ICERs that exceed typical cost-effectiveness thresholds.

When bevacizumab is excluded from consideration, the only regimen that is associated with an ICER lower than £20,000/QALY remains 3-monthly ranibizumab used in BSEs only. Restricting the decision space to the regimens detailed in SPCs (Table 44) shows that treating better-seeing eyes with aflibercept has an ICER lower than £20,000/QALY. While they do not appear on the incremental cost-effectiveness frontier shown in Table 44, results for analogous ranibizumab regimens are virtually identical.

Table 44: Base-case deterministic cost–utility results – product label regimens – fully incremental analysis, non-dominated strategies shown (at confidential NHS prices)

Strategy *Treatment | Regimen | Eyes treated | VA ranged treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
No treatment	£11,936	3.842			
Aflib | 2mo->PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	[redacted]	4.201	[redacted]	0.359	<£20,000
Aflib | 2mo->PRN | Treat only BSEs | including VA >6/12	[redacted]	4.307	[redacted]	0.106	£20-30,000
Rani | Load+PRN | Treat any eye | including VA >6/12	[redacted]	4.476	[redacted]	0.169	>£30,000
Aflib | 2mo->PRN || Treat any eye | including VA >6/12	[redacted]	4.488	[redacted]	0.012	>£30,000

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

If the decision space is constrained still further to the strategies that are commonly used in current NHS practice (treating better- and worse-seeing eyes with ranibizumab loading then PRN or aflibercept 2-monthly for 1 year, then PRN), neither option is clearly cost effective over the other, evaluated at their PAS prices. A wide range of sensitivity analyses suggested that the cost effectiveness of the strategies could not be distinguished (Figure 5).

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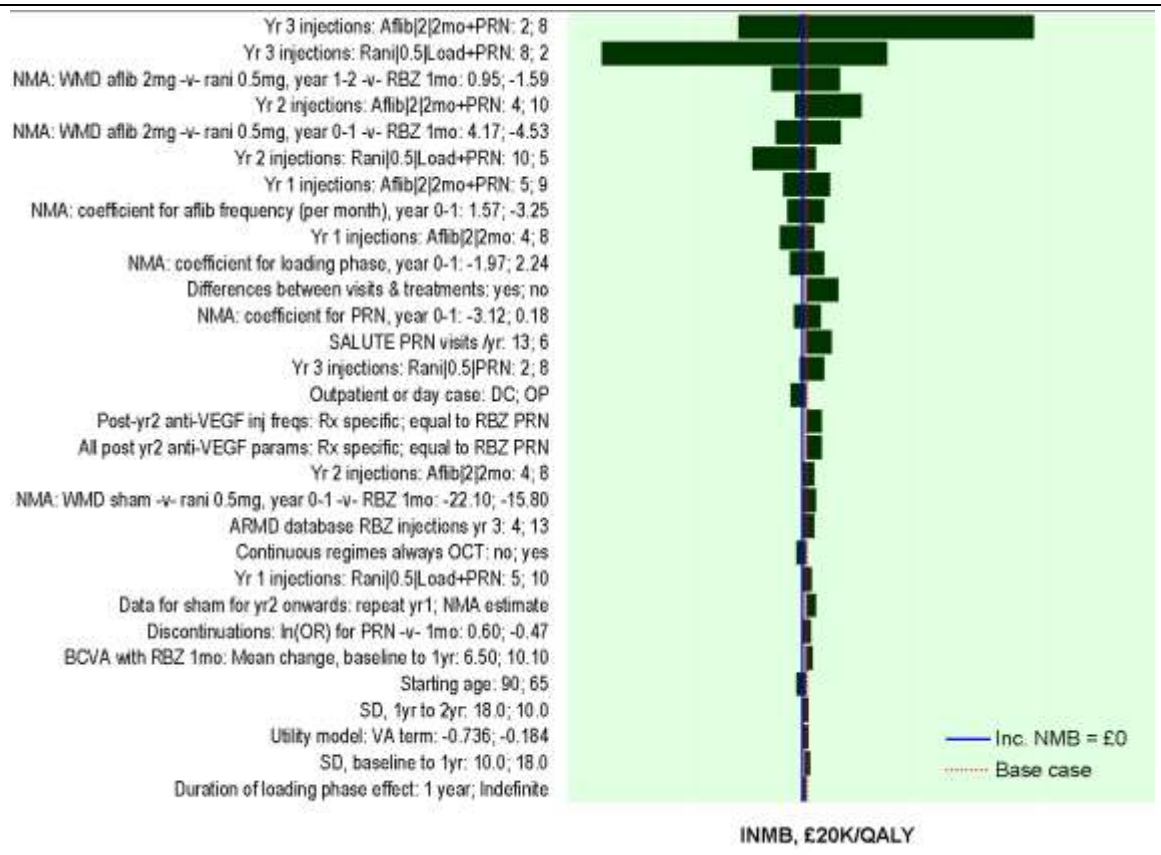

CEAC key displays all strategies that have a ≥5% probability of being cost-effective at any point along the 'value of 1 QALY' range shown. Other strategies are not shown in the key for diagram simplicity.

Bold line shows the strategy providing the highest expected NHB.

Key: 2mo->PRN, 2-monthly treatment intervals for 1 year then treatment as needed; Aflib|2.0, aflibercept; All, better and worse-seeing eyes are eligible for treatment; hi, extend treatment eligibility to include VA >6/12; Load+PRN, 3-month loading phase followed by treatment as needed; norm, eyes are eligible for treatment in the current practice VA range (6/12 to 6/96); Rani|0.5, ranibizumab.

Figure 5: Tornado diagram showing sensitivity of incremental net benefit results for ranibizumab (loading then PRN) vs. aflibercept (VIEW regimen) to scenario and parameter variation – confidential NHS prices

In any given pairwise analysis confined to a single regimen in Table 45, extending treatment to eyes presenting with VA above 6/12 becomes a cost-effective course of action compared with not doing so when the lower, NHS prices are used. Extending aflibercept or ranibizumab treatment to eyes with VA below 6/96 is also cost effective at their discounted prices, as is the case with bevacizumab, but only if treatment is restricted to better-seeing eyes.

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Table 45: Head-to-head cost–utility results of extending treatment eligibility to eyes with VA better than 6/12 compared with not extending treatment eligibility (at confidential NHS prices)

Strategy *Treatment | Regimen | Eyes treated | VA ranged treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Aflibercept, 2-monthly					
Aflib | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	[redacted]	4.365	-	-	-
Aflib | 2mo | Treat any eye | including at VA > 6/12	[redacted]	4.442	[redacted]	0.077	<£20,000
Aflibercept, 2-monthly then PRN					
Aflib | 2mo->PRN | Treat any eye | with VA in range: 6/12 to 6/96	[redacted]	4.408	-	-	-
Aflib | 2mo->PRN | Treat any eye | including at VA > 6/12	[redacted]	4.488	[redacted]	0.080	<£20,000
Ranibizumab, 3-monthly					
Rani | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	[redacted]	4.192	-	-	-
Rani | 3mo | Treat any eye | including at VA > 6/12	[redacted]	4.253	[redacted]	0.060	<£20,000
Ranibizumab, 2-monthly					
Rani | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	[redacted]	4.297	-	-	-
Rani | 2mo | Treat any eye | including at VA > 6/12	[redacted]	4.368	[redacted]	0.070	<£20,000
Ranibizumab, loading then PRN					
Rani | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	[redacted]	4.397	-	-	-
Rani | Load+PRN | Treat any eye | including at VA > 6/12	[redacted]	4.476	[redacted]	0.079	<£20,000

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

10.1.3 Evidence statements – effectiveness of antiangiogenic therapies for treatment of late AMD (wet active)

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively. Details of the network meta-analyses are provided in Appendix G.

10.1.3.1 Photodynamic therapy versus placebo

10.1.3.1.1 Visual acuity

Pairwise analyses

Moderate- to high-quality evidence showed that people receiving PDT were less likely to have a loss of visual acuity compared with people receiving placebo at 2 years' follow-up (loss of 15 or more letters RR 0.80 [95%CI 0.73 to 0.89]; loss of 30 or more letters RR 0.66 [95%CI 0.55 to 0.78]; 4 RCTs of 1,381 people).

High-quality evidence showed that people receiving PDT were more likely to gain 15 or more letters of visual acuity compared with people receiving placebo at 2 years' follow-up (RR 2.59 [95%CI 1.33 to 5.06]; 3 RCTs of 941 people).

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Network meta-analysis

Moderate-quality evidence from a network meta-analysis showed that people receiving PDT have better visual acuity than those receiving placebo. At 1 year's follow-up, the difference fell short of clinical importance (MD 4.7 ETDRS letters [95%CI 2.3 to 7.1]; 0.392 probability that PDT is at least 5 ETDRS letters better) but, at 2 years' follow-up, this was no longer the case (MD 5.2 ETDRS letters [95%CI 2.6 to 7.8]; 0.563 probability that PDT is at least 5 ETDRS letters better) (up to 26 RCTs of 10,925 people).

10.1.3.1.2 Adverse events

Pairwise analyses

Moderate-quality evidence could not differentiate the probability of acute severe visual acuity decrease between photodynamic treatment and placebo at 1 to 2 years' follow-up (RR 3.75 [95%CI 0.87 to 16.12]; 3 RCTs of 1,075 people).

Moderate-quality evidence showed that people receiving photodynamic treatment were more likely to experience visual disturbance compared with people receiving placebo at 1 to 2 years' follow-up (RR 1.56 [95%CI 1.2 to 2.01]; 3 RCTs of 1,075 people).

Very low-quality evidence could not differentiate the probability of injection site adverse events between photodynamic treatment and placebo at 1 to 2 years' follow-up (RR 1.36 [95%CI 0.50 to 3.71]; 3 RCTs of 1,075 people).

High-quality evidence showed that people receiving photodynamic treatment were much more likely to experience infusion-related back pain compared with people receiving placebo at 1 to 2 years' follow-up (RR 9.93; [95%CI 2.82 to 35.02]; 4 RCTs of 1,439 people).

Low-quality evidence could not differentiate the probability of allergic reactions between photodynamic treatment and placebo at 1 to 2 years' follow-up (RR 0.94 [95%CI 0.35 to 2.51]; 2 RCTs of 948 people).

Very low-quality evidence could not differentiate the probability of photosensitivity reactions between photodynamic treatment and placebo at 1 to 2 years' follow-up (RR 2.73 [95%CI 0.08 to 97.96]; 2 RCTs of 948 people).

10.1.3.2 Anti-VEGF compared with control

10.1.3.2.1 Visual acuity

Pairwise analyses

Low- to moderate-quality evidence showed that people receiving bevacizumab were much more likely to have a large improvement in visual acuity and less likely to have a large deterioration in visual acuity compared with those receiving control treatment at 1 year's follow-up (gain of 15+ ETDRS letters RR 8.43 [95%CI 2.65 to 26.80]; loss of fewer than 15 ETDRS letters RR 1.32 [95%CI 1.13 to 1.54]; 2 RCTs of 159 people).

Moderate- to high-quality evidence showed that people receiving ranibizumab were much more likely to have a large improvement in visual acuity and less likely to have a large deterioration in visual acuity compared with those receiving control treatment at 1 year's follow-up (gain of 15+ ETDRS letters RR 3.25 [95%CI 1.44 to 7.33]; loss of fewer than 15 ETDRS letters RR 1.51 [95%CI 1.41 to 1.63]; 4 RCTs of 1,415 people).

High-quality evidence reported that people receiving ranibizumab had substantially better visual acuity than those receiving control treatment at 1 year's follow-up (MD 17.80 ETDRS letters [95%CI 15.95 to 19.65]; 3 RCTs of 1,322 people).

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Network meta-analysis

High-quality evidence from a network meta-analysis showed that people receiving anti-VEGF treatments have better visual acuity than those receiving placebo (the probability that all anti-VEGF regimens are at least 5 ETDRS letters better than placebo was 0.999 at 1 year and 0.995 at 2 years) (up to 26 RCTs of 10,925 people).

High-quality evidence from a network meta-analysis showed that people receiving anti-VEGF treatments have better visual acuity than those receiving PDT (the probability that all anti-VEGF regimens are at least 5 ETDRS letters better than PDT was 0.999 at 1 year and 0.983 at 2 years) (up to 26 RCTs of 10,925 people).

10.1.3.2.2 Adverse events

Pairwise analyses

Low-quality evidence could not differentiate the probability of serious ocular and systemic adverse events between people receiving bevacizumab and control treatment at 1 year's follow-up (ocular AE RR 1.86 [95%CI 0.73 to 4.74]; systemic AE RR 2.03 [95%CI 0.19 to 21.85]; 1 RCT of 131 people).

Low-quality evidence could not differentiate the probability of serious systemic adverse events between people receiving ranibizumab and control treatment at 1 year's follow-up (myocardial infarction RR 2.08 [95%CI 0.23 to 18.45]; stroke or cerebral infarction RR 1.04 [95%CI 0.09 to 11.28]; treatment-emergent hypertension RR 0.67 [95%CI 0.36 to 1.24]; non-ocular haemorrhage RR 1.90 [95%CI 0.78 to 4.62]; 2 RCTs of 603 people).

Moderate- to high-quality evidence reported people receiving ranibizumab had more serious ocular inflammation than people receiving control treatment (PDT or sham injections) at 1 year's follow-up (RR 2.71 [95%CI 1.36 to 5.42]), but could not differentiate the probability of serious elevated intraocular pressure (30mmHg or more increase RR 2.22 [95%CI 0.99 to 4.98]) or cataract (RR 1.48 [95%CI 0.83 to 2.66]; 2 RCTs of 603 people).

10.1.3.2.3 Vision-related quality of life

High-quality evidence showed greater vision-related quality of life (NEI-VFQ-25) in people receiving ranibizumab compared with people receiving control treatment at 1 year’s follow-up (MD 6.69 [95%CI 3.38 to 9.99]; 2 RCTs of 1,134 people).

10.1.3.3 Anti-VEGF agents compared with each other

10.1.3.3.1 Visual acuity

Pairwise analyses

High-quality evidence showed that there is no difference in visual acuity between people receiving bevacizumab and those receiving ranibizumab at 1 year’s follow-up (MD -0.48 ETDRS letters [95%CI -1.47 to 0.51]; gain of 15+ ETDRS letters RR 0.96 [95%CI 0.85 to 1.08]; loss of fewer than 15 ETDRS letters RR 1.00 [95%CI 0.98 to 1.02]; 8 studies of 3,101 people).

High-quality evidence showed that there is no difference in visual acuity between people receiving aflibercept and those receiving ranibizumab at 1 year’s follow-up (MD -0.15 ETDRS letters [95%CI -1.47 to 1.17]; gain of 15+ ETDRS letters RR 0.97 [95%CI 0.85 to 1.11]; 2 RCTs of 2,412 people).

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Network meta-analysis

Moderate- to high-quality evidence from a network meta-analysis showed that there is no difference in visual acuity between people receiving different anti-VEGF treatments at up to 2 years' follow-up (the probability that any anti-VEGF agent is at least 5 ETDRS letters better than any other was 0.045 at 1 year and 0.060 at 2 years) (up to 26 RCTs of 10,925 people).

Moderate- to high-quality evidence from a network meta-analysis showed that there is no difference in categorical changes in visual acuity (measured by the percentage of people who had gained or lost 15 or 30 ETDRS letters) amongst people receiving different anti-VEGF treatments at up to 2 years' follow-up (up to 26 RCTs of 10,925 people).

10.1.3.3.2 Adverse events

Pairwise analyses

Moderate-quality evidence showed that people receiving bevacizumab were more likely to have gastrointestinal disorders than people receiving ranibizumab at 1 year's follow-up (RR 1.85 [95%CI 1.01 to 3.40]; 5 RCTs of 3,038 people).

Low-quality evidence could not differentiate the probability of adverse events between bevacizumab and ranibizumab at 1 year's follow-up (myocardial infarction RR 0.51 [95%CI 0.22 to 1.19] in 5 RCTs of 3,038 people; stroke or cerebral infarction RR 0.65 [9%CI 0.25 to 1.67] in 5 RCTs of 3,038 people; venous thrombotic event RR 2.04 [95%CI 0.61 to 6.75] in 4 RCTs of 2,721 people).

Low-quality evidence could not differentiate the probability of serious ocular adverse events between bevacizumab and ranibizumab at 1 year's follow-up (retinal detachment RR 7.05 [95%CI 0.36 to 136.28]; severe uveitis RR 4.14 [95%CI 0.46 to 36.97]; endophthalmitis RR 1.68 [95%CI 0.40 to 7.00]; retinal pigment epithelial tear RR 1.37 [95%CI 0.31 to 6.12]; cataract RR 0.51 [95%CI 0.05 to 5.62]; up to 3 RCTs of 2,280 people).

Moderate-quality evidence could not differentiate the probability of serious ocular or systemic adverse events between aflibercept and ranibizumab treatment at 1 year's follow-up (ocular AE RR 0.62 [95%CI 0.36 to 1.07]; systemic AE RR 0.99 [95%CI 0.79 to 1.25]; 2 RCTs of 2,419 people).

10.1.3.3.3 Vision-related quality of life

Pairwise analyses

High-quality evidence could not differentiate vision-related quality of life (NEI VFQ-25) between aflibercept and ranibizumab at 1 year's follow-up (MD -0.39 [95%CI -1.71 to 0.93]; 2 RCTs of 2,412 people).

10.1.3.3.4 Health-related quality of life

Pairwise analyses

Moderate-quality evidence reported no difference in quality of life (EQ-5D) between ranibizumab and bevacizumab at 1 year's follow-up (mobility RR 0.98 [95%CI 0.85 to 1.12]; self-care RR 0.96 [95%CI 0.90 to 1.04];usual activities RR 0.98 [95%CI 0.87 to 1.09]; pain/discomfort RR 1.02 [95%CI 0.89 to 1.17]; anxiety/depression RR 0.96 [95%CI 0.87 to 1.06]; 1 RCT of 548 people).

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10.1.3.3.5 Number of injections

Pairwise analyses

Moderate-quality evidence showed that people receiving bevacizumab had more injections than people receiving ranibizumab at 1 year's follow-up regardless of treatment regimen (MD 0.60 [95%CI 0.33 to 0.87], 5 RCTs of 1,660 people).

10.1.4 Evidence statements – treatment frequency of antiangiogenic therapies for treatment of late AMD (wet active)

10.1.4.1 Pro re nata (PRN) vs routine treatment

10.1.4.1.1 Visual acuity

Pairwise analyses

Low-quality evidence could not demonstrate a meaningful difference in the probability of visual acuity improvement between PRN and routine treatment schedules at 1 year's follow-up (gain of 15+ ETDRS letters RR 0.89 [95%CI 0.79 to 0.99]; 6 RCTs of 2,928 people).

Moderate-quality evidence showed that there is no difference in the probability of avoiding a large deterioration in visual acuity between PRN and routine treatment schedules at 1 year's follow-up (loss of fewer than 15 ETDRS letters RR 0.99 [95%CI 0.97 to 1.01]; 4 RCTs of 2,795 people).

Moderate-quality evidence suggested that, on average, people on PRN treatment had worse visual acuity than those on a routine treatment schedule at 1 year's follow-up, but the difference was not clinically important (fewer than 5 letters) (MD -1.45 [95%CI -2.45 to -0.45, 4 RCTs of 2,874 people).

Network meta-analysis

Moderate-quality evidence from a network meta-analysis showed that people on PRN treatment regimens have worse visual acuity than those on routine treatment regimens, but mean differences in ETDRS letter changes were not clinically important (the probability that PRN administration is at least 5 ETDRS letters worse than routine monthly regimens was 0.000 at 1 year and 0.000 at 2 years) (up to 26 RCTs of 10,925 people).

10.1.4.1.2 Adverse events

Pairwise analyses

Very low-quality evidence could not differentiate the probability of systemic adverse events between PRN treatment and routine treatment schedules at 1 year's follow-up (RR 1.07 [95%CI 0.78 to 1.63]; 2 RCTs of 2,280 people).

Low-quality evidence showed that people on PRN treatment were less likely to have serious ocular events compared with those on a routine treatment schedule at 1 year's follow-up (event RR 0.31 [95%CI 0.13 to 0.78]; 2 RCTs of 2,280 people).

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10.1.4.1.3 Number of injections

Pairwise analyses

Low-quality evidence showed that people on PRN treatment had fewer injections than those on a routine treatment schedule over 1 year's follow-up (MD −4.22 [95%CI −4.72 to −3.73]; 4 RCTs of 2,653 people).

10.1.4.2 Interval for routine treatment

10.1.4.2.1 Visual acuity

Pairwise analyses

Low-quality evidence showed that people who were routinely treated at least every 6 weeks were more likely to have vision improvement compared with those whose routine treatment intervals were longer at 1 year's follow-up (gain of 15+ ETDRS letters RR 1.28 [95%CI 1.08 to 1.52]; 4 RCTs of 1,276 people).

Low-quality evidence showed that there is no difference in visual loss between people who are routinely treated at least every 6 weeks compared with those whose routine treatment intervals are longer (loss of fewer than 15 ETDRS letters RR 0.99 [95%CI 0.92 to 1.06]; 3 RCTs of 671 people).

Low-quality evidence reported people having 6-weekly or less routine treatment intervals had better visual acuity than those having more than 6-weekly routine treatment intervals at 1 year's follow-up, but differences were not clinically important (fewer than 5 letters) (MD 1.87 [95%CI 0.36 to 3.39]; 4 RCTs of 1,276 people).

Network meta-analysis

Moderate-quality evidence from a network meta-analysis showed that people being treated with shorter treatment intervals were more likely to improve their visual acuity compared with those on longer treatment intervals, but mean differences in ETDRS letters between people on different treatment intervals were not clinically important at 1 year's follow-up (the probability that 2-monthly treatment with aflibercept is at least 5 ETDRS letters worse than 1-monthly treatment is 0.002 and the probability that 3-monthly treatment with aflibercept is at least 5 ETDRS letters worse than 1-monthly treatment is 0.078; the probability that 2-monthly treatment with bevacizumab or ranibizumab is at least 5 ETDRS letters worse than 1-monthly treatment is 0.000 and the probability that 3-monthly treatment with bevacizumab or ranibizumab is at least 5 ETDRS letters worse than 1-monthly treatment is 0.063) (up to 26 RCTs of 10,925 people).

10.1.4.2.2 Adverse events

Pairwise analyses

Low-quality evidence could not differentiate the probability of serious ocular AEs between people who were routinely treated at least every 6 weeks compared with those whose routine treatment intervals were longer at 1 year's follow-up (ocular AE RR 1.52 [95%CI 0.86 to 2.69]; 3 RCTs of 983 people).

Low-quality evidence could not differentiate the probability of in systemic AEs between people who were routinely treated at least every 6 weeks compared with those whose routine treatment intervals were longer at 1 year's follow-up (RR 0.77 [95%CI 0.53 to 1.11]; 2 RCTs of 798 people).

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10.1.4.3 Pro re nata (PRN)

10.1.4.3.1 PRN with no loading vs loading phases

Visual acuity – pairwise analyses

Low-quality evidence showed that there is no difference in best-corrected visual acuity change between people on PRN treatment schedules with or without loading phases at 1 year's follow-up (MD 1.20 ETDRS letters [95%CI -2.51 to 4.91], 2 RCTs of 189).

Very low-quality evidence could not differentiate the probability of visual gain between people on PRN treatment schedules with or without loading phases at 1 year's follow-up (gain of 15+ ETDRS letters RR 0.83 [95%CI 0.43 to 1.63], 1 RCT of 60 people; gain of 10+ ETDRS letters RR 0.93 [95%CI 0.38 to 2.25]; 1 RCT of 99 people).

Visual acuity – network meta-analysis

Moderate-quality evidence from a network meta-analysis showed that there is no difference in visual acuity between people on PRN treatment regimens with or without loading phases at up to 2 years' follow-up (the probability that PRN with loading is at least 5 ETDRS letters better or worse than PRN without loading was 0.000 at 1 year and 0.000 at 2 years; up to 26 RCTs of 10,925 people).

Number of treatments (injections) – pairwise analyses

Low-quality evidence could not differentiate the number of injections received between people on PRN with or without loading phase over 1 year's follow-up (MD −0.30 [95%CI −1.93 to 1.32]; 2 RCTs of 189 people).

Vision-related quality of life – pairwise analyses

Low-quality evidence reported a very small difference in NEI-VFQ-25 between people on PRN with or without loading phase at 1-year follow-up (MD -0.06, 95%CI not estimated; 1 RCT of 99 people).

10.1.4.3.2 PRN with 4-weeks and 12 weeks intervals loading phases

Visual acuity – pairwise analyses

Very low- to moderate-quality evidence could not differentiate the probability of visual gain between people on PRN with 4-week-interval and 12-week-interval loading phases at 1 year's follow-up (gain of 15+ ETDRS letters RR 0.94 [95%CI 0.51 to 1.72]; 1 RCT of 126 people).

Very low- to moderate-quality evidence showed that there is no difference in visual loss between people on PRN with 4-week-interval and 12-week-interval loading phases at 1 year's follow-up (loss of fewer than 15 letters RR 1.05 [95%CI 0.94 to 1.18]; 1 RCT of 126 people).

Low-quality evidence could not differentiate best-corrected visual acuity between people on PRN with 4-week-interval and 12-week-interval loading phases at 1 year's follow-up (MD 3.41 ETDRS letters [95%CI -0.16 to 6.98]; 1 RCT of 126 people).

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10.1.4.4 Treat-and-extend vs routine (monthly) treatment

Visual acuity – pairwise analyses

Moderate-quality evidence showed that visual acuity was not different between people on treat-and-extend and routine (monthly) treatment at 1-year follow-up (MD -1.46 ETDRS letters [95%CI -3.26 to 0.34]; 2 RCTs of 703 people), and very low-quality evidence could not differentiate the probability of visual gain of 15+ ETDRS letters between the 2 groups (RR 1.02 [0.78 to 1.33]; 2 RCTs of 646 people).

Visual acuity – network meta-analysis

Moderate-quality evidence from a network meta-analysis could not differentiate visual acuity between people on treat-and-extend and monthly routine or PRN treatment at 1 year's follow-up (the probabilities that treat-and-extend is at least 5 ETDRS letters better or worse than monthly routine were 0.002 and 0.000, respectively; up to 26 RCTs of 10,925 people). Low-quality evidence confirmed this finding at 2 year's follow-up (the probabilities that treat-and-extend is at least 5 ETDRS letters better or worse than monthly routine were 0.008 and 0.279, respectively; up to 26 RCTs of 10,925 people).

Number of treatments (injections) – pairwise analyses

High-quality evidence showed people on treat-and-extend received fewer injections than those on routine (monthly) treatment at 1-year follow-up (MD -2.40 [-2.80, -2.00]; 1 RCT of 643 people).

Adverse events – pairwise analyses

Very low-quality evidence could not differentiate the probability of serious ocular and systemic AEs between people on treat-and-extend and routine (monthly) treatment over 1 year's follow-up (ocular AE RR 1.61 [0.61 to 4.22]; systemic AE RR 1.04 [0.68 to 1.58]; 2 RCTs of 709 people).

10.1.4.5 PRN-and-extend[9] vs PRN

Visual acuity – pairwise analyses

Very low-quality evidence could not differentiate visual acuity or the probability of visual gain between people on PRN-and-extend and PRN regimens at 1-year follow-up (MD 4.50 ETDRS letters [95%CI -3.78 to 12.78]; gain of 15+ ETDRS letters RR 1.48 [95%CI 0.72 to 3.05]; 1 RCT of 67 people).

Visual acuity – network meta-analysis

Low-quality evidence from a network meta-analysis could not differentiate visual acuity between people on PRN-and-extend and monthly routine or PRN treatment at 1 year's follow-up (the probabilities that PRN-and-extend is at least 5 ETDRS letters better or worse than monthly routine were 0.449 and 0.013, respectively; up to 26 RCTs of 10,925 people).

[9] Eldem et al (2015). After 3 loading doses, patients were invited to return 1 month later. For patients with no active lesions at this visit, treatment was not administered and the interval to the next visit was extended by 2 weeks to a maximum of 8 weeks between visits. Patients whose lesions became active at any of these visits were re-treated and the follow-up schedule started over.

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Adverse events – pairwise analyses

Very low-quality evidence could not detect a difference in ocular and serious systemic adverse events between people on PRN-and-extend and PRN regimens over 1 year's follow-up (ocular AE RR 0.99 [95%CI 0.70 to 1.38]; systemic AE RR 1.71 [95%CI 0.44 to 1.38]; 1 RCT of 67 people).

10.1.5 Evidence statements – health economic evidence

10.1.5.1 New cost–utility analysis

One directly applicable health economic model with minor limitations compared comprehensive treatment strategies, including different dosing regimens of aflibercept (2.0 mg), ranibizumab (0.5 mg), bevacizumab (1.25 mg), PDT and no active treatment. At values of £20,000 and £30,000 per QALY, **bevacizumab** administered **every 2 months** to any eye with visual acuity better than 6/96, **including eyes with visual acuity better than 6/12**, produces the highest net health benefit, with an ICER of £17,895 per QALY gained compared with a similar strategy treating only better-seeing eyes. Probabilistic sensitivity analysis suggests that this strategy has a 30.6% probability of providing best value for money at £20,000 per QALY, and a 34.8% probability at £30,000 per QALY. This regimen still produces the highest net health benefit when the confidential NHS prices of aflibercept and ranibizumab are used.

Extending treatment to include eyes with visual acuity better than 6/12 produces ICERs far below £20,000 if bevacizumab is used, and if 3-monthly or PRN ranibizumab is used (evaluated at list prices). When confidential NHS prices are used, the pairwise ICERs for extending treatment this way with aflibercept (2-monthly or 2-monthly followed by PRN) or ranibizumab (2-monthly, 3-monthly or PRN) are below £20,000 when each strategy is compared with restricting the same regimen to eyes with acuity of 6/12 or better. In strategies that restrict treatment to better-seeing eyes only, including eyes with visual acuity worse than 6/96 typically produces cost-effective QALYs compared with not doing so. This is not true for strategies that also allow worse-seeing eyes to be treated.

In an analysis without bevacizumab strategies, using ranibizumab to treat better-seeing eyes with visual acuity between 6/12 and 6/96, once every 3 months, has an ICER of £15,967 per QALY gained, when evaluated at its list price, compared with no treatment. It has a probability of 36.2% of being optimal at a value of £20,000 per QALY. Extending treatment to eyes with visual acuity better than 6/12 has an ICER of £27,521 per QALY gained. Ranibizumab for better-seeing eyes with visual acuity between 6/12 and 6/96, once every 3 months, remains the only strategy with an ICER below £20,000 per QALY gained when treatments are evaluated at their confidential NHS prices.

When the array of potential strategies is further restricted to regimens that are commonly used in current practice, there is no active treatment that produces an ICER below £20,000 per QALY gained when evaluated at their list prices. Aflibercept given every 2 months for 1 year, followed by as needed, has an ICER below £20,000 compared with no treatment when evaluated at its confidential NHS price, but only if treatment is restricted to better-seeing eyes. If providing no treatment is removed from the decision space, ranibizumab given as needed is more likely to be more cost effective than aflibercept given every 2 months for 1 year, followed by as needed, when evaluated at their list prices. The cost effectiveness of the 2 regimens becomes impossible to differentiate when their confidential NHS prices are applied.

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10.1.5.2 Antiangiogenic therapies

A literature search and systematic review of economic evaluations identified 20 unique cost–utility analyses comparing anti-VEGF therapies and/or PDT with each other and/or no active treatment. Ten were directly applicable and 10 were partially applicable. Fourteen studies had potentially serious limitations and 6 had very serious limitations.

- All studies that included a bevacizumab arm found that no alternative had an ICER of less than £20,000 per QALY gained compared with bevacizumab.
- Of the 5 studies that compared aflibercept and ranibizumab without a bevacizumab arm, 3 found aflibercept to have an ICER of less than £20,000 per QALY gained, and 2 found ranibizumab to have an ICER of less than £20,000 per QALY gained.
- 7 out of 9 studies comparing PDT with no active treatment found PDT had an ICER above £20,000 per QALY gained.
- 6 cost–utility analyses were funded, at least in part, by a pharmaceutical manufacturer and found the sponsor's drug to have an ICER of £20,000 or less compared with alternative treatments. 8 out of 9 analyses that included a bevacizumab arm and were not funded by industry found bevacizumab to have an ICER of £20,000 or less compared with alternative treatments.

10.1.5.3 Treatment frequency of antiangiogenic therapies

Six unique cost–utility analyses, 1 directly applicable and 5 partially applicable, compared different dosing frequencies of the same anti-VEGF therapy. All 6 studies had potentially serious limitations. Five studies found that treatment with an anti-VEGF therapy on an 'as needed' (*pro re nata*) basis was associated with an ICER of less than £20,000 per QALY gained compared with continuous monthly treatment with the same therapy.

10.1.6 Evidence to recommendations

See section 10.2.4.

10.1.7 Recommendations

See section 10.2.5

10.1.8 Research recommendations

See section 10.2.6.

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10.2 Treatment in people presenting with visual acuity better than 6/12 or people presenting with visual acuity worse than 6/96

Review questions:

- What is the effectiveness of treatment of neovascular AMD in people presenting with visual acuity better than 6/12?
- What is the effectiveness of treatment of neovascular AMD in people presenting with visual acuity worse than 6/96?

10.2.1 Evidence review

The aim of this review was to determine the effectiveness of first-line antiangiogenic therapy in people presenting with visual acuity better than 6/12 or people presenting with visual acuity worse than 6/96.

The review focused on identifying studies that fulfilled the conditions specified in Table 43 and Table 44. For full details of the review protocol please see Appendix C.

Table 46: PICO table – treatment in people presenting with visual acuity better than 6/12

Population	Adults (18 years and older) diagnosed with neovascular AMD presenting with visual acuity better than 6/12
Interventions	First-line therapy (anti-VEGF drugs)
Comparator	• Placebo (sham injection) • No treatment (monitoring)
Outcomes	• Clinical outcomes (critical): visual acuity (LogMAR) • Safety and adverse events (important) • Functional capacity, participation, independence and ability to carry out activities of daily living (important) • Health related quality of life (important) • Impact on carers • Resource use and costs (critical)

Table 47: PICO table – treatment in people presenting with visual acuity worse than 6/96

Population	Adults (18 years and older) diagnosed with neovascular AMD presenting with visual acuity worse than 6/96
Interventions	First-line therapy (anti-VEGF drugs)
Comparator	• Placebo • No treatment (monitoring)
Outcomes	• Clinical outcomes (critical): visual acuity (LogMAR) • Safety and adverse events (important) • Functional capacity, participation, independence and ability to carry out activities of daily living (important) • Health related quality of life (important) • Impact on carers • Resource use and costs (critical)

Randomised controlled trials (RCTs) and systematic review of RCTs were included if they compared anti-VEGF treatments for people presenting with visual acuity better than 6/12 (70

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letters) or worse than 6/96 (25 letters). If there is no RCT study, observational studies were included. But studies were excluded if they:

- were not published in the English language
- reported outcomes not stratified by baseline visual acuity
- were abstracts, conference proceedings, guideline/health technology assessment report, narrative reviews, case-studies, non-comparative studies

10.2.1.1 Description of included studies

A systematic search identified 4,035 references. The references were screened on their titles and abstracts and 59 references were ordered for full-text review. Following review of full-text papers, a total of 10 studies were included in the review (the analysis of 2 of included studies were based on same set of data, Writing committee for the UK age-related macular degeneration EMR Users group 2014 and Lee A 2016). There was no RCT study, and included studies were observational studies, which reported outcomes based on stratified baseline visual acuity. An update search carried out near the end of guideline development identified further 1 study. A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

A brief summary of included studies is provided in Table 48. References of included studies are listed in Appendix I.

Table 48: Summary of included studies

	Population	Intervention and Comparison	Outcome
Buckle 2016 [UK] – includes people with good and poor vision at baseline	People with neovascular AMD (n=1,278 people, 1,483 eyes)	Ranibizumab, visual acuity over 5-years study follow-up	Proportion of people lost visual acuity stratified by baseline VA
Fang 2013 [China] – includes people with poor vision at baseline	People with neovascular AMD (n=144 people)	Bevacizumab (every 6 weeks) Bevacizumab (every 6 weeks for 3 injections, then every 12 weeks)	Visual acuity score change
El-Mollagyess 2013 [Lebanon] – includes people with good and poor vision at baseline	People with neovascular AMD (n=90 people)	Bevacizumab, visual acuity change from baseline to 12-months follow-up	Visual acuity stratified by baseline VA
Gillies 2015 [Australia, New Zealand, and Switzerland] – includes people with good and poor vision at baseline	People with neovascular AMD that received at least 1 anti-VEGF injection (n=1,043 people, 1,212 eyes)	Anti-VEGF injection, visual acuity over 5-years study follow-up	Visual acuity stratified by baseline visual acuity
Writing Committee for the UK EMR user group 2014 [UK] - – includes people with good	People treated with ranibizumab for neovascular AMD (n=11,135 people, 12,951 eyes)	Ranibizumab, visual acuity over 2-years study follow-up	Mean visual acuity

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	Population	Intervention and Comparison	Outcome
and poor vision at baseline			
Regillo 2015 [USA] – includes people with good vision at baseline	People with active subfoveal wet AMD (n=500 people)	Ranibizumab, monthly/PRN vs Ranibizumab, PRN/monthly, visual acuity by baseline VA ((>6/12 or ≤6/12)	Proportion of patients with a gain of 15 or more letters)
Vogel 2016 [USA] – includes people with poor vision at baseline	People with late AMD (wet active) (n=1,410 people)	Anti-VEGF (ranibizumab, or bevacizumab or aflibercept, visual acuity at 12-months study follow-up	Visual acuity between people with worse than 6/120 and people with 6/120 or better vision
Williams 2011 [UK] – includes people with good and poor vision at baseline	A consecutive series of people with late AMD (wet active) (n=615 eyes)	Ranibizumab, visual acuity from baseline to 52-weeks study follow-up	Mean change in visual acuity at 52 weeks for each baseline vision
Ying 2012 [USA] - includes people with good and poor vision at baseline	People with neovascular AMD, baseline visual acuity 20/25 (6/7.5) to 20/320 (6/96) (n=1,105 people)	Bevacizumab (ranibizumab), Ranibizumab (bevacizumab), visual acuity at 12-months study follow-up stratified by baseline VA	Change in visual acuity
Zhu 2015 [Australia] – includes people with good and poor vision at baseline	A consecutive series of people with subfoveal neovascular AMD (n=208 people, 208 eyes)	Ranibizumab, visual acuity over 5-years study follow-up	Visual acuity change over five years of treatment stratified by baseline visual acuity

10.2.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. Two references were retained for these review questions. Both references contained cost—utility analyses related to treating people with presenting VA better than 6/12. One reference also presented an analysis related to relating people with presenting VA worse than 20/400, and therefore worse than 6/96.

10.2.2.1 Review of included cost—utility analyses

Butt et al. (2015)

Butt et al. (2015) presented a cost-utility analysis comparing treating wet AMD in people with presenting VA better than 6/12 (immediate treatment) with waiting until their VA falls to below 6/12 (delayed treatment). Patients were assumed to be treated with monthly ranibizumab. A 2-year Markov model was developed, with 5 VA health states, using data from an observational UK AMD database (Tufail et al., 2014). On the delayed treatment arm, after a time spent in the 'VA >6/12' state, patients are distributed between the <6/12 states according to the distribution of eyes at diagnosis. This is likely to bias against the 'delayed treatment' arm, by increasing the visual impairment associated with not treatment eyes with VA better than 6/12. In clinical practice, it is likely that these eyes, with known late AMD (wet active), would be subject to close monitoring, and would therefore typically have better VA at the point of treatment than first eyes at the point of diagnosis. Transition probabilities on treatment thereafter, after VA reaches 6/12, are substantially better on the early treatment

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arm. Direct costs were from the NICE TA 294 costing template (2012 £). Quality of life was related to VA using the Brown et al. (2000) utility weights.

The central estimates of total costs from 10,000 Monte Carlo simulations were £7,460 for delayed treatment and £8,470 for immediate treatment. Total QALY estimates were 1.35 and 1.59, respectively. Incremental costs and QALYs were £1,010 and 0.24, producing a mean ICER for immediate treatment of £4,252 per additional QALY compared with delayed treatment. Immediate treatment was reported to have an ICER of £20,000 or less in over 90% of simulations.

Wu et al. (2016)

Wu et al. (2016) developed a Markov model to evaluate the relative cost-effectiveness of ranibizumab, bevacizumab, PDT and usual care (no active treatment) in China, with costs reported in 2012 US dollars. The analysis is detailed in Appendix J. Results were presented by AMD subtype, and ICERs were also presented graphically stratified by presenting VA. ICERs were presented separately for each active treatment compared with usual care.

The graphical ICERs, of each treatment compared with usual care, suggest that active treatments are less cost-effective in people with low presenting VA if they have occult/no classic AMD. In other AMD subtypes, there appears to be little systematic variation between treating people with presenting VA ≤20/400 and higher levels of VA.

10.2.2.2 Health economic analysis

No directly applicable studies with only minor limitations were found that covered review questions regarding treating eyes with VA better than 6/12 and worse than 6/96. A new economic analysis was therefore undertaken. A full description of the health economic model can be found in Appendix J; a summary is presented in Section 10.1.2.2 of this chapter. The model was developed in line with the NICE reference case (NICE, 2012) and Guidelines Manual (NICE, 2014).

Cost—utility results

Base-case NHB results from the new economic analysis are presented in Table 40. The model estimates that removing the lower VA threshold – thereby allowing eyes with VA ≤25 letters (worse than 6/96) to be treated – is not typically a cost effective strategy (full table in Appendix J). This is shown by comparing the NHB of strategies that are identical except one uses current practice VA thresholds whereas the other extends treatment to eyes with low VA. The gains in QALYs made by treating eyes with low VA are very small, and poor value for money relative to the cost of doing so. The quality of life of people remains low because their absolute VA remains at a low level. However, extending treatment to people with VA of less than 6/96 is much more likely to be cost-effective if only better-seeing eyes are considered eligible for treatment, given that this extension would only apply to people with severe visual impairment overall. When both better- and worse-seeing eyes are considered for treatment, then extending treatment in the other direction, by allowing eyes with VA >70 (better than 6/12) to be treated, is much more likely to be a cost effective strategy.

At an opportunity cost of £30,000 per QALY, the following strategy is found provide the highest NHB: **bevacizumab**, injected **every 2 months**, regardless of whether an eye is the **better or worse-seeing eye**, and **including eyes with VA better than 6/12**. More detail is provided in Section 10.1.5.1, and full details are provided in Appendix J.

10.2.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively. Where no

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comparator is specified in the evidence statement, the data come from a non-comparative study.

10.2.3.1 Clinical evidence

10.2.3.1.1 People presenting with visual acuity better than 6/12

Visual acuity at 1 year follow-up

Low-quality evidence reported people presenting with visual acuity better than 6/12 had better visual acuity after 1 year's anti-VEGF treatment than those with those with baseline VA between 6/12 and 6/96 (MD 16.52 letters [95%CI 13.41 to 19.64]; 2 studies of 11,914).

Change in visual acuity

Moderate-quality evidence reported people presenting with visual acuity better than 6/12 lost more letters after 1 year's anti-VEGF treatment compared with those with baseline VA between 6/12 and 6/96 (MD -6.34 [95%CI -7.33 to -5.36]; 3 studies of 12,529 eyes).

Low-quality evidence reported people presenting with visual acuity better than 6/12 lost more letters at 5-year follow-up after anti-VEGF treatment than those with baseline VA between 6/12 and 6/60 (MD -11.75 [95%CI -18.98 to -4.92]; 1 study of 186 eyes).

Loss of visual acuity

Very low-quality evidence could not differentiate the chance of visual deterioration (losing 3 or more lines) after 1 year's anti-VEGF treatment between people presenting with visual acuity better than 6/12 and those with baseline acuity between 6/12 and 6/100 (RR 0.41 [95%CI 0.04 to 3.94]; 2 studies of 1,398 eyes).

Gain of visual acuity

Moderate-quality evidence showed people presenting with visual acuity better than 6/12 were less likely to gain 15 or more letters after 1 year's anti-VEGF treatment than those with baseline VA worse than 6/12 (RR 0.16 [95%CI 0.12 to 0.22]; 4 studies of 2,310 eyes).

10.2.3.1.2 People presenting with visual acuity worse than 6/96

Visual acuity at 1 year follow-up

Moderate-quality evidence reported people presenting with visual acuity worse than 6/96 had worse visual acuity after 1 year's anti-VEGF treatment than those with those with baseline VA between 6/12 and 6/96 (MD -17.23 letters [95%CI -22.36 to -12.10]; 1 study of 8,888 eyes).

Change in visual acuity

Moderate-quality evidence reported people presenting with visual acuity worse than 6/96 gained more letters after 6 months' anti-VEGF treatment than those with baseline VA better than 6/96 (MD 7.77 [95%CI 5.44 to 10.10]; 2 studies of 9,023 eyes).

Moderate-quality evidence reported people presented with visual acuity worse than 6/96 gained more letters after 1 year's anti-VEGF treatment than those with baseline VA between 6/96 and 6/12 (MD 13.99 [95%CI 10.39 to 17.59]; 1 study of 8,888 eyes).

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Gain of visual acuity

Very low-quality evidence reported people presenting with visual acuity worse than 6/120 were more likely to gain 15 or more letters after 6–12 months' anti-VEGF treatment than those with baseline VA 6/120 or better (RR 1.44 [95%CI 1.02 to 2.01]; 2 studies of 239 eyes).

10.2.3.2 Health economic evidence

10.2.3.2.1 New cost–utility analysis

One directly applicable health economic model with minor limitations compared comprehensive treatment strategies, including different visual acuity thresholds that define when an eye can and cannot commence treatment. The evidence statement summarising the new cost—utility analysis is presented in Section 10.1.5.1.

10.2.3.2.2 People presenting with visual acuity better than 6/12

One directly applicable cost—utility analysis with potentially serious limitations compared the immediate treatment of wet AMD in people who present with VA better than 6/12 with delaying treatment until VA is worse than 6/12. Immediate treatment was found to have an ICER of £4,252 per QALY gained compared with delayed treatment.

One partially applicable cost—utility analysis with very serious limitations compared multiple treatments with usual care, and stratified patients by AMD subtype and presenting VA. The ICERs suggest that there is little variation in the cost-effectiveness of early treatment (VA > 20/40) compared with usual care at different levels of initial VA.

10.2.3.2.3 People presenting with visual acuity worse than 6/96

One partially applicable cost—utility analysis with very serious limitations compared multiple treatments with usual care, and stratified patients by AMD subtype and presenting VA. The ICERs suggest that, in people with occult/no classic AMD, treatment may be less cost-effective in people with initial VA ≤20/400 than in people with better initial VA, compared with usual care.

10.2.4 Evidence to recommendations

Note that the following section refers to all recommendations regarding the use of antiangiogenic therapies based on the evidence presented in sections 10.1 and 10.2 of this chapter.

Relative value of different outcomes	The committee acknowledged that best-corrected visual acuity (BCVA) outcomes were the most common in the evidence included for the different review questions associated with antiangiogenic treatments and treatment frequency. Included studies commonly report visual acuity in 2 ways: 1) the proportion of patients who gained and lost more than a given number of ETDRS letters; 2) the mean change in visual acuity. The committee accepted visual acuity as a useful and important outcome for comparing the effectiveness of antiangiogenic therapies, with a preference for absolute visual acuity over change in visual acuity, as it is the former that ultimately affects a person's quality of life. The committee reaffirmed that a visual acuity change of at least 5 letters in either direction is necessary for the change to be considered clinically significant. The committee also discussed the adverse event rates of different antiangiogenic treatments, noting that the number of adverse events in trials was typically very small, and any differences between groups tended to be statistically insignificant. The committee discussed the evidence of a higher risk of gastrointestinal side effects associated with treatment with bevacizumab, and agreed that it is not considered a clinically meaningful difference compared with other anti-VEGF treatments. The committee also

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	noted the different adverse event profile associated with PDT compared with anti-VEGF treatments. The committee agreed that the adverse event risks of different treatments were sufficiently similar and low for safety outcomes not to be a crucial to their decision-making. The committee discussed the value of visual acuity outcomes when comparing the treatment of late AMD (wet active) in people presenting with good visual acuity (better than 6/12, equivalent to 70 ETDRS letters) or poor visual acuity (below 6/96, equivalent to 25 ETDRS letter). The committee noted that change in visual acuity may be less informative for such comparisons, as people with good baseline visual acuity have less potential to improve due to a ceiling effect (and greater potential to decline), while people with poor baseline visual acuity have more potential improve (and less potential to decline). The committee agreed that, without treatment, eyes at all levels of baseline visual acuity would converge towards poor visual acuity (25–30 letters) over time. Comparison of mean visual acuity change showed the extent of change between populations with different visual thresholds but did not reflect the actual difference in visual acuity between populations both at the baseline and the end of study follow-up. Therefore, for these comparisons in particular, absolute visual acuity was viewed as the most valuable outcome; maintaining good visual acuity over time (even if there is no gain in visual acuity) would be seen as a positive response to treatment.
Trade-off between benefits and harms	**The effectiveness of antiangiogenic therapies** The committee discussed the evidence regarding the effectiveness of photodynamic therapy (PDT) for treating people with late AMD (wet active). As expected, the visual acuity of people who received PDT improved compared with those who received a placebo; however, the NMAs suggested that the benefit is relatively small, for the average patient (around 5 letters, compared with sham, after 2 years' treatment). The committee noted that, since the development of anti-VEGFs, it has become extremely uncommon to offer PDT alone as first-line treatment for people with neovascular AMD. However, some practitioners believe it has value as part of combination therapies, particularly when treating polyps (see section 10.3 for evidence and recommendations on use of PDT as an adjunct to anti-VEGF therapy). The committee therefore made a recommendation that PDT should not be used as monotherapy for late AMD (wet active). The committee agreed that the evidence indicated anti-VEGF therapies to be a highly effective treatment. As a first-line treatment, anti-VEGF agents are substantially more effective than PDT monotherapy. The committee discussed the relative effectiveness and safety of the 3 anti-VEGF agents, and were satisfied that the visual acuity outcomes were neither clinically nor statistically significantly different between aflibercept, bevacizumab and ranibizumab, such that they can be considered equally effective. Of adverse events reported, the committee agreed that back pain was 1 of main complaints that people had after photodynamic therapy. The numbers of adverse events reported were small in anti-VEGF trials. The committee discussed the evidence of a higher risk of gastrointestinal side-effects associated with treatment with bevacizumab, noting that these side-effects were prominent in earlier RCTs but less so in more recent trials. It noted that no particular gastrointestinal events had been found to be more prevalent with bevacizumab (which would be expected if there were reliably different systemic effects) and emphasised the potential for artefactual findings when a large number of endpoints are being explored. Therefore, the committee concluded that the gastrointestinal side effect profile of bevacizumab is not a clinically significant consideration. The committee noted that people could experience an increase in intraocular pressure after anti-VEGF injection, and such an increase would usually resolve within 24 hours (although, if it is sustained, it should be reported as a serious adverse event). Evidence showed that, overall, there was little difference in adverse events between anti-VEGF agents and that the safety

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profiles of all 3 anti-VEGF therapies can be considered to be comparable. Balancing the clinical effectiveness and safety, the committee were confident in agreeing to recommend the use of anti-VEGF therapies to treat late AMD (wet active).

The committee discussed the use of different doses of anti-VEGF therapies, acknowledging that 2 mg ranibizumab and 0.5 mg aflibercept were captured in the evidence base, but these doses are not routinely used or available in practice. The committee agreed that these doses should not be considered relevant for its decision-making (although it agreed that it was sensible to retain them in the 'synthesis set' for network meta-analyses, as they could help to inform treatment effect estimates for treatments that are available in practice). The committee also discussed the potential use of pegaptanib for the treatment of late AMD (wet active), noting that it is not available for prescription, and was therefore also considered not relevant for its decision making. The committee therefore opted not to make any explicit recommendations about 2 mg ranibizumab, 0.5 mg aflibercept or pegaptanib. Some included trials used 0.3 mg and/or 0.5 mg ranibizumab when evaluating clinical effectiveness, and the committee suggested that the effects of these 2 doses were considered to be identical.

The effectiveness of anti-VEGF for people with good or poor visual acuity at the baseline

In current practice, as informed by the technology appraisals incorporated in this guideline, anti-VEGF treatments tend to be offered to people with visual acuity between 6/12 and 6/96. The committee discussed the evidence regarding treating late AMD (wet active) when the presenting eye's visual acuity is better than 6/12 or worse than 6/96. The committee acknowledged that the evidence presented in this review suggested treating AMD when visual acuity is good leads to the eye maintaining good visual acuity over time. The committee noted that this was in line with clinical experience, where treating AMD before significant visual impairment occurs commonly leads to maintenance of vision (and may lead to fewer injections being required overall).

The committee was aware that the evidence showed that people who present with initial visual acuity worse than 6/96 gain more letters from treatment than those who have better BCVA, and that this was consistent with those eyes having greater potential to improve. Despite this, the evidence also showed that the absolute visual acuity of eyes starting with poor visual acuity remained low over time. The committee agreed that maintenance of good visual acuity is likely to have more impact on a person's quality of life than ostensibly larger changes in acuity, when absolute acuity remains poor.

The committee also agreed that the observational evidence available to it reflected a selected subgroup of people with low BCVA whose eyes were deemed by their clinicians to have the potential to respond to antiangiogenic therapy. This would not be expected in all people with low BCVA; for example, an improvement in visual function would not be expected in those with permanent structural damage to the fovea.

The committee discussed whether the benefits and harms to patients of treating eyes with visual acuity lower than 6/96 would vary depending on which eye was being treated. The committee agreed that a patient would be unlikely to notice any improvement in their visual function from being treated in an eye with very low visual acuity if their fellow eye has better visual acuity. The committee discussed the risk of not treating the worse-seeing eye in this scenario, where the better-seeing eye might deteriorate due to unforeseen circumstances, at which point the opportunity for treating the worse-seeing eye has been missed. The committee agreed that the risk of catastrophic vision loss in the better eye is very low in people at the typical age of AMD onset. The committee discussed whether a recommendation to treat at visual acuities lower than 6/96 only in the

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	better-seeing eye should be made. It was noted that this would prevent treatment in people with AMD in an eye with visual acuity lower than 6/96 and also low visual acuity in the fellow eye, albeit slightly higher (e.g. 6/60). Treating the worse-seeing eye may, in some cases, reasonably be expected to improve the person's overall visual function in this scenario. The committee therefore recommended that treatment at visual acuity lower than 6/96 should be considered, only if the clinician expects doing so to have a positive impact on the patient's overall visual function, noting that, in most cases, this would be when it represented the patient's better-seeing eye. **The effectiveness of anti-VEGF treatment frequency** The committee discussed the evidence relating to different dosing regimens (frequency of treatment). The committee was aware that low- to moderate-quality evidence suggested that routine (constant interval) regimens, and regimens with shorter intervals, were associated with a higher likelihood of visual acuity improvements, and that this was reflected in the network meta-analyses and, by extension, the economic model. The committee discussed the feasibility of treating at intervals of 2 and 3 months, and agreed that a 3-month interval between anti-VEGF injections would be considered to be too long according to current clinical practice. The committee explained that the effect of an anti-VEGF injection would be expected to wear off after around 2 months, and that visual acuity would decline in a 3-month period, substantially so in some individuals. The committee suggested that current practice sees patients treated typically monthly or 2-monthly; therefore, a prolonged 3-month treatment intervals would be perceived as a reduction in the quality of care and worse outcomes, as reflected by the clinical evidence. The committee discussed the effectiveness evidence for treat-and-extend dosing (TREX), including the TREND study published during development of the guideline. The committee was aware that this study dominates the TREX-AMD study in a synthesis of the 2, and agreed that the study showed treat-and-extend was not superior to continuous treatment over 1 year, but that long-term effectiveness remains uncertain. The committee therefore chose to make a research recommendation for more evidence regarding the effectiveness of TREX compared with other treatment protocols beyond 1 year of follow up. Clinical evidence showed that 'as needed' (PRN) regimens were not more effective than routine injection schedules. The committee acknowledged that PRN regimens were not found to be cost-effective in the new economic analysis, but noted that the previous technology appraisal recommendations for ranibizumab and aflibercept were to be incorporated into this guideline, which permit PRN treatment with those therapies as per their SPCs. The committee therefore chose not to recommend a particular treatment frequency.
Trade-off between net health benefits and resource use	The committee discussed the health economic evidence presented, including the new economic model developed for this guideline. The committee noted that the model results showed strategies producing better health outcomes (more QALYs) were associated with higher overall costs. The committee acknowledged that, when all 137 base-case strategies were compared, bevacizumab regimens were the only strategies with incremental cost-effectiveness ratios (ICERs) of less than £20,000 per QALY gained; aflibercept and ranibizumab regimens were associated with much higher ICERs; and PDT was not cost effective in any analysis presented. The committee was aware that these results were also true when the confidential patient access scheme (PAS) prices of aflibercept and ranibizumab were used in the model, noting that only low-intensity treatment, and largely restricted to only better-seeing eyes, produced superior net health benefits than providing no treatment. The committee noted that the ICERs for ranibizumab tended to be higher than in its initial technology appraisal (TA 155). The committee was aware of the

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differences between previous models and the new model: it is a lifetime 2-eye model, using a more comprehensive, up-to-date range of evidence on both treatment effects and long-term disease progression, and it provides a fully incremental analysis of a wider range of comparators including population-level treatment eligibility criteria. The committee agreed that the new model is likely to provide the most robust and applicable health economic evidence available to it.

The committee understood that there are strong methodological grounds for considering all relevant decisions (agent, frequency, upper and lower threshold for initiating treatment, fellow-eye status) in a single analysis, rather than in a 'piecewise' manner. It agreed that the new analysis provided convincing evidence that, across all these dimensions, the optimal balance of benefits, harms and costs is achieved by a strategy of: bevacizumab, injected every 2 months, for any eye with BCVA better than 6/96 (including those with VA better than 6/12), regardless of whether it is the person's better- or worse-seeing eye; and that this was the case regardless of whether the aflibercept and ranibizumab PAS prices were applied.

Choice of agent

The committee noted the clear evidence that all the strategies providing best value for money were those based on bevacizumab. It saw that this finding was maintained across all sensitivity analyses, including a scenario in which the risk of endophthalmitis associated with bevacizumab injections was increased to an implausibly high level, in order to explore risks that some people fear may be associated with the preparation of unlicensed bevacizumab for intraocular use.

However, the committee was mindful that bevacizumab may not be available to NHS prescribers, as it does not have a UK marketing authorisation for intraocular use, and any such use is considered unlicensed by the MHRA. It therefore considered the optimal choice of agent when bevacizumab is excluded from consideration. It noted that, under this circumstance, only very low-intensity ranibizumab regimens (for example, treating better-seeing eyes only on a 3-monthly basis) are estimated to provide greater net health benefits to the NHS than providing no treatment, when list prices are used. The committee understood that no aflibercept-based regimens are among those that are cost effective compared with no treatment; however, it is likely that a 3-monthly aflibercept regimen (which has not been researched) would have similar results to the equivalent ranibizumab strategy.

The committee, noting that the kinds of low-intensity strategy that had been shown to be optimal were not consistent with aflibercept's and ranibizumab's current marketing authorisations, further narrowed the strategies under consideration to those dosing regimens explicitly specified in the products' SPCs, thereby analysing regimens typically used in the NHS. The committee agreed that none were close enough to the range of ICERs considered to represent good value for money compared with no treatment, at their list or PAS prices, unless treatment was restricted to only better-seeing eyes. However, given that both aflibercept and ranibizumab are recommended as treatment options in the technology appraisals incorporated in this guideline, 'no treatment' may not be a useful comparator. If this option is removed, and if treatments are assumed to be available regardless of fellow-eye status (as the committee suggest is commonly the case in current practice), ranibizumab PRN is more likely to be cost effective than aflibercept (2-monthly for 1 year then PRN) at their list prices. However, the committee also saw cost–utility results evaluated at the PAS prices, and agreed that there is very little to choose between the PRN regimens of aflibercept and ranibizumab in terms of cost effectiveness, based on sensitivity analysis results at PAS prices. These results showed the optimal strategy (of the 2) to be highly sensitive to individual parameter variation and alternative scenarios. When current

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practice VA ranges and extending to VA better than 6/12 strategies were included, for PRN aflibercept and ranibizumab (i.e. 4 strategies in total), no single strategy had a >50% likelihood of having an ICER under £20,000 compared with the other 3 in probabilistic sensitivity analysis. This suggests that there is little to choose between the 2 agents, a result that is consistent with the findings of other authors: the committee understood that CUAs comparing aflibercept and ranibizumab tend to be funded by the manufacturer of one of the products, and tend to find in favour of that product, but that claimed health benefits are invariably small (typically less than 0.2 QALYs). The committee was aware that, in TA294, a similar comparability of outcomes was also prominent in sensitivity analysis (including additional work done by the Evidence Review Group).

Frequency of administration

The committee noted that other published health economic analyses have found that PRN regimens of ranibizumab are cost effective compared with routine monthly administration. The new model also found that, for all anti-VEGF agents, a PRN approach provides better value for money than a monthly one, at both PAS and list prices. However, the model developed for this guideline is the first to include 2- and 3-monthly regimens, and the committee agreed that this has important implications. The NMAs suggested that routine 2-monthly treatment with any anti-VEGF has similar benefits to PRN strategies, and the evidence also suggests a similar number of injections (around 6 per year). However, 2-monthly approaches benefit from fewer appointments and scans, with the net result that they have similar effects with lower costs. For this reason, the new cost–utility analysis suggests routine 2-monthly bevacizumab and ranibizumab strategies are always cost effective compared with analogous PRN regimens (regardless of eligibility of eyes). This would be even more obvious if routine injection strategies did not involve OCTs at every appointment (on the grounds that they would not be needed to guide the basic treatment decision – though they would still be needed in some cases to monitor things such as pathological progression and fellow-eye status).

Three-monthly approaches provide fewer QALYs than more frequent dosing, because they are associated with worse VA outcomes. Nevertheless, they would be preferred in the case of ranibizumab (and probably aflibercept, too, though there is no RCT evidence) because, given the additional cost of the drug, the cost savings incurred by reduced frequency are sufficient to outweigh the loss in QALYs. In this instance, it would also optimise cost effectiveness to restrict treatment to better-seeing eyes only. The committee was aware that these findings were true of the analysis using the PAS prices as well as the list prices.

The committee was aware that the clinical evidence synthesis used to inform the new economic analysis had potentially slightly underestimated the effectiveness penalty associated with extending the interval between injections. This is because the 2-monthly and 3-monthly injections evidence is influenced, in some but not all cases, by loading phases, which could not be disentangled from the data. Using a loading phase upon initiation of a 2-monthly treatment regimen would require 1 additional injection compared with not having a loading phase (which would occur during the second month of treatment). The committee agreed that it had not seen compelling evidence for or against the use of a loading phase in routine 2-monthly or 3-monthly treatment regimens, but agreed that the resource implication of 1 additional visit (for 2-monthly regimens) is likely to be small.

The committee reviewed the scenario analyses in which PRN-and-extend regimens had been included in the model. It understood that its effect estimate was connected to the network of evidence by 1 small RCT, and was therefore subject to considerable uncertainty. The point estimate suggested that PRNX approaches are superior to routine monthly treatment. The committee agreed that such a finding is extremely unlikely, given the expected dose–response relationship. The wide credible intervals

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around the parameter estimates showed that this improbable finding was entirely consistent with simple sampling error (at a 95% confidence level), and the committee understood that the lack of certainty was appropriately propagated through the probabilistic decision model. Nevertheless, on average, PRNX strategies benefit from favourable effect estimates, and the positive tail of the effect distributions would lead to a degree of prominence in cost-effectiveness acceptability curves (which only focus on the probability that an approach is 'best' and do not show the complementary probability that it is worst, which would be equally exaggerated for approaches with wider credible intervals). As a chance counterbalance to this issue, PRNX strategies were associated with high-and-uncertain dropout rates in the NMA.

The net result of these uncertainties is that PRNX feature among the approaches that provide best value for money in the model, though relatively small alterations to parameters might lead to a different result.

In view of the substantial uncertainties surrounding PRNX regimens, the committee agreed that more powerful, high-quality, randomised evidence is needed to reach a robust view on the balance of benefits, harms and costs with which they are associated.

Thresholds for treatment initiation

The committee considered the economic evidence related to treating late AMD (wet active) in eyes with visual acuity better than 6/12 or worse than 6/96. The committee noted that the new economic model suggested that extending current practice to treat eyes with visual acuity better than 6/12 consistently produced additional QALYs and, if the agent given was bevacizumab, it did so at a cost-effective level compared with current visual acuity thresholds. Regimen-specific pairwise analyses suggested that extending current practice to treat eyes with visual acuity better than 6/12 is likely to be cost effective if the agent given is aflibercept or ranibizumab, when evaluated at their confidential PAS prices, with ICERs below £20,000 per QALY gained compared with not extending treatment this way. The committee discussed the implications of treating eyes with VA better than 6/12, noting that it is only cost effective with aflibercept or ranibizumab when compared with something that is, itself, cost ineffective. Because the analysis had convincingly shown that there are many strategies (not only those involving bevacizumab) that would deliver greater net benefit to the NHS than simply extending current treatment to a wider range of eyes, the committee considered it inappropriate to make a recommendation explicitly mandating such an approach. Instead, the committee opted to make an awareness-raising recommendation noting that offering anti-VEGF to eyes with acuity better than 6/12 could provide cost-effective benefits, depending on the regimen used.

The committee discussed the model results associated with treating at visual acuities worse than 6/96, noting that these strategies were not typically cost effective in the economic analysis when both better- and worse-seeing eyes were considered eligible for treatment. The committee was aware that the model predicts minimal difference in QALYs from extending treatment to patients with BCVA lower than 6/96, compared with current visual acuity thresholds. This result arises, in part, because the disutility associated with injections and adverse events is not counterbalanced by functionally meaningful benefits in BCVA, as it is in people with less baseline impairment. The committee agreed that this finding was consistent with members' experience. The model also reflected the committee's expectation, discussed above, that, where an eye with BCVA of worse than 6/96 represents a person's better-seeing eye, it is more likely to be an effective use of NHS resources to offer anti-VEGF treatment, compared with the current practice of excluding such eyes from anti-VEGF therapy. For this reason, the committee agreed that a 'consider' recommendation, qualified to limit treatment to patients who can be

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	expected to experience a meaningful improvement in overall visual function, represented a reasonable conclusion. **Anti-VEGF recommendations** The committee understood that the existing technology appraisal recommendations regarding aflibercept (TA 294) and ranibizumab (TA 155) would be incorporated into this guideline. The committee agreed that the new model – along with other published economic evidence – showed that treatment with bevacizumab would be unequivocally cost effective when compared with aflibercept and ranibizumab, and that it would ideally like to make a recommendation in favour of bevacizumab. However, the committee was aware that the use of bevacizumab for the treatment of late AMD (wet active) is judged by the MHRA to represent unlicensed prescribing. The committee therefore agreed that it could not explicitly recommend bevacizumab over the alternative anti-VEGFs, and agreed to make a class-level recommendation that anti-VEGF therapy should be offered for the treatment of late AMD (wet active). The committee agreed that a class-level recommendation, that anti-VEGF therapy should be offered for the treatment of late AMD (wet active), has the benefit of 'future-proofing' the guidance so that it will remain valid in the event of any changes to the regulatory position. **PDT** The committee acknowledged that the new economic model indicated that PDT is not a cost-effective use of healthcare resources, and that this was consistent with most previous economic evaluations of PDT. The committee noted that the model did not capture any patient subgroups by AMD subtype, and that the potential benefit of treating certain subtypes (in particular, classic with no occult subfoveal choroidal neovascularisation) may have been diluted. However, the committee was satisfied that PDT was still unlikely to be cost effective, especially in the era of anti-VEGFs. The committee therefore recommended that PDT should not be used as monotherapy for late AMD (wet active).
Quality of evidence	The committee acknowledged that there was, overall, a large body of good-quality evidence comparing different antiangiogenic treatments for the treatment of people with late AMD (wet active). The committee discussed the clinical significance of the changes in visual acuity observed in the clinical evidence. The committee noted that a 5-letter change had previously been judged as clinically significant, with changes of fewer than 5 letters being less noticeable to the patient and susceptible to measurement error. The committee discussed the extent to which a population-level increase of less than 5 letters would be a positive change, and agreed that, across the whole population, a small gain, for instance of 2 letters, would be worthwhile if there were no resource implications. However, the committee agreed that, for decision-making purposes, a 5-letter threshold for a visual acuity change to be clinically meaningful is still a suitable threshold. The committee discussed whether the participant selection criteria used in the RCTs affects the generalisability of the evidence to inform recommendations for routine practice, noting that the RCT evidence is used directly in the economic model developed for this guideline. The committee agreed that the trial inclusion and exclusion criteria were somewhat stringent, meaning trial cohorts are likely to systematically differ to patients seen in real-life routine practice. For instance, the trial could be likely to include people with potential to be benefit from the treatment. The committee acknowledged that they had also seen evidence from observational studies which did not have stringent selection criteria, and that these were also included in the economic model (such as the data informing the relationship between baseline BCVA and treatment-related change in BCVA). The committee agreed that, on balance, the mixed

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evidence base provided a robust basis to inform decision-making regarding the use of antiangiogenic therapies.

There was no RCT evidence identified through the search examining the effectiveness of anti-VEGF therapy when treating eyes presenting with acuity of better than 6/12 or worse than 6/96. Observational studies reporting visual acuity outcomes stratified by initial visual acuity were included in the review. Although some of observational studies included a large sample size, the committee was aware that the clinical evidence was of very low to moderate quality. The committee suggested that outcomes related to gains and losses in visual acuity were likely to have been subject to ceiling and floor effects – for example, eyes with better initial visual acuity have less potential visual acuity to gain. However, the committee was aware that the new economic model analyses were based on mean change outcomes, and included an adjustment to capture the impact of baseline visual acuity on the subsequent treatment effect. The committee noted that the observational data showing visual acuity change stratified by baseline visual acuity may have been subject to 'lead time' bias, whereby better visual acuity indicates that an eye's AMD was identified earlier, at which time it may be more sensitive to anti-VEGF therapy, which might produce better outcomes. The committee also discussed the presence of selection bias in the observational data, where only those eyes considered to have a reasonable likelihood of response to treatment will have been treated and captured in the data. The committee agreed that these biases did not limit the usefulness of the evidence for their decision-making.

The committee acknowledged that the published health economic evidence base was large but subject to potentially serious limitations throughout, and that no previous economic analysis had captured an exhaustive set of possible treatment strategies. The committee agreed that the new economic model represented an advancement in the quality of cost–utility analyses for the treatment of AMD. The committee was uncertain as to whether the model had captured all possible treatment regimens, but agreed that it covered a sufficient number of strategies to form inferences about different options – for example, that any PRN regimen is likely to be cost effective compared with monthly administration of the same agent, but unlikely to be cost effective compared with less frequent routine treatment. The committee agreed that the new model was of sufficient quality to inform recommendations regarding treatments and treating eyes with visual acuity better than 6/12 or worse than 6/96.

The committee discussed the quality of evidence regarding the effectiveness of different treatment frequencies. The committee accepted that more frequent injections provide better visual acuity outcomes, but was uncertain about whether the evidence is sufficient to accurately estimate the size of treatment effects between regimens, particularly discontinuous regimens (PRN and treat-and-extend). The committee considered that PRN regimens were potentially too heterogeneous to be captured in a single term, and that some had potentially been omitted from the model, such as 2-monthly treatment followed by PRN treatment. At the discussion of monitoring strategies, people's treatment could expect to change according to disease activities such as the presence of fluid, the occurrence of vision distortion, and people on the PRN regimen would also expect to be treated or re-treated if visual changes were present. Based on clinical experience, it is expected that people who are on a PRN regimen and have not required treatment for an extended length of time (for instance 1 year) would be discharged from treatment.

The committee discussed the extent to which individual patient factors affect response to different treatment frequencies, and agreed that all patients respond differently due to a number of factors, including pathological progression and age. The committee acknowledged that the model provided population-level results for the average patient, but agreed that this could not tease out the important individual-level patient factors in selecting a frequency of treatment.

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	The committee discussed the clinical evidence for treat-and-extend regimens, and acknowledged that all comparisons with treat-and-extend in the economic model were predominantly reliant on 1-year evidence, with only a small trial providing 2-year evidence. The committee agreed that, while the model results appeared plausible, uncertainty remains regarding the long-term effectiveness of TREX treatment protocols. The committee therefore chose to make a research recommendation to identify the effectiveness and resource use of treat-and-extend regimens beyond 1 year.
Other considerations	The committee agreed that all treatment decisions should consider the needs and preferences of the particular individual with AMD at that moment in time, regardless of the population-level guideline. This section also incorporates the recommendations from the NICE technology appraisals on ranibizumab and aflibercept, with the exception of the recommendations on treatment stopping, which have been updated as part of this guideline.

10.2.5 Recommendations

Note that the following recommendations relate to all review questions concerning the use of antiangiogenic therapies in sections 10.1 and 10.2 of this chapter.

21. **Offer intravitreal anti-vascular endothelial growth factor (VEGF) treatment[10] for late AMD (wet active) for eyes with visual acuity within the range specified in recommendation 26.**

22. **Be aware that no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments[11] have been seen in the trials considered by the guideline committee.**

23. **In eyes with visual acuity of 6/96 or worse, consider anti-VEGF treatment for late AMD (wet active) only if a benefit in the person's overall visual function is expected (for example, if the affected eye is the person's better-seeing eye).**

24. **Be aware that anti-VEGF treatment for eyes with late AMD (wet active) and visual acuity better than 6/12 is clinically effective and may be cost effective depending on the regimen used.[12,13]**

[10] At the time of publication (January 2018), bevacizumab did not have a UK marketing authorisation for, and is considered by the Medicines and Healthcare products Regulatory Agency (MHRA) to be an unlicensed medication in, this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines, and the MHRA's guidance on the supply of unlicensed medicinal products ("specials"), for further information. The guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation but does not amount to an approval of or a recommendation for such use.

[11] Given the guideline committee's view that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab), comparable regimens will be more cost effective if the agent has lower net acquisition, administration and monitoring costs.

[12] At the time of publication (January 2018), bevacizumab did not have a UK marketing authorisation for, and is considered by the Medicines and Healthcare products Regulatory Agency (MHRA) to be an unlicensed medication in, this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines,, and the MHRA's guidance on the supply of unlicensed medicinal products ("specials"), for further information. The guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation but does not amount to an approval of or a recommendation for such use.

[13] Given the guideline committee's view that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab), comparable regimens will be more cost effective if the agent has lower net acquisition, administration and monitoring costs.

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25. **Do not offer photodynamic therapy alone for late AMD (wet active).**

Recommendations from NICE technology appraisals

26. **Ranibizumab, within its marketing authorisation, is recommended as an option for the treatment of wet age-related macular degeneration if:**
    - all of the following circumstances apply in the eye to be treated:
      - the best-corrected visual acuity is between 6/12 and 6/96
      - there is no permanent structural damage to the central fovea
      - the lesion size is less than or equal to 12 disc areas in greatest linear dimension
      - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

      and
    - the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012). [This recommendation is from Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (NICE technology appraisal guidance 155).]

27. **Pegaptanib is not recommended for the treatment of wet age-related macular degeneration. [This recommendation is from Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (NICE technology appraisal guidance 155).]**

28. **People who are currently receiving pegaptanib for any lesion type should have the option to continue therapy until they and their clinicians consider it appropriate to stop. [This recommendation is from Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (NICE technology appraisal guidance 155).]**

29. **Aflibercept solution for injection is recommended as an option for treating wet age‑related macular degeneration only if:**
    - it is used in accordance with the recommendations for ranibizumab NICE technology appraisal guidance 155 (re‑issued in May 2012 [see recommendation 26]) and
    - the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme. [This recommendation is from Aflibercept solution for injection for treating wet age‑related macular degeneration (NICE technology appraisal guidance 294).]

30. **People currently receiving aflibercept solution for injection whose disease does not meet the criteria in recommendation 29 should be able to continue treatment until they and their clinician consider it appropriate to stop. [This recommendation is from Aflibercept solution for injection for treating wet age‑related macular degeneration (NICE technology appraisal guidance 294).]**

10.2.6 Research recommendations

10. **What is the long-term effectiveness and cost effectiveness of 'treat-and-extend' regimen compared with alternative regimens (dosing frequencies)?**

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Why this is important

Treat-and-extend regimens are authorised by the SPCs of both ranibizumab and aflibercept, and the guideline committee advised that they are commonly used in practice. Recent research (the TREND RCT) has provided robust evidence on the comparative effectiveness of this approach using ranibizumab at 1 year's follow-up. However, most other regimens for anti-VEGFs have 2-year randomised data whereas, with the exception of a single RCT comprising 60 participants, equivalent data for the treat-and-extend approach are lacking. This introduced substantial uncertainty in the estimated effect of treat-and-extend regimen at 2 years (and, by extrapolation, at all future junctures in the original economic model developed for this guideline). Therefore, a well conducted RCT with at least 2 years' follow-up would resolve important uncertainty, in this area.

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10.3 Adjunctive therapies

Review questions:

- What is the effectiveness of adjunctive therapies for the treatment of late AMD (wet active)?

10.3.1 Evidence review

The aim of this review was to determine the effectiveness of adjunctive therapies for late wet active AMD in first line treatment. The review focused on identifying studies that fulfilled the conditions specified in Table 49. For full details of the review protocol see Appendix C.

Table 49: PICO table – adjunctive therapy for people with late AMD (wet active)

Population	Adults (18 years and older) diagnosed with late AMD (wet active, treatment naïve)
Interventions	Comparative and head-to-head trials of: • Combination therapies (adding in photodynamic therapy [PDT], or steroids [dexamethasone, fluocinolone acetonide, triamcinolone acetonide]) along with the following Anti-VEGF agents: ○ Aflibercept ○ Bevacizumab ○ Pegaptanib Sodium ○ Ranibizumab
Comparator	Anti-VEGF monotherapy alone Anti-VEGF monotherapy and placebo (same injection)
Outcomes	• Clinical outcomes: ○ Visual acuity (LogMAR) ○ Number of injections • Safety and adverse events • Functional capacity, participation, independence and ability to carry out activities of daily living. • Health related quality of life • Impact on carers • Resource use and costs

Randomised controlled trials (RCTs) and systematic review of RCTs were included if they compared adjunctive therapies with anti-VEGF monotherapy. Papers were excluded if they:

- were not published in the English language
- compared adjunctive therapy with treatments other than anti-VEGF monotherapy alone or anti-VEGF monotherapy and placebo
- were abstracts, conference proceedings, guideline/health technology assessment report, narrative reviews, case-studies, diagnostic studies, non-comparative studies or observational studies

10.3.1.1 Description of included studies

A systematic search identified 1,566 references. The references were screened on their titles and abstracts and 77 references were ordered for full-text review. A total of 17 RCTs were included in the review – 12 with ranibizumab as the anti-VEGF used and 5 with bevacizumab. Fourteen studies compared anti-VEGF monotherapy with anti-VEGF + PDT, 2 compared anti-VEGF monotherapy with anti-VEGF + steroids and 1 compared anti-VEGF + PDT with anti-VEGF + PDT + steroids. There were also 2 systematic reviews identified in the search but these included no additional new evidence, so were not included. For the list of

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excluded studies with reasons, see Appendix F. An update search carried out near the end of guideline development identified further 1 study.

A brief summary of included studies was provided in Table 50. References of included studies are listed in Appendix I.

Table 50: Summary of included studies

Study [country]	Study population	Intervention	Comparator	Outcomes
PDT combined with anti-VEGF				
Bashshur Z F et al 2011 [Lebanon]	Patients with neovascular AMD (n=30 people, 40 eyes)	Verteporfin photodynamic therapy combined with as-needed ranibizumab treatment	Ranibizumab monotherapy	Proportion of patients who lost <15 letters in best-corrected visual acuity; Mean change in BCVA
Datseris I et al 2015 [Greece]	Patients with predominantly classic and occult choroidal neovascularisation in one or both eyes (n=100 people)	Photodynamic therapy combined with intravitreal bevacizumab	Bevacizumab monotherapy	Mean number of re-injection; Corrected distance visual acuity
Gomi F et al 2015 [Japan]	Patients with treatment-naïve polypoidal choroidal vasculopathy (n=72 people, 72 eyes)	Photodynamic Therapy in combination with ranibizumab	Ranibizumab monotherapy	Change in best corrected visual acuity
Hatz K et al 2015	Patients with subfoveal choroidal neovascularisation secondary to AMD (n=40 people)	Verteporfin photodynamic therapy plus ranibizumab	Ranibizumab monotherapy	Number of ranibizumab retreatment; Best-corrected visual acuity
Kaiser P K, et al 2012	Patients had subfoveal choroidal neovascularisation secondary to neovascular age-related degeneration (n=321 people)	Verteporfin plus ranibizumab	Ranibizumab monotherapy	Best-corrected visual acuity
Koh A et al 2012 [Hong Kong, Singapore, South Korean, Taiwan, Thailand]	Treatment naïve patients with symptomatic macular polypoidal choroidal vasculopathy (n=61 people)	Verteporfin photodynamic therapy in combination with ranibizumab	Ranibizumab monotherapy	The proportion of patients in achieving complete regression of polyps; Mean best-corrected visual acuity
Krebs I et al 2013 [Austria]	Patients with subfoveal choroidal neovascularisation secondary to neovascular age-related degeneration; patients with predominantly classic lesions;	Combination of photodynamic therapy with ranibizumab	Ranibizumab monotherapy	The number of Ranibizumab injections; Mean changes in best-corrected visual acuity

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Study [country]	Study population	Intervention	Comparator	Outcomes
	Evidence that CNV extends under the geometric centre of the foveal avascular zone (n=48 people)			
Larsen M, et al 2012 [12 European countries]	Patients with a diagnosis of AMD related active subfoveal choroidal neovascularisation (n=255 people)	Verteporfin plus ranibizumab	Ranibizumab monotherapy	Mean change in best-corrected visual acuity
Lazic R. et al 2007	Patients with minimally classic or occult choroidal neovascularisation due to AMD in one or both eyes (n=156 people)	Verteporfin therapy and intravitreal bevacizumab combined	Bevacizumab monotherapy	Best-corrected visual acuity; Central foveal thickness
Lim J Y et al 2012. [Korean]	Patients with neovascular AMD or polypoidal choroidal vasculopathy (n=47 people)	Photodynamic therapy combination with intravitreal bevacizumab	Bevacizumab monotherapy	Best corrected visual acuity; Central foveal thickness
Semeraro F, et al 2015	Naïve eyes affected by neovascular AMD (n=75 people)	Photodynamic Therapy combined ranibizumab	Ranibizumab monotherapy	Best corrected visual acuity
Vallance J H et al 2010.	FFA demonstrating choroidal neovascularisation secondary to AMD (n=18 people)	Combination photodynamic treatment and intravitreal ranibizumab	Ranibizumab monotherapy	Best corrected visual acuity
Weingessel 2016 [Austria]	People with new onset CNV due to CNV (n=34 people)	Combination photodynamic treatment and intravitreal ranibizumab	Ranibizumab monotherapy	Best corrected visual acuity
Williams P D et al. 2012	Patients with untreated subfoveal neovascular AMD (n=60 people)	Combined and photodynamic therapy and intravitreal ranibizumab	Ranibizumab monotherapy	Visual acuity
Anti-VEGF combined with steroids				
Ahmadieh H. et al 2011 [Iran]	Patients with subfoveal choroidal neovascularisation (n=120 people)	Combined intravitreal bevacizumab and triamcinolone	Bevacizumab monotherapy	Change in best-corrected visual acuity
Kuppermann Baruch D et al 2015	Patients with choroidal neovascularisation secondary to AMD (n=310 people)	Dexamethasone intravitreal implant as adjunctive therapy to ranibizumab	Ranibizumab monotherapy	The ranibizumab injection free interval; Best-corrected visual acuity
Ranchod T M, et al 2013.	Patients with neovascular AMD (n=40 people)	Ranibizumab plus dexamethasone combination therapy	Ranibizumab monotherapy	Best corrected visual acuity

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Study [country]	Study population	Intervention	Comparator	Outcomes
PDT combined with anti-VEGF and steroids				
Piri Niloofar, et al 2014 [Iran]	Patients with subfoveal choroidal neovascularisation of all types (predominantly classic, minimally classic, occult and retinal angiomatous proliferation) secondary to AMD and no history of treatment (n=84 people)	Photodynamic therapy and intravitreal bevacizumab with triamcinolone	Photodynamic therapy and intravitreal bevacizumab without triamcinolone	Change in best corrected visual acuity

10.3.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. No references were identified as being relevant to this review question. Health economic modelling was not prioritised for this review question.

10.3.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

10.3.3.1 Anti-VEGF + PDT vs anti-VEGF

10.3.3.1.1 Visual acuity

Low-quality evidence could not differentiate best-corrected visual acuity (number of ETDRS letters) between combination therapy and anti-VEGF monotherapy at 3 months' follow-up (MD -7.25 [95%CI: -19.82 to 5.31]; 1 RCT of 106 people).

High-quality evidence showed that best-corrected visual acuity (number of letters) is not different between combination therapy and anti-VEGF monotherapy at 6–12 months' follow-up (MD −0.54 [95%CI: −1.29 to 0.21]; 11 RCTs of 1025 people).

Moderate-quality evidence showed a higher proportion of those given anti-VEGF monotherapy gained 15 or more letters compared with those given combination therapy at 6–12 months' follow-up (RR 0.76 [95%CI: 0.63 to 0.92]; 9 RCTs of 923 people).

10.3.3.1.2 Number of injections

Low-quality evidence showed people given combination therapy received fewer reinjections of anti-VEGF than those given anti-VEGF monotherapy at 6–12 months' follow-up (MD −1.43 [95%CI: −2.42 to −0.45]; 5 RCTs of 488 people).

Low-quality evidence showed people given combination therapy received fewer total anti-VEGF injections than those given anti-VEGF monotherapy at 6–12 months' follow-up (MD −0.94 [95%CI: −1.76 to −0.12]; 6 RCTs of 474 people).

Low-quality evidence could not differentiate proportions of people needing retreatment at 12 months' follow-up between combination therapy and anti-VEGF monotherapy (RR 0.69 [95%CI: 0.42 to 1.13]; 1 RCT of 40 people).

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10.3.3.1.3 Adverse events

High-quality evidence showed that proportions of people having ocular adverse events were not different between combination therapy and anti-VEGF monotherapy (RR 1.03 [95%CI: 0.88 to 1.21]; 5 RCTs of 762 people).

Moderate-quality evidence could not differentiate proportions of people having non-ocular adverse events between combination therapy and anti-VEGF monotherapy (RR 1.03 [95%CI: 0.82 to 1.29]; 1 RCT of 255 people).

10.3.3.2 Anti-VEGF + steroids vs anti-VEGF

10.3.3.2.1 Visual acuity

Moderate-quality evidence showed that best-corrected visual acuity (number of letters) was not different between combination therapy and anti-VEGF monotherapy at 6–12 months' follow-up (MD 0.82 [95%CI: −1.91 to 3.55]; 3 RCTs of 267 people).

Very low-quality evidence could not differentiate proportions of people gaining 15 or more letters between combination therapy and anti-VEGF monotherapy at 6–12 months' follow-up (RR 1.20 [95%CI: 0.53 to 2.70]; from 2 RCTs of 152 people).

10.3.3.2.2 Number of injections

Very low-quality evidence could not differentiate total numbers of anti-VEGF injections received between combination therapy and anti-VEGF monotherapy at 12 months' follow-up (MD −0.50 [95%CI: −1.30 to 0.30]; 1 RCT of 37 people).

Very low-quality evidence could not differentiate proportions of people needing retreatment between combination therapy and anti-VEGF monotherapy at 6 months follow-up (RR 0.65 [95%CI: 0.42 to 1.00]; 1 RCT of 115 people).

10.3.3.2.3 Adverse events

Very low-quality evidence could not differentiate proportions of people having ocular adverse events between combination therapy and anti-VEGF monotherapy (RR 1.20 [95%CI: 0.91 to 1.59]; 2 RCTs of 333 people).

10.3.3.3 Anti-VEGF + PDT vs anti-VEGF steroids + PDT

10.3.3.3.1 Visual acuity

Low-quality evidence could not differentiate best-corrected visual acuity (number of ETDRS letters) outcomes between groups treated with an anti-VEGF, PDT and steroids and those treated with only an anti-VEGF and PDT at 6 months' follow-up (MD 0.5 [95%CI: [-6.04 to 7.04]; 1 RCT of 84 people).

10.3.3.3.2 Number of injections

Low-quality evidence could not differentiate numbers of reinjections between groups treated with an anti-VEGF, PDT and steroids and those treated with only an anti-VEGF and PDT at 6 months' follow-up (MD 0.40 [95%CI: −0.83 to 0.03]; 1 RCT of 84 people).

Low-quality evidence could not demonstrate a meaningful difference in proportions of people needing retreatment between a group treated with an anti-VEGF, PDT and steroids and a group treated with only an anti-VEGF and PDT at 6 months' follow-up (RR 0.84 [95%CI: 0.71 to 0.98]; 1 RCT of 84 people).

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10.3.3.4 Health economic evidence

No cost–utility analyses were identified that were relevant to adjunctive therapies.

10.3.4 Evidence to recommendations

Relative value of different outcomes	The committee agreed that visual acuity is the key outcome to determine the effectiveness of adjunctive therapies for the first-line treatment of late AMD (wet active). It agreed that the included studies capture the extent of visual acuity changes amongst people receiving adjunctive therapies and anti-VEGF monotherapies, and that the evidence showed a consistent effect on visual outcomes, with a slightly better visual improvement in people given monotherapy than those receiving adjunctive therapies. The committee discussed the value of number of injections as an outcome. The committee noted that people receiving adjunctive therapies had about 1 fewer anti-VEGF injection per year than those receiving anti-VEGF monotherapies. However, the committee noted that the adjunctive therapies themselves involve invasive procedures with intravenous or intraocular injections, so the net number of treatments is not importantly different. The committee also discussed the trade-off between visual acuity change and the number of injections. However, the effect sizes in both outcomes were small, and therefore the committee agreed that slightly lower numbers of injections did not outweigh slightly worse visual outcome when using adjunctive therapies for treating late AMD (wet active).
Trade-off between benefits and harms	**PDT** The committee agreed that there are 2 primary risks to using PDT as an adjunct to anti-VEGF for the treatment of late AMD (wet active). Firstly, PDT may cause scarring, potentially leading to visual loss. Secondly, people could experience systemic adverse events including back pain during treatment and photosensitivity and skin rashes following it. Whilst the committee noted that the total number of injections given to people receiving PDT combination therapy was less than the number given to people only having anti-VEGF, it agreed that the absolute difference in the number of injections between the two groups was just 1 injection, and such an effect would be unlikely to lead to substantial benefits (in quality of life) when treating people with late AMD (wet active). The committee agreed the evidence presented justified a ‘do not offer’ recommendation for PDT as a first-line adjunct, but noted there were no studies identified in second-line treatment (see also section 10.4), and therefore agreed a research recommendation and ‘only in research’ clinical recommendation were appropriate in this context. The committee noted that PDT is still commonly used alone or as an adjunct to anti-VEGF when treating polypoidal choroidal vasculopathy (PCV; ‘polyps’). The application of PDT can seal polyps, which should reduce fluid leakage and haemorrhage, and help to reduce anti-VEGF burden. However, only 2 included studies compared adjunctive therapy and anti-VEGF monotherapies for the treatment of PCV, and there was no evidence that acuity outcomes were any better in this group than in trials with broader inclusion criteria. The committee agreed that further research will be helpful to examine the effectiveness of PDT combined therapies for the first-line treatment of PCV. **Intraocular steroids** The committee discussed that there was some anecdotal evidence suggesting that the use of steroids as an adjunct to anti-VEGF could reduce leakage from blood vessels. However, current evidence did not identify any visual acuity benefit among people who received

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	steroid adjunctive therapy, and therefore the committee agreed that steroids should not be used as first-line or second-line treatment. As with the trade-off shown in PDT adjunctive therapy, people receiving adjunctive steroids had fewer anti-VEGF injections than those having anti-VEGF monotherapy, but the absolute difference was less than 1 injection, which the committee did not consider a sufficient benefit to justify the extra cost and inconvenience of additional initial treatment.
Consideration of health benefits and resource use	No health economic evidence was found and this review question was not prioritised for health economic modelling. The committee agreed that it would be inappropriate to incur the additional costs of adjunctive therapies in the absence of robust evidence on their benefits. Although it is theoretically plausible that the use of adjunctive therapies could result in a lower number of anti-VEGF injections – and, therefore, a net decrease in overall costs – the included evidence did not demonstrate a meaningful difference, in this area.
Quality of evidence	The committee agreed that the overall quality of the evidence was sufficient to demonstrate that there were no clinically significant differences in visual acuity, the number of injections and the number of adverse effects between people who had adjunctive therapies and anti-VEGF monotherapies. Therefore, it agreed that current evidence did not support the use of adjunctive therapies as first-line treatment for people with late AMD (wet active). As this review question was to assess the effectiveness of adjunctive therapies as a first-line treatment, the committee noted that 3 included studies had people with some previous treatment history; however, it was noted that a sensitivity analysis excluding these studies (see appendix H) showed no difference from the main analysis. Therefore, this issue was judged to have little impact on the overall quality of evidence presented. The committee noted that none of the included evidence on steroids as an adjunct to anti-VEGFs reported the cataract status of their populations; this was considered to be a potentially important confounder of treatment effect. This is because, in committee member's experience, cataract formation is very common in people receiving intraocular steroids, meaning any benefit the treatment has on the macula may not be apparent due to lens opacification. The committee therefore suggested that the quality of evidence should be downgraded for its failure to take this issue into account. The committee noted that all included studies had short follow-up times (the longest study follow-up was 12 months), and suggested that long-term follow-up could provide more concrete evidence on the effect of the treatment. The committee indicated that, if people with late AMD (wet active) did not respond to initial treatment, it was unlikely that extended treatment follow-up would result in visual improvement. However, longer follow-up could have an impact on the frequency of injections and visual benefits of re-injections; for instance, a reduction in re-injection frequency might persist until the second or third year of follow-up. The committee suggested that future trials of adjunctive interventions should follow participants for at least 2 years, to establish long-term results.
Other considerations	The evidence presented 2 types of visual acuity measurements – logMAR and ETDRS letters – and the committee indicated these 2 measures could be unified using the conversion formula so as to pool relevant visual outcomes together in the meta-analysis.

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10.3.5 Recommendations

31. **Do not offer photodynamic therapy as an adjunct to anti-VEGF as first-line treatment for late AMD (wet active).**

32. **Only offer photodynamic therapy as an adjunct to anti-VEGF as second-line treatment for late AMD (wet active) in the context of a randomised controlled trial.**

33. **Do not offer intravitreal corticosteroids as an adjunct to anti-VEGF for late AMD (wet active).**

10.3.6 Research recommendations

11. **What is the long-term effectiveness and cost effectiveness of PDT as an adjunct to anti-VEGF as first-line treatment for polypoidal choroidal vasculopathy (PCV) (at least 2 years)?**

Why this is important

Photodynamic therapy (PDT) is still commonly used alone or as an adjunct to anti-VEGF when treating polypoidal choroidal vasculopathy (PCV; 'polyps'), a subtype of late AMD (wet active). The application of PDT can seal polyps (which should reduce fluid leakage and haemorrhage, and help to reduce anti-VEGF burden). A limited amount of studies (2) compared PDT adjunctive therapy and anti-VEGF monotherapies for the treatment of PCV but provided no evidence that can conclude the effectiveness of PDT combined therapies for the first-line treatment of PCV. Well conducted randomised controlled trials comparing PDT plus anti-VEFG to anti-VEGF alone would fill an important gap in the evidence base around whether PDT combined interventions is effective when treating people diagnosed with PCV.

12. **What is the effectiveness and cost-effectiveness of PDT as an adjunct to anti-VEGF as second-line treatment for late AMD (wet active)?**

Why this is important

Current evidence showed no any visual acuity benefit among treatment naïve people who received combination therapies adding in photodynamic therapy or steroids along with anti-VEGF drugs, and therefore the committee agreed that adjunctive therapies should not be used as first-line treatment. A number of studies (2) included people with previous treatment but the visual effect of adjunctive therapies was not consistent. Well conducted randomised controlled trials comparing PDT plus anti-VEGF to anti-VEGF alone would fill an important gap in the evidence base around whether combined interventions including PDT are effective when being used as second-line treatment for people with late AMD (wet active).

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10.4 Switching and stopping antiangiogenic treatment for late AMD (wet)

Review questions:

- What are the indicators for treatment failing and switching?
- What factors indicate that treatment for neovascular AMD should be stopped?
- What is the effectiveness of switching therapies for neovascular AMD if the first-line therapy is contraindicated or has failed?

10.4.1 Evidence review

Two separate evidence reviews were conducted for this question, with the aim of answering the 3 questions listed above. The review focused on identifying studies that fulfilled the conditions specified in Table 51. For full details of the review protocol please see Appendix C.

Table 51: PICO characteristics of review questions

	Effectiveness of switching therapies	Factors for treatment switching or stopping
Population	Adults (18 years and older) diagnosed with late wet (neovascular) AMD in whom first-choice (anti-VEGF agent monotherapy only) treatment has failed	Adults (18 years and older) being treated for late wet (neovascular) AMD
Intervention	Comparative trials of: • Aflibercept • Bevacizumab • Pegaptanib Sodium • Ranibizumab • Anti-VEGF drug in combination with photodynamic therapy or intravitreal steroids (dexamethasone, fluocinolone acetonide, triamcinolone acetonide) • Placebo (or sham injections) • No treatment	Indicators for: • Remission and monitoring Different criteria for: • Switching treatment • Stopping treatment or discharge
Comparison	Any of the above	Not stopping or switching treatment in someone with one or more of the above clinical features.
Outcomes	Clinical outcomes: • Visual acuity (LogMAR) • Safety and adverse events • Functional capacity, participation, independence and ability to carry out activities of daily living. • Health related quality of life • Impact on carers • Resource use and costs	Clinical outcomes: • Visual acuity (LogMAR), [for example dichotomous outcomes (such as loss of 15 or more letters) • Safety and adverse events • Functional capacity, participation, independence and ability to carry out activities of daily living • Health related quality of life • Impact on carers • Resource use and costs • List of authors and conflicts of interest

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	Effectiveness of switching therapies	Factors for treatment switching or stopping
Study design	• RCT and systematic review of RCTs If insufficient evidence on RCT studies revert to: • Cohort studies If insufficient evidence on cohort studies revert to: • Before-and-after studies	• RCT • Cohort studies • Reviews and guidance describing stopping rules and switching rules (citation search of these studies) • English only

The aim of the review of the effectiveness of switching therapies is to determine the most effective treatment of late AMD (wet active) for those in whom first-choice therapy has failed. Comparative RCTs of people with late AMD (wet active) were considered, including the following treatments:

- Aflibercept
- Bevacizumab
- Ranibizumab
- Anti-VEGF drug in combination with photodynamic therapy or intravitreal steroids (dexamethasone, fluocinolone acetonide, triamcinolone acetonide).

Studies were also considered if any of treatment above compared with placebo or no treatment. The outcomes of interest included: visual acuity, safety and adverse events, functional capacity, health-related quality of life, and resource use and costs.

RCTs were considered to be the most appropriate study design to derive comparative effectiveness, mean difference, or risk ratio measures, and were therefore considered to be the highest quality within a GRADE framework. When RCT data were not sufficient, cohort study and before–after study evidence could be used. All other study designs were excluded from this review, including case–control studies, and case reports.

The aim of the review of factors that suggest switching or stopping treatment was to identify and describe the clinical features associated with treatment remission and failure. Interventions were considered in this review including: indicators of remission and monitoring, different criteria for switching treatment or stopping treatment.

Reviews and guidance describing switching and stopping rules were considered. Consensus recommendations / guidelines were assessed using the AGREE (appraisal of guideline research and evaluation) II critical appraisal tool, which consists of 6 domains (scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, editorial independence) alongside an overall clinical assessment of the guideline. Each domain consists of a series of items, each scored out of 7, with 1 being strongly disagree and 7 strongly agree. Two assessors independently undertook the quality assessment. The overall score is then calculated based on the maximum and minimum possible scores for each domain. The scaled domain score is then calculated as follows:

$$\frac{\text{Obtained score (total score given by all the assessors)} - \text{Minimum possible score (calculated above)}}{\text{Maximum possible score (calculated above)} - \text{Minimum possible score (calculated above)}}$$

10.4.1.1 Description of included studies

10.4.1.1.1 Summary of included studies in the review of the effectiveness of switching therapies

A total of 6,218 studies was identified in the initial search, and 70 studies appeared potentially relevant based on their titles and abstracts. On perusal of full-text publications, 40 studies were considered relevant to the effectiveness of switching therapies and included in

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the review. Of 40 studies, only 1 was an RCT, comparing switching from ranibizumab to aflibercept to continuing on ranibizumab (Mantel et al. 2016). Two cohort studies were included, both comparing switching from ranibizumab to bevacizumab versus switching from bevacizumab to ranibizumab (Ehlken et al. 2014; Kucukerdonmez et al. 2015). Table 52 gives a summary of the included comparative studies

Thirty-seven before-and-after studies (in 38 papers) that were relevant to the protocol were identified and included. Thirteen studies looked at switching from ranibizumab to aflibercept, 1 study looked at switching from bevacizumab to bevacizumab plus intravitreal steroids (triamcinolone acetonide), 15 studies looked at switching from ranibizumab and/or bevacizumab to aflibercept, 2 studies looked at switching from bevacizumab to aflibercept and there was 1 study for each of the following comparisons: switching from bevacizumab to ranibizumab; switching from ranibizumab to bevacizumab; switching from bevacizumab and/or pegaptanib to ranibizumab; and switching from ranibizumab to pegaptanib. Four of these studies could not be analysed due to incomplete reporting, and 2 studies included 1 arm or outcome that could not be meta-analysed. An update search carried out near the end of guideline development identified further 2 before-and-after studies reported visual outcome amongst people who switched from ranibizumab to aflibercept (Gerding 2015, Sarao 2016).

Table 52: Summary of comparative studies included in the review of the effectiveness of switching therapies

Study	Intervention and comparison	Population	Outcomes	Comments
RCT				
Mantel 2016	Group A – switched from ranibizumab to aflibercept: n = 10 Group R – continued on ranibizumab: n = 11	Neovascular AMD Required monthly retreatment with ranibizumab after 24 months of treatment	Best-corrected visual acuity (logMAR)	
Cohort studies				
Ehlken 2014	Switch from bevacizumab to ranibizumab: n = 114 Switch from ranibizumab to bevacizumab: n = 24	Exudative AMD At least three consecutive monthly injections with bevacizumab or ranibizumab who were unresponsive to treatment	Visual acuity (logMAR)	Retrospective cohort study Only p values are given for the outcome, not actual values (presented graphically) cannot be meta analysed
Kucukerdo-nmez 2015	Switch from bevacizumab to ranibizumab: n = 43 Switch from ranibizumab to bevacizumab: n = 44	Neovascular AMD Minimum of three injections with bevacizumab or ranibizumab with poor treatment effect	Best-corrected visual acuity (logMAR)	Retrospective cohort study

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10.4.1.1.2 Summary of included studies and evidence in the review of factors for treatment switching or stopping

A total of 1,719 references was identified in database search; 19 references were considered potentially relevant to factors for treatment switching or stopping. On perusal of full-text publications, 5 references were included.

Table 53 shows a summary of included studies; full details are provided in evidence tables in Appendix E. Of the included studies, Elshout et al. (2012) looked at a method that could be used to determine whether a treatment should be continued or stopped based on changes in visual acuity from baseline at year 1. The study used data from a randomised controlled trial (Rosenfeld et al., 2006) for its analysis. Four papers (Amoaku et al., 2015; McKibbin et al., 2015; Mitchell et al., 2010; RCOphth 2013) met the inclusion criteria – 2 clinical guidelines and 2 series of recommendations based on discussions. Only 1 study – Mitchell et al. (2010) – carried out a systematic review of the clinical evidence. The other guidelines did not follow a systematic approach and were graded as low-quality. RCOphth 2013 included a patient representative in their development group; the remaining recommendations or guidelines were developed by groups only including retinal specialists as part of the development process.

Table 53: Summary of RCTs data included in the review of factors for treatment switching or stopping

Study	Intervention/ comparison groups	Population	Outcomes	Comments
Elshout 2012 (based on Rosenfeld et al., 2006 RCT data)	Data taken from the MARINA RCT Ranibizumab group (n=238) versus Sham group (n=238)	People with neovascular AMD	Change in visual acuity to inform continuing or stopping treatment Subgroup analysis: • Follow-up time • Effect modifiers (age, initial VA, CNV lesion size, CNV lesion type)	Compares the VA change from baseline up to year 2 in the 2 groups (assuming data are normally distributed), and proposes a rule for estimating what changes are due to the treatment effect.

Table 54 Summary of guidelines included in the review of factors for treatment switching or stopping

Guideline	Development methods	Data sources considered	Guideline development group	Comments
Amoaku 2015	Assumed discussions/ methods were not clearly stated.	Medline search. Terms were not listed. No quality assessment.	16 panellists; retinal specialists from the UK	Main author: consultancy services to Alcon, Allergan, Bayer, Novartis and Thrombogenics. Travel grants from Allergan, Bayer and Novartis. Clinical trial funding from Allergan,

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Guideline	Development methods	Data sources considered	Guideline development group	Comments
				Novartis and Pfizer. Research grants from Allergan and Novartis for non-clinical studies and CentreVue (Italy) for clinical studies. Other authors have no conflicts of interest.
McKibbin 2015	Roundtable discussion. No further information given	Review of the VIEW study results and audit data from the specialist's institutions. No literature review carried out.	11 panellists; retinal specialists from the UK	Sponsored by Bayer HealthCare. Authors have consulting fees, research funding, educational grant and/or lecture fees from ≥1 of the following: Bayer, Novartis, Almera Sciences, Alcon, Allergan, Fight for Sight, Roche, Howard, MDS+Bayer, FFS and NHIR+Bayer.
Mitchell 2010	No information given.	SR of PubMed, the Cochrane Register of Controlled Trials and the Cochrane Database of Systematic Reviews.	Unclear, assume all the authors; 8 authors from their respective Department of Ophthalmology in Australia, France, Italy, Germany, Austria, Japan and Switzerland.	Funding of medical writing (Complete Medical Communications) assistance by Novartis (unconditional). Authors have consulting fee, lecture fees/honoraria, patents +/- royalties from ≥ 1 of the following: Novartis, Pfizer, Solvay, Allergan, Bayer Schering, Alcon, Thea, NeoVista, QLT, Optimedica, Iridex Co., Acucela, Carl Zeiss Meditec, Bausch & Lomb Japan, Santen.
RCOphth 2013	Guideline Development group discussions. No further information given.	PubMed, the Cochrane Library, Current Contents and their own personal collections. No quality assessment.	1 Chair (Amoaku); 8 retinal specialists; 1 college scientific adviser; 2 vison scientists, 1 patient representative	The Chair of the guideline group has received funding from Novartis Pharma, Pfizer, Bausch and Lomb, Bayer and Pfizer, and is a member of the Scientific Advisory Board of The Macular Disease Society. The commercial relationships of other members of the group have been declared in writing to the chair.

10.4.1.1.3 Summary of clinical and guideline evidence by criteria (switching or stopping treatment)

Table 55: Summary of evidence from other guidelines (switching or stopping)

Treatment decision	Amoaku 2015	McKibbin 2015	Mitchell 2010	RCOphth 2013
Agent and time point considered in guideline				

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Treatment decision	Amoaku 2015	McKibbin 2015	Mitchell 2010	RCOphth 2013
Non-specific VEGF	1 month after last initiation dose (month 4)	-	-	After 3 initial doses (12 weeks/3 months)
Aflibercept	-	1 year	-	Monthly dosage (4 weeks) for 1st 3 months, then every 8 weeks
Pegaptanib	-	-	-	Monthly dosage (4 weeks) for 1st 3 months, then every 6 weeks
Ranibizumab	-	-	No specific time point listed	Monthly dosage (4 weekly)
Treatment decision				
Definition of disease status	Responses (good, partial, poor, non) are based on morphological (SD-OCT) and functional (VA) criteria	In the opinion of the treating physician	Assessed through history, VA, slit-lamp fundus examination and OCT (abnormal retinal thickness with evidence of intraretinal or subretinal fluid by OCT, intraretinal or subretinal haemorrhage, enlargement of CNV size on FFA unless solely due to dry, fibrotic staining, new persistent leakage on FFA)	Retinal, subretinal, or sub-RPE fluid or haemorrhage, as determined clinically and/or on OCT, lesion growth on FFA (morphological), and/or deterioration of vision (functional)
Criteria to continue treatment as is	Good response in VA or morphology, partial response in VA and morphology. More imaging/ consider switch if good response in VA but no or poor response in morphology, OR partial response in VA with partial response in morphology. If poor visual potential (poor or no response VA) change therapy even if good response in morphology	Eyes with active disease but stable VA at year 1 (fixed 8 weekly dosing)	-	There is persistent evidence of lesion activity The lesion continues to respond to repeated treatment There are no contra-indications to continuing treatment

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Treatment decision	Amoaku 2015	McKibbin 2015	Mitchell 2010	RCOphth 2013
Continue treatment (change interval between treatments)	Briefly described no definite recommendations given	Eyes with inactive disease and stable VA (extend interval by 2 weeks, max of 12 weeks interval)	-	No recommendations made. Stated that "Further research is required into appropriate duration and optimal regimen in terms of frequency of injections. It still remains to be seen whether less frequent dosing of ranibizumab or aflibercept than that used in the pivotal trials will achieve the same visual benefit."
Criteria to stop treatment and monitor	Not discussed.	Inactive disease and stable VA for ≥ 3 consecutive visits, trial of monitoring without treatment with extended F/U intervals (2 week extension up to max 12 weeks)	If disease is inactive, retreatment can be deferred. Patient review the following month. If the clinical signs remain quiescent for> first 12 months, extending the follow up may then be justified.	Temporarily discontinue treatment if: There is no disease activity* Or One or more adverse events related to drug or injection procedure*
Criteria to switch treatment	Briefly described, no recommendations given	Not described.	Not described.	Not specifically described. Advised to discontinue treatment permanently if: Hypersensitivity reaction Reduction in BCVA (<15 letters (absolute), 2 consecutive visits, due to AMD/no other cause) Reduction in BCVA (30+ letters compared to baseline/best recorded level since baseline) Deterioration of lesion morphology

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Treatment decision	Amoaku 2015	McKibbin 2015	Mitchell 2010	RCOphth 2013
Criteria for discharge	Not discussed.	Those suitable for discharge to be seen by ophthalmologist in person to allow for full informed discussion. Or regular follow up in the community (both eyes)	Not described.	The decision to discontinue a licensed anti-VEGF agent permanently has been made OR There is no evidence of other ocular pathology requiring investigation or treatment OR There is low risk of further worsening or reactivation of nvAMD that could benefit from restarting treatment e.g. very poor central vision and a large, non-progressive, macular scar.
Criteria for re-starting treatment	Not discussed	Any active disease to return to the clinic for treatment	If active disease is present or recurs, additional treatment should be initiated quickly to improve functional outcomes	Only ophthalmologists experienced in the management of patients with AMD should decide on initiating treatment and permanent cessation of treatment

10.4.2 Health economic evidence

A literature search was conducted jointly in all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. No references were identified as being relevant to this review question. Health economic modelling was not prioritised for these review questions.

10.4.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

10.4.3.1 Effectiveness of switching therapies

10.4.3.1.1 Ranibizumab to aflibercept versus continuing on ranibizumab

Low-quality evidence could not demonstrate a meaningful difference in visual acuity between switching from ranibizumab to aflibercept and continuing on ranibizumab at 12 months' follow-up (MD −2.5 ETDRS letters [95%CI −4.87 to −0.13]; 1 RCT of 21 people).

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10.4.3.1.2 Ranibizumab to bevacizumab versus bevacizumab to ranibizumab

Very low-quality evidence could not differentiate visual acuity between switching from ranibizumab to bevacizumab and switching from bevacizumab to ranibizumab at 12 months' follow-up (MD 0.05 logMAR [95%CI −2.84 to 2.94]; 1 cohort study with 87 participants).

10.4.3.1.3 Bevacizumab to ranibizumab

Very low-quality evidence could not differentiate between visual acuity before and 3 months after a switch from bevacizumab to ranibizumab (MD −0.02 logMAR [95%CI −0.11 to 0.07]; 1 before–after study with 110 participants).

10.4.3.1.4 Bevacizumab to aflibercept

Very low-quality evidence could not differentiate visual acuity before and after a switch from bevacizumab to aflibercept:

- after more than 3 but less than 12 months' follow-up (MD 2.8 ETDRS letters [95%CI −2.35 to 7.95]; 1 before–after study with 94 participants)
- at least 12 months' follow-up or more (MD −2.4 ETDRS letters [95%CI −10.15 to 5.35]; 1 before–after study with 39 participants).

10.4.3.1.5 Bevacizumab and/or ranibizumab to aflibercept

Very low-quality evidence comparing visual acuity before and after a switch from ranibizumab to aflibercept showed that

- There was an improvement when measured after more than 3 but less than 12 months' follow-up (MD −0.07 logMAR [95%CI −0.10 to -0.04] in 6 before–after studies with 413 participants; MD 0.44 ETDRS letters [95%CI -2.59 to 3.48] in 2 before–after studies with 104 participants)

At other durations of follow-up, it was not possible to differentiate visual acuity before and after the switch:

- after 1 injection of aflibercept (MD 0.02 logMAR [95%CI −0.06 to 0.09]; 2 before–after studies with 134 participants)
- after 2 injections of aflibercept (MD 0.00 logMAR [95%CI −0.16 to 0.16]; 1 before–after study with 32 participants)
- after 3 injections of aflibercept (MD −0.10 logMAR [95%CI −0.27 to 0.047 in 1 before–after study with 32 participants; MD −0.2 ETDRS letters [95%CI −5.95 to 5.55]; 1 before–after study with 31 participants)
- after 12 months' follow-up or more (MD 0.00 logMAR [95%CI −0.01 to 0.02]; 5 before–after studies with 159 participants)

10.4.3.1.6 Bevacizumab to bevacizumab and triamcinolone acetonide

Very low-quality evidence could not differentiate visual acuity before and 7 months after a switch from bevacizumab to bevacizumab plus triamcinolone acetonide (MD −0.02 logMAR [95%CI −0.21 to 0.17]; 1 before–after study with 31 participants).

10.4.3.1.7 Ranibizumab to aflibercept

Very low-quality evidence comparing visual acuity before and after a switch from ranibizumab to aflibercept showed that

- There was an improvement when measured after 3 injections of aflibercept (MD −0.07 logMAR [95%CI −0.11 to −0.02]; 3 before–after studies with 123 participants).
- At other durations of follow-up, it was not possible to differentiate visual acuity before and after the switch:

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- after 1 injection (MD −0.02 logMAR [95%CI −0.17 to 0.13]; 1 before–after study with 71 participants)
- after 2 injections (MD 0.01 logMAR [95%CI −0.14 to 0.16]; 1 before–after study with 66 participants)
- after 4 injections (MD −0.22 logMAR [95%CI −0.58 to 0.14]; 1 before–after study with 12 participants)
- after more than 3 but less than 12 months' follow-up (MD −0.07 logMAR [95%CI −0.19 to 0.04] in 3 before–after studies with 115 participants; MD 0.57 ETDRS letters [95%CI -0.43 to 1.56] in 4 before–after studies with 1216 participants)
- after 12 months' follow-up or more (MD −0.03 logMAR [95%CI −0.12 to 0.07] in 1 before–after study with 80 participants; MD 3.06 ETDRS letters [95%CI −0.86 to 6.92] in 2 before–after studies with 141 participants)

10.4.3.1.8 Ranibizumab to pegaptanib

Very low-quality evidence could not differentiate visual acuity before and 12 months after a switch from ranibizumab to pegaptanib (MD −0.07 logMAR [95%CI −0.23 to 0.09]; 1 before–after study with 50 participants).

10.4.3.2 Factors for treatment switching or stopping

From the four guidelines identified, three recommended that treatment should be stopped and monitored if the disease was inactive and visual acuity remained stable. Treatment should also be stopped if 1 or more treatment-related adverse events occurred. The guidelines provided no recommendations for criteria that should lead to a change in treatment. The guidelines suggested that treatment should be continued if a person showed a good response in visual acuity or morphology, if visual acuity was stable despite active disease or there was persistent evidence of lesion activity and the lesion responded to repeated treatment.

10.4.3.3 Health economic evidence

No cost–utility analyses were identified that were relevant to switching and stopping antiangiogenic treatment.

10.4.4 Evidence to recommendations

Relative values of different outcomes	**Effectiveness of switching therapies** Evidence was identified for the outcome of visual acuity, measured by logMAR or ETDRS letters, but the review did not find evidence on other outcomes the committee had identified as relevant to the decision to switch therapies. The committee agreed that visual acuity was an important outcome to guide treatment decisions in clinical practice. The committee discussed other indications when considering switching therapies – for instance, structural damage including presence of fluid, retinal thinning, and fibrosis could also be an indication of treatment effectiveness. In some cases, people's vision might not be affected despite structural damage (i.e. scarring in retina). However, there are no widely accepted or adopted criteria for switching or stopping therapies based on structural findings; it is visual acuity which typically defines such decisions in practice. The committee also indicated potential associations between visual acuity and outcomes such as quality of life. There is no direct evidence on how treatment switching affects patients' quality of life, and uncertainty remains about the precise relationship between changes in visual acuity and individuals' quality of life.

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	In addition, people are commonly affected by AMD in both eyes, and quality of life gains will depend on visual acuity in not only the treated eye but the fellow eye as well. If a person has good vision in their fellow eye, they may gain relatively little overall functional benefit, even if vision in the treated eye improves to a substantial degree. The committee suggested that both eyes' visual acuity had to be taken into account when assessing the effectiveness of switching therapies. Therefore, a combination of indicators, including visual acuity, structural damages, quality of life and functional vision, as well as the state of the both eyes of people with AMD need to be considered when deciding on whether treatment has failed and/or switching is indicated. The committee suggested that the 5-letter visual gain might not be sufficient to indicate a clinically meaningful improvement as the measurement error for repeated observations on the same day might be as much as 5 letters. Nonetheless, such a marginal gain might be important for the mental wellbeing of people with AMD who are faced with a degenerative condition with a prognosis of worsening eyesight. **Factors for switching therapies, treatment failure or stopping treatment** The outcomes considered for this review were visual acuity, safety and adverse events, health-related quality of life, impact on carers, resource use and costs, and functional capacity, participation, independence and ability to carry out activities of daily living. This review did not identify any of these outcomes, and the committee noted that there was a lack of existing evidence-based criteria to indicate treatment stoppage. Following early discussion, the committee suggested that structural changes could be an important factor when considering treatment switching or stoppage, as the clinician had to consider the justification and potential benefit of continuing treatment if an individual had permanent structural damage. Moreover, the committee noted that it is also important to think about what follow-up support and care (low-vision services, for example) would be available for people with AMD after stopping treatment.
Quality of the evidence	**Effectiveness of switching therapies** A total of 40 studies was included in this review. The evidence was generally of very low quality, which was mainly due to very serious risk of bias (particularly as regards the shortcomings of the before-and-after study design) and imprecision. The committee noted that it was difficult to use the Mantel et al. (2016) study to inform decisions on whether treatments should be switched or stopped, as the criteria for switching were not reported. Participants in the study were recruited from the 'Observe and Plan' case series, which included patients with treatment-naive late AMD (wet active). The committee noted that OCT was used to monitor disease progression in this study and that, in clinical practice, OCT and, when needed, FFA are used to assess the need to retreat patients based on the findings of those imaging techniques. The committee noted the importance of establishing individuals' baseline visual acuity, and suggested the measurement of visual acuity at each treatment visit but noted that a monthly assessment would not necessarily give a better indication of treatment response. The committee discussed the extent of observational evidence on the effectiveness of treatment switching, noting that the studies provide limited applicability for decision-making as they do not provide evidence of the counterfactual (what would have happened had switching not occurred). The committee also cited evidence showing that acuity tends to improve somewhat in eyes meeting plausible criteria for switching anti-VEGF agent even when they continue on the same treatment (Ferris et al.

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	JAMA Ophthalmol. 2017;135(2):145–49). This suggests that any benefits observed in the included before-and-after studies are very likely to represent regression to the mean. **Factors for switching therapies, treatment failure or stopping treatment** The review of factors for switching therapies, treatment failure or stoppage identified 2 clinical guidelines and 2 consensus-based sets of recommendations that, while not presented as evidence-based guidelines, were amenable to appraisal using criteria for guidelines. Quality of evidence in the included guidelines and series of recommendations was assessed using the AGREE II critical appraisal tool. One guideline (RCOphth 2010) and 1 series of recommendations (Mitchell et al., 2010) received overall scores of 58.3% and 50.0%, respectively, and the reviewers appraised them as potentially fit for use with modifications. The other guideline (Amoaku et al., 2015) and series of recommendations (McKibbin et al., 2015) received low overall scores of 33.3% and 41.7%, respectively. Based on the reviewers' methodological assessment using AGREE II criteria, they would not be recommended for use. In addition, 1 publication was identified that proposed a method for estimating a BCVA threshold that could be used to define whether people are gaining benefit from antiangiogenic therapy (Elshout et al. 2012). The committee considered this approach, but ultimately dismissed it, as it relies on strong assumptions: • that change in BCVA follows a normal distribution – this assumption has been made by other authors (including in this guideline) and is likely to be reasonable; however, Elshout et al. had access to patient-level data that would have enabled them to test the assumption in the context of the data they were analysing, and they apparently made no attempt to do so; and • that there is no correlation between the expected outcomes for any individual with and without treatment. The committee believed that this latter assumption was particularly difficult to support: in its view, the people who experience substantial loss of vision despite therapy are highly likely to have lost even more vision if they had not been treated, and the approach proposed by Elshout et al. effectively assumes that the reality of an individual's treated outcome and the counterfactual of how people tend to do without treatment are completely independent. Adopting a stopping rule based on this assumption would result in therapy being discontinued for people who are very likely to be gaining substantial benefit from it, relative to how they would fare without treatment. Therefore, the committee concluded that it would be a dangerous approach to recommend.
Trade-off between clinical benefits and harms	**Effectiveness of switching therapies** Two sources of evidence showed a potential difference when switching treatment. Evidence from an RCT found that switching from ranibizumab to aflibercept versus continuing on ranibizumab resulted in a statistically significant reduction in visual acuity; however, the difference was too small to meet the committee's predefined definition of minimal importance (MD -2.5 ETDRS letters, 95%CI -4.87 to -0.13). In contrast, evidence from 3 before-and-after studies found a pooled benefit after 3 injections when switching from ranibizumab to aflibercept (logMAR scale, MD -0.07, 95%CI -0.11 to -0.02). Again, this difference is not large enough to meet the minimally important difference. Moreover, no such effect was found at any other follow-up point in the same evidence-base. Overall, the limited evidence suggested no observable clinical benefit from switching treatment. The committee felt that this was consistent with their expectations, explaining that there is no biomedical rationale

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for which one antiangiogenic therapy would have a positive effect where another had not, other than a minor one via a possible effect on adherence to injection appointments.

The committee emphasised that the trade-off in relative benefits and harms in individual cases had to be examined with reference to the visual acuity and disease status of the fellow eye. In people with poor vision in the fellow eye, switching therapies in order to effect even a very small gain (or prevent a small loss) of vision could have disproportionate benefits compared with a situation in which the fellow eye has good visual function.

The committee also discussed that, in practice, there was a tendency of either over-treating or under-treating people with AMD, because of a lack of evidence on what clinical features define treatment benefits in switched cohorts, and because of studies that have emerged suggesting that patients had been undertreated. The committee noted that the treatment history of patients in the evidence presented was poorly captured, and that people who had been refractory to therapy in the past then enrolled in a study in which they are told they are getting a new drug might, because of an understandable desire for the 'new' treatment to work, put greater effort into trying to see the ETDRS letters and thus be more likely to see a small benefit like 5 letters. However, the committee also agreed that, because of the designs of the studies presented, it was not possible to quantify the margin of visual acuity that would have been lost in the event of not switching. This would be a significant uncaptured benefit for patients who could conceivably have lost 15 letters, for example.

Therefore, research is needed to address this question so as to establish the effectiveness of switching or stopping treatment. The committee discussed on-going trials including EMERGE and PrONTO, preliminarily indicating some potential benefits from switching treatments. However, the committee stressed that caution should be taken when interpreting trial results since study populations were different in these trials. In addition, in those trials, participants were often allocated to tightly controlled treatment regimens, and any benefit observed might be ascribable to the frequency of treatment rather than the individual agents provided.

In addition, the committee suggested patient choice or preference also should be valued and considered when switching therapies, and clinicians needed to be mindful why individuals want to switch or stop treatment. Adverse effects of therapies might be a reason to pause treatment or switch agent, and patients may prefer to have a treatment regimen that has fewer injections (for example, aflibercept is normally provided on a bi-monthly schedule) or be better able to adhere to treatments with less frequent visits. The committee noted that the quality of life implications of switching therapies did not capture these preferences, and that focusing on visual acuity alone was somewhat limited in that regard. Therefore, the committee emphasised that patients needed to be involved in treatment decision-making, and switching therapies should be an option available to patients, but the change of treatments should not be built upon individuals' expectation in therapeutic benefits.

Factors for treatment failure

This review did not identify any criteria that indicate that treatment had failed. However, the committee agreed that if an eye experiences severe, progressive visual loss whilst being treated, this would be an indication of treatment failure and lead to the treatment being appropriately stopped.

Factors for a stopping treatment

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	The RCOphth guideline (2013) and recommendations (Mitchell et al., 2010) suggested that treatment should be stopped and the disease monitored if the condition was inactive or 1 or more treatment-related adverse events had occurred. The committee discussed that, in practice, treatment might be stopped or paused due to adverse events including allergic reaction, stroke or vascular events, but there was no formal guidance on when anti-VEGF treatments should be stopped. The committee suggested that the AMD classification it had developed (see section 5) could be used as a proxy for treatment stoppage, since the classification specified a range of pathological changes associated with disease progression indicating response to antiangiogenic therapy would not be expected. Therefore, the committee agreed it was appropriate to stop anti-VEGF treatment if an eye met the defined criteria of late AMD (wet inactive), and/or if it was determined that there was no prospect of visual improvement as a result of continued treatment Another consideration was that the technology appraisal guidance incorporated in this guideline (TA155 and TA294) restrict starting ranibizumab and aflibercept to eyes with BCVA between 6/12 and 6/96. The appropriateness of these starting rules is explored in section 10.2; however, it is also important to consider whether treatment should be discontinued in eyes that, having started treatment within this range, no longer meet the criteria. In particular, the committee discussed whether anti-VEGF should be stopped if people's visual acuity becomes worse than 6/96, and agreed that, in practice, few people would continue to receive antiangiogenic therapy in an eye that has reached that degree of impairment despite optimal treatment, and it was likely that the deterioration in acuity would be accompanied by the kinds of structural changes that correspond to late AMD (wet inactive). The committee was concerned that inefficient treatment may inadvertently lead to treatment discontinuation, where ongoing, efficient treatment might actually be effective. Inefficient treatment, for example provided too infrequently, might cause a loss in visual acuity that leads to treatment discontinuation. To avoid this, the committee felt it was appropriate to explicitly state that treatment should be given as recommended in the guideline prior to determining whether it should be discontinued. The committee also agreed it may be appropriate to consider pausing treatment in people with stable disease. However, these people should be both monitored and continue to self-monitor, so that treatment can be quickly re-initiated if their vision starts to deteriorate.
Trade-off between net clinical effects and costs	No cost-effectiveness evidence was identified for this review question. The committee discussed in broad terms the need to consider the opportunity cost of continuing therapy by switching to another agent where there is little evidence of continuing benefit. The committee agreed that, on its view of currently available evidence, treatment switches are seldom associated with obvious therapeutic benefit. Therefore, if a clinician has reached the conclusion that the originally prescribed anti-VEGF agent is no longer achieving a meaningful effect, there is little prospect that an alternative agent will provide better results, though it will obviously be associated with additional costs. For this reason, the committee agreed that, while there may be good practical reasons to switch from one anti-VEGF agent to another while therapeutic effect is still being experienced, it would not usually be a reasonable use of resources to try a second agent in the hope that it will succeed where the first choice has failed. The committee also discussed potential cost-savings of pausing therapy when patients have late AMD (wet inactive).

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Other considerations	**Effectiveness of switching therapies** The committee noted that, although there was no observable benefit in switching treatment, in the context of before-and-after studies, vision may have been preserved or a decline in vision may have been prevented. The committee was concerned that, historically, AMD may have been undertreated in comparison to the treatment regimens adopted in trials. Aggressive treatment schedules such as those in the included studies might have been responsible for the effect observed. Such regimens tend not to be reproduced in clinical practice due to limitations in resources, appointment time and staffing. Using its experience, the committee agreed that the 'as required' regimen was beneficial as it allowed for an assessment of the need to continue treatment in patients with stable and non-responsive AMD. It was noted that the potential to respond to treatment should always be considered. The committee agreed that any future research should give consideration to the number of visits, injections and measurement of visual acuity when assessing the effectiveness of a treatment. The committee formulated a research recommendation on the impact of patient preference on switching treatments and the implications for quality of life. A trial could be conducted that randomised patients who might need to have a switch or their treatment stopped. The impact a switch or stopping treatment would have on both eyes and overall visual function would be outcomes of interest. In the light of the evidence presented, the committee noted that a trial on a broader population could potentially see a more generalisable benefit or harm of switching treatment after 6 months. The committee discussed another potential trial design which could precede the design above, including treatment-naive patients whose treatment should be stopped once certain predefined criteria are met. This allows for conclusions on the effectiveness of current practice and for the identification of an objective switching rule, to subsequently be tested in a randomised trial. The committee felt that stopping treatment was high priority area for future research, including both the identification of a rule and the effectiveness of applying that rule. **Factors for treatment failure** The committee agreed that a reduction of vision was an indicator for failure of treatment, but also acknowledged that there was not enough evidence to quantify loss of vision in this context. As with switching therapy, the committee emphasised the important context of the fellow-eye's visual acuity. In people with poor binocular vision the committee discussed the increased likelihood that the treating physician would be reluctant to conclude that treatment had failed, even if visual acuity continued to decline. This is an appropriate attitude, because, in such people, there could well be substantial quality of life benefit from an improvement (or a reduced decline) in acuity that would be of negligible value in a person with good fellow-eye vision. The committee also discussed the importance of irreversible structural damage, such as scarring, when deciding on whether treatment should be continued. The committee agreed that, for patients with fibrotic scarring and retinal thinning, the presence or absence of fluid is largely irrelevant and should not guide treatment. **Factors for stopping treatment** The committee discussed the justification for continuing treatment and the potential benefits of continuing treatment and preserving vision in the good eye in people with permanent structural damage. When considering stopping treatment, the committee agreed that it is important to think about continued follow-up and monitoring of the disease.

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The committee agreed that it is usually appropriate for a visual acuity of less than 6/96 to trigger stopping treatment. It was also noted that good clinical practice necessitates that any severe allergic reactions to a drug should also lead to immediate stopping of the treatment. Under this circumstance, consideration could be given to switching agents.

The committee agreed that it is important that clinicians ensure that there has been a prior conversations with any patients regarding the proposed treatment plan and the possible prognosis. Stopping treatment can cause exceptional distress for patients who are not prepared for all eventualities.

General considerations

The committee discussed the classification of AMD (see section 5). It was agreed to be important that the definition of late AMD (wet inactive) should include structural damage of the fovea, cystic degeneration (fluid that does not decrease with antibiotic treatment) and the degree of useful vision left.

10.4.5 Recommendations

34. **Consider switching anti-VEGF treatment for people with late AMD (wet active) if there are practical reasons for doing so (for example, if a different medicine can be given in a regimen the person prefers), but be aware that clinical benefits are likely to be limited.**

35. **Consider observation without giving anti-VEGF treatment if the disease appears stable (in this event, see section 11 for recommendations on monitoring and self-monitoring).**

36. **Consider stopping anti-VEGF treatment if the eye develops severe, progressive loss of visual acuity despite treatment as recommended in 13 and 21 to 30.**

37. **Stop anti-VEGF treatment if the eye develops late AMD (wet inactive) with no prospect of functional improvement.**

38. **Ensure that patients are actively involved in all decisions about the stopping or switching of treatment (see section 12 on patient information).**

10.4.6 Research recommendations

13. **How does patient preference impact on switching treatments, and how does switching affect quality of life?**

Why this is important

Switching therapies are considered to be associated with a number of factors such as changes in visual acuity, structural damage in eyes, adverse events and people's quality of care. Additionally, patient's preference should be considered and valued when switching therapies, and clinicians needed to be mindful why individuals want to switch or stop treatment. Currently no available data on how patient's preference affect switching therapies, and subsequent influence on their quality of life. Research that evaluates patients' preference in their treatment decision-making would therefore be of value. This research should also evaluate how individual's preference subsequently influence their quality of life after switching therapies.

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14. When should anti-VEGF treatment be suspended or stopped in people with late AMD (wet)?

Why this is important

Anti-VEGF therapy is associated with inconvenience, risk of adverse event and – especially when aflibercept or ranibizumab is used – substantial costs. People typically receive anti-VEGF for extended periods, and it is unclear whether it is always beneficial. After successful treatment the disease can become sufficiently dormant that treatment could be safely suspended. After ineffective treatment, there may be no benefit in continuing to treat eyes with advanced damage. The committee agreed that this gap in evidence could be addressed by a 2-stage research strategy. Observational research (for example, using registries recording administration of anti-VEGF and relevant outcomes) should be undertaken to establish the point at which the benefits of continuing treatment are unclear. This would involve eyes in which disease has responded well to treatment, and eyes in which pathological appearances or visual acuity suggest that disease is not responding to antiangiogenic treatment. This research should then be used to establish a protocol for suspending or stopping treatment. The protocol would be assessed in a non-inferiority randomised controlled trial (RCT) in which participants would be randomised to protocol-dependent stopping rules or usual care (continued treatment at clinician discretion). The committee agreed that the first step would be necessary to fulfil the ethical requirements of an RCT, as no consensus currently exists about the point(s) at which it may be safe to stop treatment.

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11 Monitoring

AMD is a common cause of severe and irreversible visual loss amongst older adults, affecting their quality of life and independence. In 2008, AMD accounted for over half of all blind and partial sight certifications in the UK (Bunce 2008). AMD is a progressive disease and people can receive a diagnosis at different stages of the disease which subsequently impacts on treatment decisions. Additionally people with AMD may progress differently through the different stages of the disease so it is important to ensure they are monitored and managed in the right part of the care pathway.

There is currently no treatment available for late AMD (dry), whilst late AMD (wet) is treatable if diagnosed early and monitored effectively. When treating late AMD (wet active), anti VEGF therapy is commonly used as a first line treatment; however, the therapeutic benefit of any single injection can be short-lived and patients require frequent monitoring and regular injections to stabilise vision.

Clinical monitoring often involves the assessment of visual functional and any structural changes to the macula. Different types of clinical monitoring tools such as ophthalmoscopy and fundus fluorescein angiography (FFA) are available to help clinicians guide treatment decisions. Whilst recent developments in imaging technology have led to the widespread use of spectral-domain optical coherence tomography (SD-OCT) in practice.

Between 10–15% of people with early AMD can progress to develop late AMD (wet) (Hageman et al., 2009), and 8–12% of people with late AMD (wet active) in one eye develop the same condition in the second eye every year (Maguire 1997). Self—monitoring can play an important role in detecting the onset of new symptoms or visual changes amongst people with non-neovascular AMD. Self-monitoring requires an awareness of the symptoms of AMD and an understanding of the need to access services promptly when deterioration in vision or distortion is detected. A range of self-monitoring tools are available but many people with AMD are not confident monitoring their own vision and have limited awareness of what tools are available. This review will evaluate self-monitoring interventions and the evidence for monitoring frequency for people at different stages of AMD.

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11.1 Frequency of monitoring

Review questions:

- How often should people with early AMD, indeterminate AMD, or advanced geographic atrophy be reviewed?
- How often should people with early AMD, indeterminate AMD, or advanced geographic atrophy have their non-affected eye reviewed?
- In people with neovascular AMD who are not being actively treated, how often should they be reviewed?
- How often should people with neovascular AMD have their non-affected eye reviewed?

11.1.1 Evidence review

The aim of these reviews was to establish the risks and benefits of different frequencies of monitoring for people with AMD. Separate review questions sought to identify evidence for different frequencies of monitoring by

- AMD classification (early AMD, indeterminate AMD, late AMD (dry AMD) and late AMD (wet active)
- Eyes affected and unaffected by AMD

The main outcomes for this review were visual acuity, functional capacity, participation, independence and ability to carry out activities of daily living, health-related quality of life, impact on carers, resource use and costs, plus time from symptoms to diagnosis to treatment. The review identified studies that fulfilled the conditions specified in Table 56. For full details of the review protocol please see Appendix C.

Table 56 PICO table – frequencies of monitoring for people with AMD

Population	• Adult (18 years and older) with non-neovascular AMD [early AMD, indeterminate AMD and late–dry AMD]: ○ affected eyes ○ unaffected eyes • Adult (18 years and older) with neovascular AMD [late–wet AMD]: ○ affected eyes but not in treatment (either being deferred or being discharged due to quiescent condition) ○ unaffected eyes
Interventions	Review schedules of varying frequency
Comparator	Standard care (can include self-presenting) or different frequencies of monitoring
Outcomes	• Visual acuity (LogMAR) • Functional capacity, participation, independence and ability to carry out activities of daily living. • Health related quality of life • Impact on carers • Resource use and costs • Time from emergence of symptoms of disease progression to identification and treatment

Randomised controlled trials (RCTs), comparative cohort studies and systematic reviews of RCTs and comparative cohort studies were included if they compared different frequencies of reviews or schedules of varying frequency of reviewing. Papers were excluded if they:

- were not published in the English language.

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- were abstracts, conference proceedings, guideline/health technology assessment report, narrative reviews, case-studies, diagnostic studies or non-comparative studies.

11.1.1.1 Description of included studies

A systematic search identified 2,479 references. The references were screened on their titles and abstracts and 21 references were ordered for full text. No studies reported data on the link between different frequencies of monitoring and outcomes for people with AMD. Four studies identified were applicable to review question 23 on monitoring strategies and were included as part of that review. One study was applicable to review question 17 on barriers and facilitators to appointment attendance and uptake of treatment for people with AMD and was included in that review.

For the full list of excluded studies, with reasons, see Appendix F.

11.1.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. No references were identified as being relevant to this review question. Health economic modelling was not prioritised for this review question.

11.1.3 Evidence statements

No evidence was identified for these review questions.

11.1.4 Evidence to recommendations

Relative value of different outcomes	The review found no relevant evidence on the association between frequency of review and outcomes for people with AMD. The guideline committee agreed that the key outcomes to address this question would be long-term measures of visual acuity and subsequent changes in function and quality of life. If these were not available, a useful proxy measure would be the delay from onset of symptoms to either diagnosis or treatment, as this could then potentially be linked to data on the relationship between time-to-diagnosis and outcomes. The committee considered how frequency of review likely affected early identification of symptom changes and condition progression amongst people with AMD, which subsequently could have an impact on management strategies.
Trade-off between benefits and harms	The committee agreed that, in the absence of any evidence showing benefits of routine monitoring versus less frequent monitoring or patient self-referral, it would be inappropriate to recommend routine monitoring for people not at a high risk of progression. Further, the committee agreed that it was important that people who did notice deterioration of their vision were able to gain timely access to eye services for testing, and this might be made more difficult if a large proportion of the capacity of these services was used to support routine monitoring. By consensus, the committee agreed that a more appropriate strategy, at a population level, was to promote people with early AMD or late AMD (dry) to self-monitor, and to be promptly seen by an appropriate healthcare professional if their vision started to deteriorate. However, it was also acknowledged that individual clinicians may wish to routinely monitor patients who are either unable to appropriately self-monitor or who are deemed to be at a high risk of progression. The committee indicated that, in current clinical practice, people with late AMD (wet active) are already routinely monitored throughout their treatment period, and for a period of time following disease

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	inactivation. It was agreed to be standard practice that both eyes would be tested at all such follow-up points, and therefore any changes in vision were likely to be identified in scheduled appointments and no additional monitoring appointments were required.
Trade-off between net health benefits and resource use	No health economic evidence was found and this review question was not prioritised for health economic modelling. However, the committee noted that the key uncertainty in this question was around the cost effectiveness of frequent, scheduled review appointments, as this would be likely to involve a substantial increase in the burden on eye services. Further, the committee also agreed that there was a low probability of robust RCTs being conducted to specifically address the question of the optimal monitoring strategy for people not currently being treated, as randomising people to different frequencies of routine monitoring is unlikely to be a practical study design. Therefore, it was agreed the most appropriate research to address this question would be a health economic decision-model, which could synthesise data on the link between treatment delay and outcomes to estimate the cost-effectiveness of different monitoring strategies.
Quality of evidence	No evidence was identified for these review questions.
Other considerations	The committee agreed that, given the priority currently placed on self-monitoring, specific consideration should be given to those groups of people who are unable to monitor their own vision (for example, people with comorbidities such as impaired cognitive function). The committee agreed that the role of family members and carers had to be specifically acknowledged for this group of people, and it was important to provide support and advice for carers/family members on appropriate monitoring techniques to monitor vision changes in people who are unable to self-monitor. The committee agreed the appropriate way to do this was via a cross-reference to the recommendation made in section 11.2 about advising carers and family members of people unable to self-monitor.

11.1.5 Recommendations

39. Do not routinely monitor people with early AMD or late AMD (dry) through hospital eye services

40. Advise people with late AMD (dry), or people with AMD who have been discharged from hospital services to:

- self-monitor their AMD
- consult their eye-care professional as soon as possible if their vision changes (see section 11.2)
- continue to attend routine sight-tests with their community optometrist.

41. For people being monitored for late AMD (wet inactive), review both eyes at their monitoring appointments.

11.1.6 Research recommendations

15. What is the long-term effectiveness, in terms of patient-relevant outcomes including best-corrected visual acuity and quality of life, of different review frequencies/strategies for people at risk of progression to late AMD (wet active)?

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Why this is important

There is currently no evidence on the different frequencies for monitoring people with AMD. This means that it is not possible to identify an optimum monitoring strategy for people at different stages of AMD, leading to uncertainty in how to correctly manage treatment for individuals or how to configure eye care services to support patients. . A study of the needs of people at risk of progression to late AMD (wet active) to identify the optimum review arrangements would remove this uncertainty. Trials would need to measure visual outcomes and health service resource use to measure the trade-offs between the optimal management of people at risk of disease progression in relation to the use of resource.

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11.2 Self-monitoring strategies

Review question:

- What strategies and tools are useful for self-monitoring for people with AMD?

11.2.1 Evidence review

The aim of this review was to establish the risks and benefits of interventions to promote self-monitoring for people with AMD. The main outcomes for this review were visual acuity, safety and adverse events, functional capacity, participation, independence and ability to carry out activities of daily living, health related quality of life, impact on carers, resource use and costs. The review identified studies that fulfilled the conditions specified in Table 57. For full details of the review protocol see Appendix C.

Table 57: PICO table – frequencies of monitoring for people with AMD

Population	Adult (18 years and older) with non-neovascular AMD (early AMD, intermediate AMD and late dry AMD)
Interventions	• Amsler Grid or computerised Amsler • M-Charts • Visual acuity test (e.g. Snellen or LogMAR excluding low light/mesopic) • MCPT-Macular Computerised Psychophysical Test • Preferential hyperacuity perimetry (PHP) (e.g. ForSeeHome Device) • Macular mapping test • Multibit test (MBT) • Entopic perimetry (e.g. My Vision Test) • Noise-field campimetry • Journals (e.g. keep sight journal)
Comparator	No self-monitoring
Outcomes	Clinical outcomes: • Visual acuity • Safety and adverse events • Functional capacity, participation, independence and ability to carry out activities of daily living. • Health related quality of life • Impact on carers • Resource use and costs

Randomised controlled trials (RCTs) and systematic review of RCTs were included if they compared self-monitoring with standard (usual) care provided by healthcare professionals. Papers were excluded if they:

- were not published in the English language
- reported monitoring tests performed by healthcare professionals
- were abstracts, conference proceedings, guideline/health technology assessment report, narrative reviews, case-studies, diagnostic studies, non-comparative studies and observational studies

11.2.1.1 Description of included studies

A total of 1,751 references were identified through the search. These references were screened on their titles and abstracts and the full texts of 22 references that were potentially relevant to the review question were requested.

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Two RCTs were included (Chew et al., 2014; Brittner et al., 2014), both comparing self-monitoring tools (the ForeseeHome device, the Vision and memory stimulation journal) with standard/usual care to examine whether self-monitoring tools resulted in:

- better visual acuity at the time neovascular AMD is identified
- more frequent vision self-monitoring and greater confidence in self-monitoring of their vision

A brief summary of included studies was provided in Table 58. References of included studies are listed in Appendix I. For the list of excluded studies with reasons, see Appendix F.

Table 58 Summary of included studies

Study details	Study population	Intervention	Comparator	Outcome
Chew et al 2014 [USA]	Patients at risk for developing choroidal neovascularisation age related macular degeneration (n=1,520 people)	Home monitoring of the eye (the ForeseeHome device)	Standard care	Visual acuity
Brittner et al 2014 [USA]	Patients with non-neovascular AMD (n=198 people)	The Vision and Memory Stimulating journal	Usual care	Frequency of vision monitoring Confidence in vision monitoring

11.2.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. No references were identified as being relevant to this review question. Health economic modelling was not prioritised for this review question.

11.2.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

11.2.3.1 Visual acuity

Low-quality evidence on the visual acuity of participants who developed late AMD (wet active) could not differentiate between people who had received a self-monitoring intervention and those who had received standard care (MD 5.2 ETDRS letters [95%CI −1.48 to 11.88]; 1 RCT with 1,520 participants).

Low-quality evidence on the proportion of participants with 6/12 or better visual acuity at diagnosis of choroidal neovascularisation could not differentiate between people who had received a self-monitoring intervention and those who had received standard care (RR 1.31 [95%CI 0.94 to 1.81]; 1 RCT with 1,520 participants).

11.2.3.2 Number of choroidal neovascularisation events detected

Low-quality evidence found higher rates of choroidal neovascularisation detection in participants given a self-monitoring intervention compared with those receiving standard care (RR 1.63 [95%CI 1.06 to 2.52]; 1 RCT of 1,520 people).

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11.2.3.3 Frequency of self-monitoring

Very low-quality evidence found people receiving a self-monitoring intervention were more likely to report that they self-monitored their vision weekly compared with those in the control group at 12 months' follow-up (RR 1.61 [95%CI 1.25 to 1.82]; 1 RCT of 198 people).

11.2.3.4 Confidence in self-monitoring

Low-quality evidence from found people using the Vision and Memory Stimulating journal were less likely to report no confidence in self-monitoring compared with those in the control group at 12 months' follow-up (RR 0.31 [95%CI 0.12 to 0.69]; 1 RCT of 198 people).

11.2.3.5 Health economic evidence

No cost–utility analyses were identified that were relevant to self-monitoring strategies.

11.2.4 Evidence to recommendations

Relative value of different outcomes	The guideline committee agreed that the key outcomes to address this question would be long-term measures of visual acuity and subsequent changes in function and quality of life. It agreed that it was important that studies not just demonstrate that self-monitoring strategies led to people having better visual acuity at the time of diagnosis, but also that this led to future changes in management and outcomes. However, the committee agreed that the included studies failed to establish a link between early detection and better long-term visual acuity, with the only included RCT which measures visual acuity only measuring this at the time of diagnosis, with no longer-term follow up. The committee agreed that, in future trials of self-monitoring interventions, the follow-up of participants should be sufficiently long as to establish any differences in management and long-term visual/functional outcomes that may result from earlier diagnosis and made a research recommendation to support this. The committee noted that the success of any self-monitoring strategy depends on people both being able to self-monitor and feeling confident in self-monitoring. It recognised that some people with AMD were not confident monitoring their own vision, and that their confidence level could be affected by many factors (for example, awareness of what changes in symptoms would mean it was necessary to see a healthcare professional). Therefore, the committee recognised that appropriate support is needed to promote self-monitoring amongst people with AMD.
Trade-off between benefits and harms	The committee indicated, based on their experience, that traditional self-monitoring tools such as the Amsler grid tended to have high false-positive rates (meaning they were likely to over-report changes in visual symptoms). This can have the effect on both patients (causing unnecessary worry) and the service (with an unnecessarily high workload for clinicians). The committee agreed that it did not have sufficiently robust evidence on the availability, benefits or the costs of the 2 specific interventions (ForseeHome Device; Vision and Memory Stimulating Journal) identified to be able to recommend their use in the UK. Moreover, it agreed that a range of free or cheaper self-monitoring techniques are available which people can make use of. However 2 key barriers to uptake of these techniques were discussed and agreed to be patient knowledge of their availability, and patient confidence in their ability to self-monitor. The committee agreed that it was important that people should be made aware of the range of self-monitoring tools available, enabling

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	them to choose the one they feel most comfortable with and which is most suited to their needs (for example, language independence, tools that do not require the use of a computer, etc.) Appropriate support and encouragement should be provided to people who wish to self-monitor but are either unable or do not feel confident in their ability to do so. In particular, the committee agreed that people should be made aware of the 'environmental Amsler' technique, where people look for distortions or changes in the look of objects they are familiar with. This has the benefit of allowing people with AMD to detect changes in their vision without the need to use specifically designed monitoring tools. It was agreed that people with AMD should be encouraged to use their preferred self-monitoring technique, and to report any deterioration in their vision (including blurred or grey patches in their vision, straight lines appearing distorted or objects appearing smaller than normal) to a healthcare professional as soon as possible. The specific features listed came from the clinical experience of members of the committee.
Trade-off between net health benefits and resource use	No health economic evidence was found and this review question was not prioritised for health economic modelling. The committee noted that, in the absence of robust evidence on the costs and benefits of specific self-monitoring techniques, it would be inappropriate the recommend the use of specific, potentially expensive monitoring tools. The focus should therefore be on the range of freely/cheaply available self-monitoring tools, which are already in widespread use and would therefore not have a meaningful cost impact. It was also agreed to be important that patients are given sufficient information on how to appropriately self-monitor, to both support self-referral for further testing where appropriate, and to ensure that additional, unnecessary pressure was not put on services as the result of a high rate of false-positive self-referrals.
Quality of evidence	The committee agreed that the overall quality of the evidence was low and indicated that the use of self-monitoring interventions did result in earlier diagnosis, as more people were diagnosed with late AMD (wet active) in the self-monitoring group, and these people had a higher visual acuity at time of the event. However, the committee felt there was only poor quality evidence to demonstrate that earlier diagnosis would result in improvements in long-term outcomes (e.g. visual acuity), and had no evidence on how these specific interventions compared with the less costly techniques committee members prefer. Additionally, the committee agreed that there were issues of bias in the 1 study reporting visual acuity outcomes (early stopping of the trial as it had reached its primary outcome, and selection of participants included in the analysis), which made it difficult to interpret what the results meant for a general population. The study reported a significant difference in the outcome of best-corrected visual acuity at diagnosis of choroidal neovascularisation using nonparametric test due to skewness in the data; however, given that sample sizes are reasonable (30 events in one arm; 51 in the other), it is reasonable to assume the means of the data are normally distributed. Therefore, the evidence review for this guideline adopted a parametric approach, calculated the difference in mean change in visual acuity, with a 95% confidence interval estimated and found no difference in visual acuity between the 2 groups. Further, the reduction in time from onset of symptoms to diagnosis was only 2.5 days with the use of a self-monitoring intervention, and no data were collected on whether this led to changes in management or outcomes. The committee considered whether expanding the search to include cohort studies was likely to identify any evidence that would enable specific recommendations to be made, but agreed it was unlikely it

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	would. Therefore, the study types included were not expanded beyond randomised controlled trials.
Other considerations	The committee agreed that, given the priority currently placed on self-monitoring interventions, specific consideration should be given to those groups of people who are unable to monitor their own vision (for example, comorbidities such as impaired cognitive function). The committee agreed that the role of family members and carers had to be specifically acknowledged for this group of people, and it was important to provide advice for carers/family members on how to monitor changes in people's vision.

11.2.5 Recommendations

42. **Discuss self-monitoring with people with AMD, and explain the strategies available.**

43. **Advise people with AMD to report any new symptoms or changes in the following to their eye-care professional as soon as possible:**
    - blurred or grey patch in their vision
    - straight lines appearing distorted
    - objects appearing smaller than normal.

44. **Encourage and support people with AMD who may lack confidence to self-monitor their symptoms.**

45. **If people are not able to self-manage their AMD, discuss AMD monitoring techniques with their family members or carers (as appropriate).**

11.2.6 Research recommendations

16. **What is the effectiveness and cost-effectiveness of self-monitoring strategies in improving the long-term visual, functional and quality of life outcomes of people with early, indeterminate or late AMD (dry)?**

Why this is important

Currently available evidence on self-monitoring interventions failed to establish a link between early detection and better long-term visual acuity, with only one RCT which measured visual acuity at the time of diagnosis, with no long-term follow up. There is therefore the need for studies of people with different stages of AMD using self-monitoring tool to evaluate both vision-related outcomes (long-term visual acuity, functional and quality of life) and health service resource use, to enable the results to be used to assess the effectiveness and cost-effectiveness of self-monitoring interventions.

17. **Does earlier detection of the incidence of late AMD (wet active) by self-monitoring in people diagnosed with early AMD, indeterminate AMD or late AMD (dry) lead to earlier treatment and better long-term outcomes?**

Why this is important

A review of the evidence demonstrated that self-monitoring interventions result in earlier diagnosis for people with late AMD (wet active). However, the evidence failed to demonstrate that earlier diagnosis would result in improvements in long-term outcomes such as visual acuity, and also failed to capture potential negative effects of self-monitoring (including the

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potential for increased anxiety). A study could be carried out to follow up a cohort of people diagnosed with early, indeterminate or late AMD (dry) to the time when the diagnosis of late AMD (wet active) is established. Comparisons would include time to diagnosis of late AMD (wet active), time to treatment, long-term visual acuity and participants' quality of life. This would help to establish the association between early detection and early treatment plus good long-term vision outcome. It would also help any such positive effects to be weighed against the potential for harm.

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11.3 Monitoring strategies and tools for people with late AMD (wet active)

Review question:

- What strategies and tools are useful for monitoring for people with late AMD (wet active)?

11.3.1 Evidence review

The aim of this review was to establish the accuracy of OCT for the monitoring of people with late AMD (wet active) for features including RPE rip, haemorrhage, exudate and leakage. The review focused on identifying studies that fulfilled the conditions specified in Table 59. For full details of the review protocol see Appendix C.

Table 59: PICO criteria – monitoring strategies and tools for people with late AMD (wet active)

Population	Adults (18 years and older) with late AMD (wet active)
Index tests	Optical coherence tomography (OCT)
Reference standard	Colour photography (biomicroscopy, slit lamp fundoscopy, ophthalmoscopy) Fundus fluorescein angiography (FFA)
Outcomes	Accuracy of diagnostic tests including sensitivity, specificity, positive likelihood ratios and negative likelihood ratios

Diagnostic cross-sectional evidence was considered to be the highest quality evidence available to answer this question, and studies were excluded if they did not provide sufficient data to be able to construct a 2x2 table to evaluate diagnostic accuracy. Papers were also excluded if they:

- were not published in the English language
- did not report diagnostic accuracy outcome
- were abstracts, conference proceedings, narrative reviews, case-studies or non-comparative studies.

11.3.1.1 Description of included studies

A systematic search identified 3,935 references. The references were screened for their titles and abstracts and 132 references were requested for full-text review. A total of 8 studies were included in the final review. There was a systematic review identified in the search but no additional studies were identified from this review. A detailed list of excluded studies and reasons for their exclusion is provided in appendix F.

A brief summary of included studies was provided in Table 60. References of included studies are listed in Appendix I.

Table 60: Summary of included studies

Study details	Study population	Diagnostic test	Reference test	Outcome
Coscas (2015)	Patients with a clinical diagnosis of exudative AMD (treatment naïve or already treated) (n=73 people,80 eyes)	OCT-A	Multimodal imaging (FFA, ICG, spectral domain OCT)	Comparison between OCT-A and traditional multimodal imaging in patients with exudative AMD in terms of guiding the treatment decision

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Study details	Study population	Diagnostic test	Reference test	Outcome
Eter (2005)	Patients with predominantly classic CNV secondary to AMD received PDT with verteporfin (n=60 people, 60 eyes)	OCT	FFA	Retinal morphology be means of FFA and OCT in patients who had undergone photodynamic therapy with verteporfin
Giani (2011)	Patients with CNV from neovascular AMD (n=93 people, 93 eyes)	Spectral-domain OCT (SD-OCT)	FFA	OCT in predicting angiographic leakage status.
Henschel (2009)	Patients with different types of choroidal neovascularisation (n=14 people)	Stratus OCT	FFA	The correlation between angiographic findings and OCT features of CNV in patients who underwent PDT
Khurana (2010)	Patients with CNV secondary to AMD (n=93 people, 93 eyes)	Time-domain OCT (TD-OCT) SD-OCT	FFA	Comparison between fluorescein leakage from CNV and abnormalities of TD-OCT or SD-OCT
Salinas-Alaman (2005)	Patients with signs of exudative AMD with predominantly classic CNV (n=53 people, 62 eyes)	OCT	FFA	The role of OCT in determining CNV activity before and after PDT in patients with AMD
Van de Moere (2006)	Patients received initial PDT for classic or predominantly classic subfoveal CNV secondary to AMD (n=121 eyes)	OCT	FFA	Correlation between OCT and leakage on FFA following PDT for CNV
van Velthoven (2006)	Patients with AMD and subfoveal CNV who had received at least one prior PDT treatment (n=30 people, 30 eyes)	OCT	FFA	Presence or absence of leakage in AMD patients for PDT retreatment

11.3.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. No references were identified as being relevant to this review question. Health economic modelling was not prioritised for this review question.

Mowatt et al. (2014) evaluated the cost effectiveness of a range of organisational models for diagnosing and monitoring wet AMD. The monitoring strategies included were the ophthalmologist interpretation of either OCT alone or visual acuity with sit-lamp biomicroscopy (SLB) and OCT, and nurse- or technician-led interpretation of OCT and visual acuity examinations, with referral to an ophthalmologist for positive or unclear assessments. After consideration, this study was not considered to be directly relevant to the present review question, because none of the monitoring strategies were a reference standard as described in the review protocol for this question (these are FFA and SLB, whereas the strategy that includes SLB in this study also involved visual acuity and OCT examinations). Given that the study reports on the cost effectiveness of models of combined diagnosis and monitoring, and that it considers nurse- and technician-led monitoring, this study was included for review question 5 (see section 7.2.2).

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Health economic modelling was not prioritised for this review question.

11.3.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

11.3.3.1 OCT – signs of leakage

11.3.3.1.1 Confirm the possibility of signs of leakage

Moderate-quality evidence from 2 studies of 149 people (152 eyes) shows that signs of leakage found on SD-OCT raises the probability that leakage would be detected on FFA to a **small** degree.

Low-quality evidence from 3 studies of 146 people (149 eyes) shows that signs of leakage found on TD-OCT raises the probability that leakage would be detected on FFA to a degree that is most likely to be **small**; however, at a 95% confidence level, data are also consistent with a **moderate** increase in probability.

Low-quality evidence from 2 studies of 66 people (237 sets of OCT and FFA images) shows that signs of leakage found on TD-OCT raises the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence level, data are also consistent with a **moderate** increase in probability.

Moderate-quality evidence from 1 studies of 73 people (80 eyes) shows that signs of leakage found on OCT-A raises the probability that leakage would be detected on multimodal imaging including FFA, SD-OCT and ICG to a **large** degree; however, at a 95% confidence level, data are also consistent with a **moderate or very large** increase in probability.

11.3.3.1.2 Excluding the possibility of signs of leakage

Low-quality evidence from 2 studies of 149 people (152 eyes) shows that the absence of signs of leakage found on SD-OCT decreases the probability that leakage would be detected on FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **large** decrease in probability.

Low-quality evidence from 3 studies of 146 people (149 eyes) shows that the absence of signs of leakage found on TD-OCT decreases the probability that leakage would be detected on FFA to a degree that is most likely to be **moderate**; however, at a 95% confidence level, data are also consistent with a **small** decrease in probability.

Moderate-quality evidence from 2 studies of 66 people (237 sets of OCT and FFA images) shows that the absence of signs of leakage found on SD-OCT decreases the probability that leakage would be detected on FFA to a **very large** degree; however, at a 95% confidence level, data are also consistent with a **large** decrease in probability.

Moderate-quality evidence from 1 studies of 73 people (80 eyes) shows that the absence of signs of leakage found on OCT-A decreases the probability that leakage would be detected on multimodal imaging including FFA, SD-OCT and ICG to a **very large** degree; however, at a 95% confidence level, data are also consistent with a **large** decrease in probability.

11.3.3.2 OCT – pigment epithelial detachment

11.3.3.2.1 Confirming the possibility of pigment epithelial detachment

Low-quality evidence from 1 study of 93 people (93 eyes) shows that pigment epithelial detachment found on SD-OCT raises the probability that leakage would be detected on FFA

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to a **small** degree; however, at a 95% confidence level, data are also consistent with a **small** decrease or **moderate** increase in probability.

Very low-quality evidence from 1 study of 121 people (121 eyes) found the presence of pigment epithelial detachment on TD-OCT does not alter the probability of finding leakage on FFA.

11.3.3.2.2 Excluding the possibility of pigment epithelial detachment

Moderate-quality evidence from 1 study of 93 people (93 eyes) shows that the absence of pigment epithelial detachment found on SD-OCT decreases the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence interval, data are also consistent with a **small** increase in probability.

Moderate-quality evidence from 1 study of 93 people (93 eyes) shows that the absence of pigment epithelial detachment found on TD-OCT decrease the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence interval, data are also consistent with a **small** increase in probability.

11.3.3.3 OCT – intraretinal fluid

11.3.3.3.1 Confirming the possibility of intraretinal fluid

Low-quality evidence from 1 study of 56 people (59 eyes) shows that intraretinal fluid found on SD-OCT raises the probability that leakage would be detected on FFA to a **smal**l degree; however, at a 95% confidence level, data are also consistent with a **moderate** increase in probability.

Low-quality evidence from 2 studies of 177 people (180 eyes) shows that intraretinal fluid found on TD-OCT raises the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence level, data are also consistent with a **moderate** increase in probability.

Low-quality evidence from 1 study of 14 people (61 sets of OCT and FFA images) shows that intraretinal fluid found on TD-OCT raises the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence level, data are also consistent with a **moderate** increase in probability.

11.3.3.3.2 Excluding the possibility of intraretinal fluid

Low-quality evidence from 1 study of 56 people (59 eyes) shows that the absence of intraretinal fluid found on SD-OCT decreases the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence level, data are also consistent with a **moderate** decrease in probability.

Low-quality evidence from 2 studies of 177 people (180 eyes) shows that the absence of intraretinal fluid found on TD-OCT decreases the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence level, data are also consistent with a **moderate** decrease in probability.

Low-quality evidence from 1 study of 14 people (61 sets of OCT and FFA images) shows that the absence of intraretinal fluid found on TD-OCT decreases the probability that leakage would be detected on FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **very large, large** or **small** decrease in probability.

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11.3.3.4 OCT – subretinal fluid

11.3.3.4.1 Confirming the possibility of subretinal fluid

Low-quality evidence from 1 study of 56 people (59 eyes) shows that subretinal fluid found on SD-OCT raises the probability that leakage would be detected on FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small** or **large** increase in probability.

Low-quality evidence from 2 studies of 177 people (180 eyes) shows that subretinal fluid found on TD-OCT raises the probability that leakage would be detected on FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small** or **large** increase in probability.

Low-quality evidence from 1 study of 14 people (61 sets of OCT and FFA images) shows that subretinal fluid found on TD-OCT raises the probability that leakage would be detected on FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small** or **large** increase in probability.

11.3.3.4.2 Excluding the possibility of subretinal fluid

Low-quality evidence from 1 study of 56 people (59 eyes) shows that the absence of subretinal fluid found on SD-OCT decreases the probability that leakage would be detected on FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small** decrease in probability.

Moderate-quality evidence from 2 studies of 177 people (180 eyes) shows that the absence of subretinal fluid found on TD-OCT decreases the probability that leakage would be detected on FFA to a **small** degree.

Low-quality evidence from 1 study of 14 people (61 sets of OCT and FFA images) shows that the absence of subretinal fluid found on TD-OCT decreases the probability that leakage would be detected on FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small** decrease in probability.

11.3.3.5 OCT – retinal cystoid abnormalities

11.3.3.5.1 Confirming the possibility of retinal cystoid abnormalities

Low-quality evidence from 1 study of 56 people (59 eyes) shows that retinal cystoid abnormalities found on SD-OCT raises the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence level, data are also consistent with a **small** decrease or **moderate** increase in probability.

Low-quality evidence from 1 study of 56 people (59 eyes) shows that retinal cystoid abnormalities found on TD-OCT raises the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence level, data are also consistent with a **small** decrease or **moderate** increase in probability.

11.3.3.5.2 Excluding the possibility of retinal cystoid abnormalities

Low-quality evidence from 1 study of 56 people (59 eyes) shows that the absence of retinal cystoid abnormalities on SD-OCT decreases the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence level, data are also consistent with a **moderate** decrease or **small** increase in probability.

Moderate-quality evidence from 1 study of 56 people (59 eyes) shows that the absence of retinal cystoid abnormalities on TD-OCT decreases the probability that leakage would be detected on FFA to a **small** degree however, at a 95% confidence level, data are also consistent with a **small** increase in probability.

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11.3.3.6 OCT – cystoid macular oedema

11.3.3.6.1 Confirming the possibility of cystoid macular oedema

Low-quality evidence from 1 study of 121 people (121 eyes) shows that cystoid macular oedema found on TD-OCT raises the probability that leakage would be detected on FFA to a **very large** degree; however, at a 95% confidence level, data are also consistent with a **small, moderate or large** increase in probability.

11.3.3.6.2 Excluding the possibility of cystoid macular oedema

Moderate-quality evidence from 1 study of 121 people (121 eyes) shows that the absence of cystoid macular oedema on TD-OCT decreases the probability that leakage would be detected on FFA to a **small** degree.

11.3.3.7 OCT - cystoid spaces

11.3.3.7.1 Confirming the possibility of cystoid spaces

Moderate-quality evidence from 1 study of 93 people (93eyes) shows that cystoid spaces found on SD-OCT decreases the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence level, data are also consistent with a **small** increase in probability.

Low-quality evidence from 1 study of 60 people (60eyes) shows that cystoid spaces found on TD-OCT raises the probability that leakage would be detected on FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **small, large** or **very large** increase in probability.

11.3.3.7.2 Excluding the possibility of cystoid spaces

Moderate-quality evidence from 1 study of 93 people (93eyes) shows the absence of cystoid spaces found on SD-OCT increases the probability that leakage would be detected on FFA to a **small** degree; however, at a 95% confidence level, data are also consistent with a **small** decrease in probability.

Low-quality evidence from 1 study of 60 people (60eyes) shows the absence of cystoid spaces found on TD-OCT decreases the probability that leakage would be detected on FFA to a **moderate** degree; however, at a 95% confidence level, data are also consistent with a **large** decrease in probability.

11.3.3.8 Health economic evidence

No cost–utility analyses were identified that were relevant to monitoring strategies and tools.

11.3.4 Evidence to recommendations

Relative value of different outcomes	The committee agreed that both sensitivity and specificity are important outcomes to decide the accuracy of monitoring strategies and tools when evaluating disease progression and/or treatment response amongst people with late AMD (wet active). In line with the original protocol, 7 out of 8 included studies evaluated the accuracy of OCT for detecting features including intraretinal fluid, subretinal fluid, pigment epithelial detachment and retinal cystoid abnormalities, in comparison with leakage demonstrated on FFA. Evidence on OCT was categorised to distinguish between time-domain (TD) and spectral-domain (SD) techniques. The committee noted TD-OCT has gradually been replaced by SD-OCT, and it was no longer used in most hospitals. The only study that did not compare OCT with FFA (Coscas et al., 2015) reported the accuracy of OCT-A compared with multimodal imaging for

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	identifying the presence of leakage. The committee agreed it is an important benefit of OCT-A that it is non-invasive, in contrast to FFA, which is the current standard for detecting patterns of blood and leakage suggesting vascular change in people with late AMD (wet active). Consequently, evidence of good accuracy of OCT-A could promote its wide application in clinical practice.
Trade-off between benefits and harms	Based on clinical experience and expertise, the committee suggested that OCT and FFA had different functionality when detecting and monitoring neovascular activity. FFA demonstrates functional change of neovascular disease, providing information on vascular leakage through fluorescein dye, whereas OCT is used to measure or detect anatomic and morphological consequences of leakage such as fluid accumulation. The committee agreed that OCT is used in practice to detect anatomic changes (for example, fluid accumulation) that are correlated with vessel leakage. By correctly identifying people with neovascular activity, OCT can help clinicians' decision-making on treatment and retreatment. The committee agreed that, from the perspective of the person being treated, the specificity of a monitoring test is less important than its sensitivity. False-positive findings, which will arise with imperfect specificity, lead to overtreatment; however, the potential harms of anti-VEGF treatment are relatively limited. In contrast, false-negative findings, which result from tests with imperfect sensitivity, lead to under-treatment that could have significant consequences for the person's vision. For this reason, it is more important that disease activity is spotted than it is that excess injections are avoided. Nevertheless, the committee acknowledged that anti-VEGF injections are not completely harmless, and they are associated with significant costs; therefore, it would not be appropriate to ignore the specificity of monitoring tests. The committee expected OCT accuracy in practice would be somewhat better than the evidence review suggested. It noted that many included studies selected multiple different individual features when evaluating OCT accuracy in comparison with angiographic demonstration of leakage. Common parameters included intraretinal fluid, subretinal fluid, pigment epithelial detachment, retinal cystoid abnormalities, cystoid spaces and cystoid macular oedema (CMO). Some of these features were similar, such as cystoid space, CMO and intraretinal fluid. Therefore, the assessment of the presence of individual features on OCT to predict leakage on FFA does not reflect the true accuracy of OCT as an overall technique. However, when multiple relevant features were combined, SD-OCT had a pooled sensitivity of 92% to predict leakage demonstrated on angiography, and the committee agreed that this represented an acceptably sensitive test. However, OCT was also found to have low specificity (36% pooled for SD-OCT). The committee discussed that the low specificity of OCT may be explained by the choice of reference standard. In this review, FFA was defined as a standard against which to evaluate the accuracy of OCT, since FFA is commonly used in clinical practice and there is no true gold standard. The committee agreed that FFA is a useful tool to detect and confirm neovascular leakage but noted that it is not a perfect test (that is, it is subject to false-negative and false-positive results). The committee concluded that the potential for false-negative results on FFA may have particularly important implications for judging the true specificity of OCT. It is likely that, in many cases in the included studies, a positive OCT was classified as falsely positive (because no leakage was found on FFA) but the OCT had actually identified relevant features that could not be detected by the FFA. Under this circumstance, the committee agreed that it would be appropriate to retreat the affected eye, so this potential failure of FFA would understate the true specificity of OCT. The committee considered whether a natural response to suboptimal accuracy of OCT would be to consider routine monitoring using FFA.

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	However, it agreed that, even if the specificity of OCT was as low as the review suggested, such an approach would be impractical, and would subject patients to inconvenience and potentially severe adverse events. While some anti-VEGF injections might be avoided – thereby reducing costs – the test itself is more expensive and takes longer to perform. Moreover, as it had previously noted, the committee took the view that many of the cases that would be considered negative on FFA would actually benefit from retreatment: in practice, if an individual case had positive OCT findings and negative FFA results, most clinicians would be likely to offer retreatment. On a balance of these considerations, the committee agreed that OCT was an important and appropriate monitoring tool to inform decision-making for treatment or re-treatment, so people with neovascular activity do not lose the potential benefit from treatment. In addition to OCT and FFA, the committee considered that visual acuity change also needs to be included as an important parameter for monitoring disease progression as, in some cases, the results of images might not correlate with reported symptoms. For instance, people who have macular haemorrhage often experience severe vision deterioration with no anatomic changes detected by OCT, but such haemorrhage can be picked up in detail by ophthalmoscopy, fundus photography, or a dilated fundus exam, and then by FFA to confirm any vascular changes. The committee also discussed the scenario of non-response, referring to some people who were treated but with ongoing macular abnormalities presenting on OCT. Of these non-response cases, people were likely to continue experiencing vision symptoms which should be investigated through fundoscopy or fundus photography; moreover, their initial diagnosis should also be investigated further to prompt appropriate treatment. Therefore, committee members agreed, if OCT indicates no apparent change but the patient reports worsening vision following treatment, fundoscopy or colour photography can be used to investigate possible pathological causes and FFA can be used to identify any possible vascular change. Similarly, if OCT indicates ongoing macular abnormalities for treated people whose vision symptoms do not improve, FFA will need to be considered to investigate the initial diagnosis. The committee emphasised that OCT and FFA should be used complementarily to enable clinicians to collate all relevant information to inform their decision on treatment and re-treatment for people with neovascular AMD. **OCT-angiography** The committee noted evidence on OCT-A as a monitoring tool, and it suggested that OCT-A has increasingly become available but is still not yet widely used in clinical practice. OCT-A is considered closer to FFA in its ability to identify leakage amongst people with neovascular AMD. Although only 1 study (Coscas et al., 2015) reported its accuracy, evidence showed a sensitivity of 97% detecting leakage compared with multimodal images including FFA, SD-OCT and ICG. The committee considered these results were extremely promising, but was mindful that OCT-A is currently an expensive technology, and agreed that a greater quantity of evidence is required to establish the accuracy of OCT-A in monitoring AMD progression and treatment response.
Consideration of health benefits and resource use	No economic evidence was identified for this review question and economic modelling was not prioritised. The recommendations made by the guideline committee are not expected to have a positive or negative resource impact, as they reflect current practice.
Quality of evidence	The committee noted that the quality of the evidence reported in this review ranged from very low to moderate. While there were some variations in reported sensitivity of OCT, on the whole, the evidence reported that sensitivity was lower than expected in clinical practice. Six

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	out of 8 included studies reported sensitivity and specificity of TD-OCT and 2 studies reported those of SD-OCT. SD-OCT has been widely used in clinical practice, so there is a possibility that the presented evidence underestimated the true accuracy of SD-OCT. As discussed, included studies evaluated the presence of different features within the retina to assess the role of OCT in predicting angiographic leakage status. All included studies used FFA as the reference standard with the exception of Coscas et al. (2015), which used findings from a combination of imaging techniques including FFA, SD-OCT and ICG. As all tests are potentially subject to false-negative and false-positive results, the committee suggested the use of multimodal imaging as reference standard could be an appropriate approach to increase the overall accuracy of the reference standard. Therefore, it recommended that future research should adopt this kind of approach.
Other considerations	The committee discussed monitoring and retreatment for myopic choroidal neovascularisation but concluded that it is beyond the scope of this guideline.

11.3.5 Recommendations

46. **Offer people with late AMD (wet active) ongoing monitoring with OCT for both eyes.**

47. **Offer fundus examination or colour photography if OCT appearances are stable, but:**
    - there is a decline in visual acuity **or**
    - the person reports a decline in visual function.

48. **Consider FFA to identify unrecognised neovascularisation if OCT appearances are stable, but:**
    - there is a decline in visual acuity **or**
    - the person reports a decline in visual function.

49. **If OCT results suggest macular abnormalities but the abnormalities are not responding to treatment, think about:**
    - using alternative imaging
    - alternative diagnoses.

11.3.6 Research recommendations

18. **What is the relative accuracy and cost of OCT-A compared with the reference standard of multimodal imaging?**

Why this is important

Optical coherence tomography angiography (OCT-A) has been increasingly becoming available and using in monitoring disease activities in people with late AMD (wet active). OCT-A is considered closer to FFA in its ability to provide information on patterns of blood and leakage to inform vascular change in people with late AMD (wet active). As a new imaging tool, OCT-A is an expensive procedure. Currently only a limited amount of evidence reported the accuracy of OCT-A. There is therefore, the need of studies of OCT-A, compared with multimodal imaging (such as OCT and FFA) as reference standard to assess its accuracy in monitoring AMD progression and treatment response and to provide evidence

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based for its wide application in clinical practice. The optimal study design for this question would be a cohort or cross-sectional study of people being treated for late AMD (wet active).

19. What is the clinical effectiveness of OCT-A using test-and-treat approach (OCT(+/-FFA) -v- OCT+OCT-A)?

Why this is important

In practice OCT has been commonly used as the first-line monitoring strategy to detect disease activity and treatment response for people being treated for late AMD (wet active). If OCT indicates no apparent change but the patient reports worsening vision following treatment, fundoscopy or colour photography can be used to investigate possible pathological causes and FFA can be used to identify any possible vascular change. If OCT indicates ongoing macular abnormalities for treated people whose vision symptoms do not improve, FFA will need to be considered to investigate the initial diagnosis. Therefore OCT is an important and appropriate monitoring tool, and should be used complementarily with FFA to enable clinicians to collate all relevant information to inform their decision on treatment and re-treatment for people with late AMD (wet active). Additionally with the availability of OCT-A, how well that OCT-A can correctly detect neovascular activities, and whether it can be used complementarily with OCT to improve the accuracy of monitoring the occurrence of leakage remain unclear. Well conducted test-and-treat RCTs would fill in an important gap, and provide an evidence base around the clinical effectiveness of OCT-A to be used as a potential monitoring strategy.

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12 Information

AMD is the most common cause of vision loss in older adults. When a person is suspected of having or has been diagnosed with AMD it is important that they and their family members, or carers, understand how it will affect their lives. Good support and information for both the patient and family members can contribute towards better patient outcomes and can help optimise quality of life.

Given the progressive nature of the disease and the different disease stages the information given will depend upon the stage of progression of AMD, the recommended treatment and any other illnesses/conditions the patient may have. They will want to know how they can look after their eyes and should be made aware of what to do if their vision changes.

Being diagnosed with AMD is distressing for patients and their family members or carers. Many will have little or no knowledge of AMD before they are diagnosed with it. They are likely to feel confusion, be fearful of the future and be anxious about treatment, for example about having injections into their eye. They will need reassurance and support.

This chapter will review for available evidence to identify the barriers and facilitators to treatment adherence and the information needs of people with AMD, their families and carers.

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12.1 Barriers and facilitators to appointment attendance and uptake of treatment for people with AMD

Review question:

- What are the barriers and facilitators to appointment attendance and uptake of treatment for people with AMD?

12.1.1 Evidence review

The aim of the review was to understand the barriers and facilitators to appointment attendance and uptake of treatment for people being treated for AMD from their own perspectives through their experiences of people. The review focused on identifying studies that fulfilled the conditions specified in Table 61. For full details of the review protocol, see Appendix C.

Table 61: PICO table – barriers and facilitators to adherence of appointment and treatment for people with AMD

Population	Adults (18 years and older) being treated for AMD
Factors/Interventions	Salient beliefs and barriers may include: • The difficulty of frequent visits to hospital (including length of time at hospital) • Painful injections into the eye and discomfort • Travel and expense (including hospital transport) • Travelling in the dark • Structural issues (communication, appointment organisation, signposting, hospital environment) • Mental health and lack of motivation • Fear and lack of confidence • Immobility e.g. in care settings • Co-morbidity and poor health • Lack of perceived danger e.g. complications of condition • Lack of perceived benefit e.g. importance of treatment • Lack of understanding e.g. importance how to of self-monitoring • Lack of local services e.g. low vision clinics
Outcomes	Qualitative evidence summary: • Quotes, and authors analysis • Summary of themes • Thematic analysis

Qualitative studies and systematic review of qualitative studies were included if they explored barriers and facilitators to appointment attendance and update of treatment for people with AMD. If there was insufficient qualitative evidence, quantitative studies (survey studies) were included. Evidence from qualitative studies was initially rated as high quality, and evidence from quantitative observational studies was initially rated as low quality, with the quality of the evidence for each theme/outcome downgraded or not from these points. Papers were excluded if they:

- did not include people who are being treated for AMD
- were not in English language
- were abstracts, conference proceedings and other unpublished studies.

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12.1.1.1 Description of included studies

A total of 3,707 references were identified through a systematic search. References were screened on their titles and abstracts and the full texts of 51 references that were potentially relevant to the review question were screened on full-text. Ten studies including 3 qualitative studies exploring experiences of patients with AMD and 7 quantitative studies (cross-sectional surveys) examining the reasons for dropout and discontinuation of treatments or follow-up visits were included in the review. A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

A brief summary of included studies was provided in Table 54. References of included studies are listed in Appendix I.

Table 62: A summary of included studies in the review

Study details	Study population	Methods	Outcome
Quantitative studies			
Boulanger-Scemama E et al. 2015 [France]	Patients with exudative AMD who underwent their first ranibizumab intravitreal injection (n=201)	Telephone survey (7-itemquestionnaire)	Adherence to following-up over 5 years, and factors associated with failure to continue follow-up
Droege K M et al. 2013. [German]	Patients treated with ranibizumab for exudative AMD on a PRB regimen (n=95)	16-item questionnaire	Factors and problems influencing treatment adherence in patients undergoing anti-VEGF therapy for neovascular AMD
Mitchell J, et al 2002 [UK]	Members of the Macular Disease Society (n=1,421)	Self-completed questionnaire	The experience of people with macular disease within the British healthcare system
Nunes R P, et al 2010. [Brazil]	Patients with exudative AMD who were treated with bevacizumab (n=82)	Telephone interview	The rate and cause of interruption of bevacizumab in patients with exudative AMD
Thompson A C, et al 2015. [USA]	People attending follow-up ophthalmology appointments (n=240)	Questionnaire	Factors affected poor attendance of follow-up appointments for care of chronic eye diseases, and strategies to improve adherence
Varano Monicaet al 2015. [9 countries including UK]	Patients with wet AMD (n=910)	Questionnaire	barriers to treatment from perspective of patients and caregivers
Vaze A, et al 2014 [Australia]	Patients with neovascular AMD who began treatment with ranibizumab (n=248)	Chart review	Reasons for discontinuing anti-VEGF in neovascular AMD
Qualitative studies			
Burton Amy E, et al. 2013a [UK]	People with wet AMD (n=7)	Interview (interpretative phenomenological study)	Subjective experience of patients treated with ant-VEGF injections

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Study details	Study population	Methods	Outcome
Burton A E, et al 2013 [UK]	People with AMD (n=13)	Interview (interpretative phenomenological study)	Patients' experience of eye health consultations and their perceptions of information and support provision for AMD
McCloud Cet al. 2014 [Australia]	Patients with AMD (n=34)	Interview/focus group (interpretative phenomenological study)	People's experience with AMD including those whose treatment was successful and those whose treatment had failed to maintain vision

12.1.2 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references was returned. No references were identified as being relevant to this review question. Health economic modelling was not prioritised for this review question.

12.1.3 Evidence statements

The following is a summary of the findings of the above review. The GRADE and CERQual ratings for this evidence can be found in Appendix H respectively. Evidence tables can be found in Appendix E.

12.1.3.1 Barriers to appointment attendance and uptake of treatment for people with AMD

12.1.3.1.1 Emotions related to (anticipated) treatment

Qualitative evidence

The following theme was identified from 2 qualitative studies using semi-structured (n=13) or unstructured interview (n=7) with a moderate level of confidence in the findings:

- People with AMD may decline treatment due to anxiety, fear and distress. They often described these emotions when they prepared for treatments, especially when they were relatively new to treatment or experienced disease progression.

Quantitative evidence

People being treated for late AMD (wet active) reported being **'scared about receiving an injection'** as one of the obstacles to their treatments (3.0% [95%CI: 2.0 to 4.3%]; 1 survey of 910 people; low-quality evidence).

People with AMD who stopped their follow-ups reported **'subjective dissatisfaction with injections'** as one of the reasons for their drop-out and discontinuation of treatment (50% [95%CI: 29.9 to 70.1%] and 36.8% [95%CI: 19.1 to 59.0 %]; 2 surveys of 39 people; very low-quality evidence).

People with late AMD (wet active) who underwent intravitreal anti-VEGF treatment reported **'pain and discomfort**' as one of their reasons for declining further treatment (1.2% [95%CI: 0.4 to 3.5%]; 1 case review of 248 people; very-low quality evidence).

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12.1.3.1.2 Communication with healthcare professionals

Qualitative evidence

The following themes were identified from 2 qualitative studies using semi-structured (n=13) or unstructured interview (n=7) with a moderate level of confidence in the findings:

- People with AMD expressed a sense of confusion when they had to interact with a variety of healthcare professionals throughout their treatments.
- People with AMD were concerned by hospital letters that gave little information about what each appointment was for and what they should expect at the appointment. A wide variety of information deficits after diagnosis of AMD degeneration were evident.
- People highlighted a lack of knowledge about the purpose of medical processes and procedures. There were also examples of people attempting to make their own judgement about the need for treatment as they were unsure about the duration of their treatment.

Quantitative evidence

People who interrupted their treatment reported **'lack of information about follow-up visits'** as one of their reasons for discontinuing follow-up (26.3% [95%CI: 11.8 to 48.8%]; 1 case review of 19 people; very low-quality evidence).

People reported **'lack of information or advice (about condition, prognosis etc.)'** as one of the reasons for their dissatisfaction with consultation during the treatment (43.4% [95%CI: 39.5 to 47.4%]; 1 survey of 604 people; low-quality evidence).

People reported **'specialists' attitudes (dismissive, patronising, brusque, unfeeling, uninterested in patient/condition, use of jargon, etc.)**' as one of their reasons for discontinuing follow-up (43.5% [95%CI: 39.6 to 47.5%]; 1 survey of 604 people; low-quality evidence).

12.1.3.1.3 Treatment itself (the nature of treatment/treatment regimen)

Qualitative evidence

The following theme was identified from 1 focus group/interview study (n=34), with a low level of confidence in the findings:

- People suggested that the invasiveness of the treatment and often painful recovery were significant issues when they underwent treatment.

Quantitative evidence

People with late AMD (wet active) who underwent intravitreal anti-VEGF treatments reported **'frequency of treatment visits'** as one of their reasons for declining further treatment (0.8% [95%CI 0.2 to 2.9%]; 1 case review of 248 people; very low-quality evidence).

People with AMD who were lost to follow-up reported '**burden of periodic follow-up visits'** as one of their reasons for dropout (15% [95%CI: 5 to 36%]; 1 survey of 20 people; very low-quality evidence).

People being treated for late AMD (wet active) reported '**appointments are too frequent/inconvenient'** as one of their dissatisfaction to the treatment (8.6% [95%CI: 7.0 to 10.7%]; 1 survey of 910 people; low-quality evidence).

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12.1.3.1.4 Travelling problems

Quantitative evidence

People who stopped their follow-ups reported **'long distance from home to hospital'** and **'chose treatment option closer to home'** among their reasons for discontinuation (51.7% [95%CI: 39.2 to 64.1%] and 26.3% [95%CI: 11.8 to 48.8%] respectively; 2 surveys of 77 people; very low-quality evidence).

People who interrupted their treatment reported **'travelling problems'** as one of their reasons for discontinuing follow-up (5.3% [95%CI: 0.9 to 24.6%]; 1 case review of 19 people; very low-quality evidence).

People with late AMD (wet active) who discontinued intravitreal anti-VEGF treatments reported **'being referred to a doctor locally for ongoing management'** as one of their reasons (10.9% [95%CI: 7.6 to 15.2%]; 1 case review of 248 people; very low-quality evidence).

12.1.3.1.5 Comorbidities

Quantitative evidence

People who stopped their follow-ups reported **'general comorbidities'** and '**serious general disease'** among their reasons for discontinuation (1.7% [95%CI: 0.3 to 9.1%] and 15.8% [95%CI: 5.5 to 37.6%] respectively; 2 surveys of 77 people; very low-quality evidence).

People who failed to reschedule a missed appointment reported **'other medical/physical illness'** as a barrier to attending follow-up appointments (23.5% [95%CI: 16.3 to 32.6%]; 1 survey of 102 people; low-quality evidence).

People who interrupted their treatment reported '**comorbidities such as malignancy, Alzheimer's disease and cerebral vascular disease'** as one of their reasons for discontinuing follow-up (15.8% [95%CI: 5.5 to 37.6%]; 1 case review of 19 people; low-quality evidence).

People with late AMD (wet active) who underwent intravitreal anti-VEGF treatments reported '**other medical conditions'** as one of their reasons for declining further treatment (4.4% [95%CI: 2.5 to 7.8%]; 1 case review of 248 people; very low-quality evidence).

12.1.3.1.6 Poor visual results

Quantitative evidence

People who interrupted their treatment reported '**unexpected poor visual results'** as one of their reasons for discontinuing follow-up (42.1% [95%CI: 23.1 to 63.7%]; 1 case review of 19 people; very low-quality evidence).

People with late AMD (wet active) who underwent intravitreal anti-VEGF treatments reported **'treatment not being perceived to be beneficial'** as one of their reasons for declining further treatment (2.4% [95%CI: 1.1 to 5.2%]; 1 case review of 248 people; very low-quality evidence).

12.1.3.1.7 Difficulty in rescheduling

Quantitative evidence

People who interrupted their treatment reported '**difficulty in booking new appointments'** as one of their reasons for discontinuing follow-ups (10.5% [95%CI: 2.9 to 31.3%]; 1 case review of 19 people; very low-quality evidence).

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People who did not reschedule a missed appointment reported **'difficulty in rescheduling'** as a barrier to attending follow-up appointments (37.3% [28.5 to 46.9%]; 1 survey of 102 people; low-quality evidence).

12.1.3.1.8 Lack of an escort

Quantitative evidence

People who did not reschedule a missed appointment reported '**lack of an escort'** as a barrier to attending follow-up appointments (21.6% [95%CI: 14.7 to 30.5%]; 1 survey of 102 people; low-quality evidence).

People being treated for late AMD (wet active) reported **'caregiver unable to take me to appointment'** as one of their dissatisfactions with treatment (23.5% [95%CI: 20.9 to 26.4%]; 1 survey of 910 people; low-quality evidence).

12.1.3.1.9 Financial burden

Quantitative evidence

People who were lost to follow-up reported **'financial burden'** as one of their reasons for discontinuing treatment (8.6% [95%CI: 3.7 to 18.6%]; 1 survey of 58 people; very low-quality evidence).

People who did not reschedule a missed appointment reported **'financial barriers (clinical fees, transportation costs and lost wages)'** as a barrier to attending follow-up appointments (25.5% [95%CI: 18.0 to 34.7%]; 1 survey of 102 people; low-quality evidence).

People being treated for late AMD (wet active) reported **'cannot afford to attend every appointment'** as one of their dissatisfactions with treatment (5.0% [95%CI: 3.7 to 6.5%]; 1 survey of 910 people; low-quality evidence).

People with late AMD (wet active) who underwent intravitreal anti-VEGF treatments reported **'treatment perceived to be too expensive'** as one of their reasons for declining further treatment (0.8% [95%CI: 0.2 to 2.9%]; 1 case review of 248 people; very low-quality evidence).

12.1.3.1.10 Long wait-times

Quantitative evidence

People who did not reschedule a missed appointment reported '**long wait-times'** as a barrier to attending follow-up appointments (52.0% [95%CI: 42.3 to 61.4%]; 1 survey of 102 people; low-quality evidence).

12.1.3.2 Facilitators of appointment attendance and uptake of treatment for people with AMD

12.1.3.2.1 Prior knowledge, treatment experience and peer support

Qualitative evidence

The following theme was identified from 1 interview study (n=7), with a moderate level of confidence in the findings:

- People with AMD felt that treatments were not as distressing as they had originally feared after they went through numerous treatments. They were happy to share their experience with others who were new to the treatment, helping them to ease concerns and reduce unnecessary distress.

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Quantitative evidence

Participants who attended follow-up ophthalmology appointments reported '**networking with other patients with the same eye diseases**' and '**more education on eye disease/the importance of follow-up'** as one of the potential strategies to improve attendance to follow-up appointments (41.3% [95%CI: 35.2 to 47.5%] and 70.8% [95%CI: 64.8 to 76.2%] respectively; 1 survey of 240 people; low-quality evidence).

12.1.3.2.2 Regular monitoring

Qualitative evidence

The following theme was identified from 1 interview study (n=7), with a moderate level of confidence in the findings:

- People with AMD expressed a desire for regular monitoring by healthcare professionals, as knowing that they were under the care of the hospital gave them a sense of security. They also highlighted the need to self-advocate, and they were expected to identify advancing vision loss and seek appointment and support as and when it was necessary.

Quantitative evidence

People who attended follow-up ophthalmology appointments reported **'mobile eye care van'** as a potential strategy to improve attendance of follow-up appointments (32.1% [95%CI: 26.5 to 38.2%]; 1 survey of 240 people; low-quality evidence).

12.1.3.2.3 Relationship with healthcare professionals

Qualitative evidence

The following theme was identified from 1 interview study (n=13), with a moderate level of confidence in the findings:

- People with AMD described their experience building relationship with healthcare professionals (particularly nurses) as a way to manage the distress treatment caused. Patients preferred appointments that exemplified a balanced and professional relationship and mutual respect, and that made them feel empowered about decisions they could make regarding treatment and management of their condition.

12.1.3.2.4 Treatment results (visual acuity)

Qualitative evidence

The following theme was identified from 1 interview study (n=13), with a low level of confidence in the findings:

- People expressed a clear willingness to consent to treatment if they continued to gain or maintain vision.

12.1.3.2.5 Pre-appointment reminder (by phone, text, email)

Quantitative evidence

People who attended follow-up ophthalmology appointments reported **pre-appointment reminders** as a potential strategy to improve adherence to follow-up (81.7% [95%CI: 70.6% to 93.9%]; 1 survey of 240 people; low-quality evidence).

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12.1.3.2.6 Parking voucher

Quantitative evidence

People who attended follow-up ophthalmology appointments reported parking vouchers as a potential strategy to improve adherence to follow-up (47.9% [95%CI: 41.7 to 54.2%]; 1 survey of 240 people; low-quality evidence).

12.1.3.2.7 Transportation service to and from the clinic

Quantitative evidence

People who attended follow-up ophthalmology appointments reported transportation **service to and from the clinic** as a potential strategy to improve adherence to follow-up (44.6% [95%CI: 38.4 to 50.9%]; 1 survey of 240 people; low-quality evidence).

12.1.3.3 Health economic evidence

No cost–utility analyses were identified that were relevant to barriers and facilitators to attendance and uptake of treatment.

12.1.4 Evidence to recommendations

Relative value of different outcomes	The guideline committee agreed that people's perspectives and their own accounts are valuable to understand their priorities and difficulties while they were being treated for AMD. It agreed that the included studies provided an overall view of important experiences of people with AMD during their treatment and, in many instances, a familiar reflection of committee members' own encounters. Both qualitative and quantitative studies were included in the review to enable triangulation of evidence to contribute to an improved understanding of barriers and facilitators so as to identify possible measures to promote people's adherence to their appointments and treatments.
Trade-off between benefits and harms	**Barriers** The qualitative review identified several barriers to adherence to appointments and treatment. These included problems of communication between staff and patients; lack of information about medical procedures; people's emotional responses to treatments such as anxiety, fear and distress; and the invasive nature of the treatments themselves (plus its painful recovery). All these could lead to people withdrawing from treatments. The committee agreed that these themes tallied with their own experience. In line with qualitative evidence, quantitative evidence also identified lack of information, treatment-related emotions and treatment burden as barriers to adherence to appointments and treatment. It also provided evidence on additional problems that could deter appointment attendance: travel problems, comorbidities, financial burden and difficulty in re-arranging appointments. The committee considered that all these barriers emerging from the evidence were putting people with AMD at risk of not receiving appropriate care. Committee members related their experience that comorbidity was a common reason that people with AMD miss their appointments in clinical practice. Often, patients do not turn up to their appointments for a few months because they are receiving treatment for other health problems. Transportation was also considered an important problem; for example, in some cases, it could cost some patients £30–40 just for a hospital visit, with additional cost for parking.

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	There was consistency in the evidence about a lack of information as a barrier to adherence. The committee noted that people with AMD do not always remember and absorb every piece of information that is provided orally during their appointments; therefore, written information is helpful as people can refer to it later. Therefore, the committee agreed it is important to develop accessible information that patients can take with them to enable them to fully understand critical aspects of their condition and its treatment. The committee noted in the evidence that a high proportion of patients reported dissatisfaction with the attitude of healthcare professionals, with behaviours described as dismissive, patronising and brusque. This was one of the reasons that patients may be disinclined to attend appointments. Rather than highlight these negative judgements in its recommendations, the committee agreed to emphasise the positive steps that would lead to a more satisfactory patient experience: allowing time to understand the patient's priorities and concerns and to answer their questions. The committee also emphasised that individuals' needs should also be considered in written communication between the patient and the healthcare professional. For instance, it is important to be aware that people with AMD may have difficulty in reading routine hospital correspondence. **Facilitators** Qualitative and quantitative evidence in the review also identified some facilitators that improved the adherence to appointments and treatment. Peer-support from people with previous treatment experience was found helpful, especially for those who were newly diagnosed or just started their treatment. Many felt that treatments were not as distressing as they had originally feared after they went through numerous treatments. Therefore, the committee was keen to promote peer-support (i.e. buddy) mechanisms to assist people with AMD coming to hospital for treatment. Quantitative evidence from a survey study also highlighted several facilitators that could improve appointment attendance, including pre-appointment reminders, parking vouchers, facilitated transportation and more education on eye disease as well as the importance of follow-up. Of these, the committee noted there was transportation service for patients available in the NHS, and such service could provide support for people with AMD when attending their hospital visits. However, recent changes have been introduced to NHS patient transport guidance, and many people might not be able to get access to NHS transportation under such change.
Consideration of health benefits and resource use	No health economic evidence was found and this review question was not prioritised for health economic modelling. The committee noted there is no evidence on potential costs and benefits involving adherence of appointment or treatment. Missed appointments incur costs by reducing the efficiency of clinics. On the other hand, some additional costs might result if patients require more information regarding their condition and its treatment, as this might result in longer consultation time and more input from eye care liaison officers to facilitate patients' needs. However, the committee suggested that individuals' needs at each hospital visit might vary, and not every patient would need longer consultation time since they could obtain relevant information in different ways formally or informally. This underlines the importance of providing written information for patients that they can digest at their own pace, enabling them to seek further information if required. Such an approach would ensure that unnecessary pressure would not be put on services.

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Quality of evidence	The overall quality of evidence was graded as low to moderate. The qualitative evidence was based on relatively few studies, although coherence between these studies was good throughout. Two out of 3 qualitative studies were in the NHS setting, and had high relevance and adequacy of data on treatment experience of people with AMD. The quantitative evidence was rated as very low to low quality. These survey data were from countries across different healthcare settings including UK, Germany, France, Australia, Brazil and USA. The sample size varied in the survey studies, ranging from 19 to 910. The committee agreed that caution should be taken when interpreting the results from these surveys, even though they agreed that the issues reported were relevant and congruent with the qualitative evidence.
Other considerations	Whilst acknowledging that this review was primarily concerned with barriers and facilitators to adherence of appointment and treatment the committee drew attention to and sought guidance on self-assessment of visual change, and patients felt a lack of confidence not only on how to make straightforward decision themselves, but also when and where to report any vision changes. It was noted that, while this review had identified that people with AMD are more positive about attending appointments if they feel well informed about their condition and its treatment, a separate review question explores the exact information that people with AMD and their family members find useful (see section 12.2). The committee also highlighted an ambiguity with regard to recent changes in patient transport guidance, which could potentially affect patients' accessibility to transportation support.

12.1.5 Recommendations

50. Provide information in accessible formats for people with AMD to take away at their first appointment, and then whenever they ask for it (see recommendation 53). The information should cover the following:

- information about AMD and treatment pathways, including likely timescales
- key contact details – for example, who to contact if appointments need to be altered
- advice about what to do and where to go if vision deteriorates
- available support (including transport and parking permits)
- links to local and national support groups.

51. Allow enough time to discuss the person's concerns and questions about their diagnosis, treatment and prospects for their vision. Assess the person's priorities when making management decisions.

52. Promote peer support for people with AMD, particularly for people who are beginning intravitreal injections, who may be reassured by discussion with someone who has previously had the same treatment.

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12.2 Informational needs of people with suspected or confirmed AMD and their family members/carers

Review questions:

- What information do people with suspected AMD and their family members or carers find useful, and in what format and when?
- What information do people with confirmed AMD and their family members or carers find useful, and in what format and when?

12.2.1 Evidence review

The aim of this review was to assess the informational needs of people with suspected or confirmed AMD and their family members/carers. The review focused on identifying studies that fulfilled the conditions specified in Table 55. For full details of the review protocol, see Appendix C.

Table 63: PICO table – informational needs of people with suspected AMD and their family members/carers

Population	Adults (18 years and older) suspected of having first presentation of AMD
Factors/Interventions	Salient information needs might include: • Signs and symptoms of AMD; • Pre-existing risk factors for the development of AMD, including genetic risk factors. • What is AMD and the difference between wet, dry and early forms of the disease; • Causes of AMD • Behavioural and therapeutic strategies available to reduce the risk of AMD or slow the progression of the disease. • Investigations used for the diagnosis of AMD • Who to contact if deterioration in vision is suspected e.g. GP, eye clinic, optometrist; Formats might include: • Written information • Font size, format and paper type • Accessible language • Video • Audio • Websites and apps
Outcomes	Qualitative evidence summary (thematic analysis): • Quotes, and authors analysis • Summary of themes

Table 64 PICO table – informational needs of people with confirmed AMD and their family members/carers

Population	Adults (18 years and older) with diagnosed AMD
Factors/Interventions	Salient information needs might include: • Signs and symptoms of AMD; • What is AMD and the difference between wet, dry and early forms of the disease; • Causes of AMD

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	• Behavioural and therapeutic strategies available to reduce the risk of AMD or slow the progression of the disease. • Investigations used for the diagnosis of AMD • Who to contact if deterioration in vision is suspected e.g. retinal clinic, optometrist; • Management strategies available if early/indeterminate or geographic atrophy occurs • Therapeutic strategies available if neovascular AMD occurs and information about treatment experience • Adverse effects and who to contact • Success rates of treatment • Patient experience of treatment • Low-vision support (strategies, tools, daily living advice, access to work employment) • Signposting to other services and sources of information (for instance helplines, financial support, support groups) • Driving and DVLA laws • Possible effect on other activities of daily living. • Purpose and value of CVI registration and definitions of legal blindness • Smoking cessation advice and support • Psychological support • Prognosis and treatment plan (including frequency of administration required) • Information about progress of treatment (success/failure) • Home monitoring, how to do it and how often. Local pathways to re-referral if vision changes. • Possible complications, their likelihood and who to contact (for example Charles Bonnet Syndrome) Formats might include: • Written information • Font size, format and paper type • Accessible language • Video • Audio • Websites and apps
Outcomes	Qualitative evidence summary (thematic analysis): • Quotes, and authors analysis • Summary of themes

Qualitative studies and systematic review of qualitative studies were included if they explored the information needs of people with confirmed or suspected AMD or their family members/carers. If there was insufficient qualitative evidence, quantitative studies (survey studies) were included. Papers were excluded if they:

- did not include people who are being treated for AMD
- were not in English language
- were abstracts, conference proceedings and other unpublished studies.

12.2.1.1 Description of included studies

A total of 5,575 references were identified through the search. References were screened based on their titles and abstracts and the full texts of 20 references that were potentially relevant to the review question were requested. Five qualitative studies exploring the experiences of patients with AMD or their family members/carers were included in the

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review. A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

A brief summary of included studies was provided in Table 56. References of included studies are listed in Appendix I.

Table 65: Summary of included studies

Study details	Study population	Methods	Outcome
Burton (2013)	Patients diagnosed with AMD (n=13 people)	Individual, in-depth, semi-structured interviews	Analysis of narrative to identify key themes and issues relating to patient information and support needs.
Crossland (2007)	Patients with AMD (n=15 people)	Individual, in-depth, semi-structured interviews	Exploration of the causes of AMD identified by the participants and the issues raised by the lack of knowledge that these suggested causes revealed.
Dahlin Ivanoff (1996)	Patients with AMD (n=25 people)	Focus group discussion	Examination of the issues raised and how they could be used to inform the contents of a health education programme for these patients.
McCloud (2015)	Patients with neovascular AMD (n=25 people)	Individual, in-depth, unstructured interviews	Analysis of narrative to identify key themes and issues concerning the patient experience.
Vukicevic (2016)	Carers of patients with neovascular AMD (n=643 people)	A cross-sectional, self-administered survey with two open ended questions (only the qualitative evidence was included for this question)	Information about the characteristics of carers, their experiences, emotional stresses and unmet needs.

12.2.1 Health economic evidence

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (see Appendix D). A total of 3,163 unique references were returned. No references were identified as being relevant to this review question. Health economic modelling was not prioritised for this review question.

12.2.2 Evidence statements

The following is a summary of the findings of the above review. The CERQual and evidence tables for this evidence can be found in Appendix H and Appendix E respectively.

12.2.2.1 Information needs before diagnosis

The following themes were identified from 1 questionnaire study of 643 people and 1 qualitative study (n=13), with a moderate level of confidence in the findings:

- Patients and carers want increased public awareness of the causes and symptoms of AMD to help improve public interaction with AMD patients and to provide a context for patients at diagnosis.
  - “I feel more people should get to know and learn more about what happens to people with AMD and how to help them as some people are unaware how it impacts on these peoples’ lives.” (Vukicevic 2016)

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The following theme was identified from 1 qualitative study (n=13), with a moderate level of confidence in the findings:

- Patients' experiences at the optician varied greatly and how they were told/what they were told had a big effect on the anxiety and fear they feel before formal diagnosis.
  - "It worried me….It was when they wouldn't answer me in the opticians when I said 'is it serious?' and not one of them would answer they were just looking at me. That frightened the life out of me, I thought it's something very, very bad." (Burton 2013)

12.2.2.2 Information needs at/after diagnosis

The following theme was identified from 1 qualitative study (n=13), with a moderate level of confidence in the findings:

- The information at diagnosis needs to be matched to the person's disease stage: early AMD patients needed information about monitoring their condition and spotting changes; late AMD (wet active) patients needed to know about available treatments and outcomes; patients with advanced disease needed to hear about support services and equipment.

The following themes were identified from 2 qualitative studies (n=25, n=13), with a high level of confidence in the findings:

- Patients were confused about the different names and types of AMD and were unware that AMD was so common.
  - "I didn't realise it was so common" (Burton 2013)

The following themes were identified from 4 qualitative studies, with a high level of confidence in the findings:

- Patients often lacked a clear understanding of the potential causes and risk factors associated with AMD, with many linking it to the ageing process.
  - " ….. doesn't matter if you go to your dentist, doctor, optician- it's your age" (Crossland 2007)
- Most patients were not aware of the potential effects of smoking on disease development and progression, while those patients that mentioned smoking as a cause did not necessarily believe it.
  - "They say that smoking does it- I've been smoking now since 1941, 42. .....I've got arthritis in both knees, they say that's due to smoking, high blood pressure, that's due to smoking…. [I] Just think they're all wrong, I don't know what to say" (Crossland 2007)
- The role of genetic susceptibility in developing AMD was not widely understood.

The following themes were identified from 3 qualitative studies, with a high level of confidence in the findings:

- Patients discussed a need for accurate information about disease progression to help them plan for the future and to avoid unrealistic expectations of treatment outcomes or unnecessary worry about going blind.
- Patients reported giving up favourite pastimes to help preserve their vison.
  - "I keep sort of thinking oh I will [do some painting] and I think no, I sort of put a limit on how much I use my eyes a lot, does this make sense to you?" (Burton 2013)

The following themes were identified from 3 qualitative studies, with a moderate level of confidence in the findings:

- Patients often had unrealistic expectations of treatment outcomes and this was not helped by inaccurate information from neighbours/family members.
  - "Well, [name] had something done to his eye at the hospital, didn't he? Now he can see better…… he had an operation and he can see perfect" (Burton 2013)

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- Patients did not necessarily understand the importance of the use of vitamins and certain foods to promote eye health and when they could be useful during disease progression.
- Patients did not understand why glasses were not able to correct their vision problems.
- Patients were often unaware of the purpose of hospital visits and medical procedures
  - ‘I’m going, as I say I’m going up there next month. I don’t know what the procedure is going to be, but they don’t tell you do they? They don’t tell you.” (Burton 2013)
- An understanding of the processes involved in treatment and the short -term side effects allowed patients to plan their post-treatment activities to cope with these problems.
  - “If I go there, I know I’m going to get an anaesthetic in the eye, and I’m going to get the injection, and…… and I’m going to be unable to see clearly for a number of hours. I can come back home, I can put ….just relax and when it comes back, then I’m back to normal“ (McCloud 2015)
- Information about abnormal outcomes and when to seek help would also be useful.
- Good communication regarding changes in treatment regimens was linked to better patient experience.

The following themes were identified from 1 qualitative study (n=13), with a moderate level of confidence in the findings:

- Patients were unaware of support groups or unlikely to attend them for fear of associating with depressed people.
- Patients were not necessarily aware of sources of financial help (e.g. attendance allowance) or the advantages associated with being registered as partially sighted.
  - “He said that you could be registered as part-sighted. Well what does that mean? What does it do? Does it open the door for different things?” (Burton 2013)
- Patients who were not being regularly monitored were expected to identify advancing vision loss and seek appropriate support as and when it was necessary. However, they did not understand what constituted a serious change and were worried about wasting doctor’s valuable time and NHS resources. They were also relatively unlikely to attend accident and emergency if their vision changed as they did not associate A and E with this type of care.
  - “I mean it’s fine isn’t it, for someone to say to you, well you would notice a change because…. But you can’t be sure…I’m not sure what I’m looking for! I mean obviously if I suddenly couldn’t see or some dramatic change, but would it be as dramatic as that?” (Burton 2013)

12.2.2.3 Formats of information

The following theme was identified from 1 qualitative study (n=13), with a moderate level of confidence in the findings:

- Verbal communication of information was problematic for many patients as they struggled to understand and retain the information given to them in hospital consultations. They also reported problems with hearing and understanding the doctors’ accents. The type of language used by medical staff was confusing and inaccessible.
- The use of written sources of information was potentially problematic as patients could be confused by the volume of information and find it hard to read the documents.

12.2.2.4 Additional sources of information

The following theme was identified from 1 qualitative study (n=13), with a moderate level of confidence in the findings:

- Information from non-medical sources was not always accurate. In particular, information from neighbours and friends could be very misleading and discourage people from

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seeking help in a timely manner or lead them to have unrealistic expectations from treatment.

- Support groups could be useful sources of information, but patients were not necessarily aware of them or willing to attend.
- Public presentations were raised as a useful source of information, but required pro-active patients.

12.2.2.5 Caregiver perspectives and needs

The following themes were identified from 1 questionnaire study of 643 people, with a high level of confidence in the findings:

- Carers need sufficient information to allow them to understand the condition and the physical/emotional effects on the person's wellbeing.
- Caregivers raised the point that since AMD has a genetic component it is important that all family members of AMD sufferers are aware of their increased risk and have regular eye tests.
  - "Important to be monitored and diagnosed early to access treatment to stop if possible progress of disease. Important to be educated and be aware of risk and contributing factors" (Vukjcevic 2016)
- They lack information about support services and respite care options.

12.2.2.6 Additional points

The following themes were identified from 1 qualitative study, with a moderate level of confidence in the findings:

- Patients were unaware that medical research was being carried out.
- Patient experiences were more positive if they received reassurance, support and caring communication from medical staff.

12.2.2.7 Health economic evidence

- No cost–utility analyses were identified that were relevant to the informational needs of people with suspected or confirmed AMD and their family members/ carers.

12.2.3 Evidence to recommendations

Relative value of different outcomes	The committee agreed that the most important perspectives on information needs are those of the individual and, if appropriate, their family members/carers. Therefore, the committee agreed to restrict this review to studies which qualitatively report the views and experiences of either people living with AMD or their carers. It was also noted that, as people's information needs will be affected by the way care is organised for them, recent studies conducted in the UK would be of particularly high value, as the findings would be much more directly applicable to the context of this guideline.
Trade-off between benefits and harms	The committee discussed the challenges associated with information provided by optometrists before referral for diagnosis. It agreed that a shortage of information could increase fear and anxiety, but the amount of information required varied between people. Too much detailed information at this early stage could lead some people to feel overwhelmed and, as the optometrist's provisional diagnosis does not always reflect the final diagnosis, it could also subject people to unnecessary stress. In addition, the committee reported that optometrists may not feel confident to offer a clearer diagnosis at this stage and may be worried about legal liability if they misdiagnose AMD. Optometrists

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were also perceived to be reluctant to stock information leaflets from eye charities and support services and there was some discussion that the contents of these leaflets might be too specific for people prior to formal diagnosis.

Further discussion focused on the terminology used to explain AMD throughout the diagnosis process. The committee agreed that this was inconsistent and the use of poorly chosen analogies, for example describing AMD as a 'wrinkle at the back of the eye', could lead to confusion and misconceptions by the patient. It was agreed that further research was needed to determine the best choice of terminology and how to describe the condition to people at all stages of the disease and in different healthcare settings. In particular, it wanted to avoid the implication of AMD being a result of 'wear and tear' or overuse, which could lead to unnecessary alterations in people's behaviour to try to conserve their vision.

The committee discussed the need for an increased general awareness of AMD to help provide a context for diagnosis, but this raised the concern that this could increase rather than reduce levels of anxiety for some people with suspected AMD prior to formal diagnosis.

The committee agreed that it is important to tailor the information provided to the individual person. In particular, it stressed the importance of providing specific information for working people with AMD. However it was noted that this population was not covered by the evidence collected in this review (participants' ages were 70–90 years). As a result, the committee made a research recommendation to examine the information needs of this specific subpopulation. The committee agreed that the information also needed to be matched to the stage of disease progression and should be provided at multiple points during the disease course. It discussed who would be best placed to impart this information and, from committee members' experience, agreed that an ECLO (eye clinic liaison officer) would be a good choice, if available. However, due to the lack of AMD-specific evidence in the literature on the benefits of ECLOs, the committee was unable to recommend this directly.

The committee agreed that people with AMD needed to be provided with basic information on the types, causes and frequency of AMD. However, it was concerned that the issue of genetic susceptibility could be confusing and cause increased anxiety if not explained carefully. It discussed the importance of smoking as a cause of AMD and whether further damage could be reduced by smoking cessation (see chapter 6.1 for information on risk factors for AMD).

The committee agreed that people need detailed, accurate information about disease progression and treatment options to allow them to plan for the future and to prevent disappointment associated with unrealistic expectations of recovery.

The committee agreed that people need clear information regarding the purpose of hospital visits, side-effects and the role of vitamins. It noted that there are problems associated with expecting people to monitor changes to their vision and seek help at appropriate times and that this was linked to recommendations made in section 11.2 (self-monitoring for people with AMD).

The committee discussed the need for signposting to point people to other sources of information, advice and support, and agreed that it is important for people to understand the benefits of being registered as sight impaired/severely sight impaired.

The committee discussed the importance of the manner in which the information is conveyed to people by the optometrist before formal diagnosis and by medical and support staff following diagnosis. It referred to section 12.1, and noted that the attitude of staff was a

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	potential barrier to compliance with treatment. Combined with the review evidence presented here, the importance of imparting information to people in a caring and sensitive manner was emphasised. In addition, the committee stressed that the nature of the condition makes it especially important that information is presented in an accessible format that is suitable for the particular person. The committee agreed it was important to emphasise professionals' responsibilities under the NHS Accessible Information Standard, in this regard.
Consideration of health benefits and resource use	The committee agreed that, because information provision should form part of any well organised patient pathway and is already part of routine care, there would not be expected to be any significant resource impact from the implementation of these recommendations.
Quality of evidence	The committee agreed that the evidence presented was in line with their experience, but noted that there were evidence gaps relating to the information needs of younger, working-age people with AMD and the best terminology to describe the type and causes of AMD. To supplement evidence available from published literature, the committee drew on comments made by stakeholders during consultation on the draft guideline (including a survey of 153 people with AMD carried out by the RNIB with specific reference to the draft guideline). With reference to this evidence, it agreed that some themes that had not explicitly emerged in the literature were important issues about which people with AMD would benefit from advice. In particular, multiple stakeholders noted that vision standards for driving were an important topic, and several also suggested that reference should be made to the fairly common complication of Charles Bonnet syndrome – that is, visual hallucinations associated with retinal disease – which many people with AMD may mistake as a psychotic phenomenon if they are not advised about it in advance. The committee discussed the availability of data from studies of general low-vision services but, since these studies were not AMD specific, it was unable to recommend low-vision services as a primary source of information and support for people with AMD.
Other considerations	The committee agreed that the general advice in the NICE guideline on patient experience in the NHS would also be applicable to AMD, and therefore decided to add a cross-reference to this other guideline.

12.2.4 Recommendations

53. Provide people with AMD, and their family members or carers (as appropriate), with information that is:

- available on an ongoing basis
- relevant to the stage of the person's condition
- tailored to the person's needs
- delivered in a caring and sensitive fashion.

Be aware of the obligation to provide accessible information detailed in the NHS Accessible Information Standard. For more guidance on providing information to people and discussing their preferences with them, see the NICE guideline on patient experience in adult NHS services.

54. Provide opportunities to discuss AMD with the person. Topics to cover should include:

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- what AMD is and how common it is
- types of AMD
- causes of AMD
- stopping smoking and other lifestyle advice
- how AMD may progress and possible complications
- the possibility of developing visual hallucinations associated with retinal dysfunction (Charles Bonnet syndrome)
- vision standards for driving
- tests and investigations
- treatment options, including possible benefits and risks
- who to contact for practical and emotional support
- where the person's appointments will take place
- which healthcare professionals will be responsible for the person's care
- expected wait times for consultations, investigations and treatments
- the benefits and entitlements available through certification and registration when sight impaired or severely sight impaired
- when, where and how to seek help with vision changes (see 11.2.5)
- signposting to other sources of information and support

12.2.5 Research recommendations

20. What terminology is clearest and most acceptable to patients to describe suspected or confirmed AMD throughout the pathway?

Why this is important

Being provided with clear information about the condition is important for people who are at risk of developing and/or are diagnosed with AMD, but there was inconsistent and the use of poorly chosen analogies in practice, and this could lead to confusion and misconceptions amongst the patient. Qualitative studies of the choice terminology and how to describe the condition to people at all stages of the disease and in different clinical settings (for instance both primary care and secondary care) would enable to optimisation of people's understanding about AMD and obtaining appropriate supports for people at different stages of the condition.

21. What is the impact of AMD on working people (aged<65 years or in paid/unpaid employment), and what information do they find useful and in what format and when?

Why this is important

The incidence of AMD is known to be higher in aging population (particularly aged between 70-90 years), but it can also affected people in younger age (such as 55 years onward). Little is known about the impact of AMD on this group of population, and what specific information that they consider useful may help them to live with the condition. Qualitative studies of experience living with AMD and information needs for people aged under 65 years would fill the gap in current evidence and would identify their specific needs to optimise support services for them.

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13 Glossary

Abbreviations used in this guideline	
ADL	Activities of daily living
AMD	Age-related macular degeneration
Anti-VEGF	Anti-vascular endothelial growth factor
BCVA	Best-corrected visual acuity
CBT	Cognitive behavioural therapy
CNV	Choroidal neovascularisation
CSCR	Central serous chorioretinopathy
ECLO	Eye clinic liaison officer
ETDRS	Early Treatment Diabetic Retinopathy Study
FFA	Fundus fluorescein angiography
GDS	Geriatric depression scale
ICER	Incremental cost-effectiveness ratio
ICG	Indocyanine green angiography
LogMAR	Logarithm of the minimum angle of resolution
LVR	Low vision rehabilitation
NEI-VFQ	National eye institute-vision function questionnaire
NHB	Net health benefits
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography angiography
PCV	Polypoidal choroidal vasculopathy
PDT	Photodynamic therapy
PED	Pigment epithelial detachment
POMS	Profile of mood states
QALY	Quality-adjusted-life year
RAP	Retinal angiomatous proliferation
RPE	Retinal pigment epithelium
SPC	Summary of product characteristics (for medicines)

Glossary of terms and abbreviations used in this guideline	
Adverse event	Any undesirable experience (sign, symptoms, or other health event) associated with the use of medical products, regardless of severity or hypothesised cause.
Age-related macular degeneration	A condition that is one of common causes of vision impairment in the elderly. The condition is a deterioration or breakdown of eye's macula, causing progressive loss of vision resulting in blurred or no vision in the centre of the visual field.
Amsler chart (grid)	A chart usually consisting of a grid of black lines on a white background. It is used to detect and monitor problems of central vision affecting the retina; for example, in early macular disease, the square edges of the grid may appear distorted.
Antiangiogenic treatment	Treatment to stop or slow the growth of new blood vessels. In ophthalmology, both photodynamic therapy and anti-vascular endothelial growth factor (anti-VEGF) have been used for treating late AMD (wet active).
Bruch's membrane	A layer of connective tissue that separates the RPE from the choroidal circulation. It prevents blood vessels from the choroidal

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Glossary of terms and abbreviations used in this guideline	
	circulation growing into the retina and breaks or deficits in this layer are associated with late AMD (wet)
Charles Bonnet syndrome	Charles Bonnet syndrome is characterised by visual hallucination. This occurs in people with visual impairment and is most common in elderly. People with macular degeneration can experience visual hallucination due to low vision. It is estimated about 1 on 10 people with AMD experiences Charles Bonnet syndrome.
Choroidal neovascularisation	Choroidal neovascularisation involves the growth of new blood vessels that originate from the choroid and grow through a break in the Bruch membrane into the sub-retinal pigment epithelium or sub-retinal space. It can result in a gradual and/or sudden deterioration of central vision.
Central serous chorioretinopathy	Shallow retinal detachment in the area of the macular due to a localised leakage of fluid through the retinal pigment epithelium into the subretinal space. This results in blurred or distorted vision, and mild reduction in visual acuity may persist after the fluid has disappeared.
Cystoid macular oedema	Swelling of the central area of the retina (macula).
Dexamethasone	A synthetic corticosteroid used as anti-inflammatory drugs. It suppresses inflammation by inhibiting multiple inflammatory cytokines resulting in decreased oedema, fibrin deposition, capillary leakage and migration of inflammatory cells. In the USA, it has been approved for the treatment of patients with macular oedema.
Drusen	Drusen are white or yellow deposits, of lipid rich material in Bruch's membrane of the choroid under the retina. They are often associated with macular degeneration, and the presence of drusen increases a person's risk of developing AMD.
Dyschromatopsia	It refers to any acquired loss of colour vision.
Early Treatment Diabetic Retinopathy Study	This acronym represents a standard scale to test visual acuity, which is based on letters of decreasing size on a chart (ETRDS refers to the letters used within the chart).
Eccentric viewing	It is a technique used by people with central vision loss learning to look around the blind spot to see. It involves the process of identifying a person's preferred reading locus for reading using a person's peripheral vision.
Fundoscopy	It is also referred as ophthalmoscopy. It is a test for examining the interior of the eye. Fundoscopy can be used to determine the health the retina. There are two types. The direct fundoscopy enables a fine beam of light to be directed into the eye and at the same time allows the examiner to see the spot where the beam falls inside the eye. Examiner and subject are very close together. In the indirect fundoscopy an image of the inside of the eye is formed between the subject and the examiner; it is this image that the examiner sees. The examiner and subject are almost an arm's length apart.
Fluorescein angiography	It is a technique being used to examine the circulation of the retina and choroid (part of the fundus) using a fluorescent dye. Fluorescein sodium is injected into a vein in the arm, from which it circulates through the systemic circulation. This then allows the retinal circulation to be observed and photographed.
Geographic atrophy	Geographic atrophy refers to an advanced form of dry age-related macular generation characterised by well demarcated patch or patches where the RPE, the photoreceptors and the underlying choroidal blood vessels disappear. It is one of the commonest

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Glossary of terms and abbreviations used in this guideline	
	causes of visual loss from macular degeneration. It tends to progress slowly.
Low vision	People with low vision have visual impairments that cause restriction in their everyday lives and that cannot be corrected by surgery, medicine, or glasses or contact lenses. This definition includes, but is not limited to those who are registered as sight impaired or severely sight impaired. It can include blurred vision, blind spots or tunnel vision.
Low vision service	A low-vision service provides a range of services for people with low vision to enable them to make use of their eyesight to achieve maximum potential.
Metamorphopsia	Metamorphopsia is a type of vision defect, describing an abnormal visual perception in which images distorted. For instance, straight line appear wavy or jagged.
Micropsia	Micropsia is a condition in which objects appear smaller than they really are. It is usually caused either by a stretching of the retina (for example by sub-retinal fluid) or, rarely, by a neurological disorder.
Optical coherence tomography	Optical coherence tomography is a class of optical tomographic techniques that allows high-quality micrometre-resolution images. It is a non-invasive test involves the use light waves to take cross-sectional pictures of a person's retina. OCT has been applied in medical fields for diagnosis. Particularly, in ophthalmology, where OCT allows non-invasive images of the ocular structures.
Photodynamic therapy	Photodynamic therapy is a treatment in which a light-sensitive drug is administered systemically (by intravenous injection) and the treatment target area is illuminated to activate the drug locally. It is used clinically to treat a range of medical conditions such as neovascular age-related macular generation and some types of cancers. In neovascular AMD new vessels grow under the retina distorting vision. Photo-reactive drugs are injected into the patient and irradiated with light as they pass through the neovascular membranes. Activated drugs can emit free radicals that destroy the blood vessel.
Pigment epithelial detachment	Pigment epithelial detachment is a pathological process in which the retinal pigment epithelium separates from the underlying Bruch's due to the presence of blood, serous exudate, drusen, or a neovascular membrane. AMD and central serous chorioretinopathy (CSCR) are common causes of PED.
Polypoidal choroidal vasculopathy	Polypoidal choroidal vasculopathy is characterised as choroidal vascular abnormalities by the presence of aneurysmal polypoidal lesion in the choroidal vasculature. It is a phenotype of neovascular AMD. The aneurysmal dilations, also refers as polys, may be detected at subfoveal, juxtafoveal, extrafoveal, peripapillary or peripheral regions. These polyps is seen as reddish-orange subretinal nodules during ophthalmoscopic examination.
Retinal angiomatous proliferation	Retinal angiomatous proliferation is a subtype of late AMD (wet) where the abnormal blood vessels originate from the retinal circulation and then extend outwards into the sub-retinal and sub-RPE spaces. This is in contrast to the other types of late AMD (wet) where the abnormal blood vessels arise from the choroidal circulation and then extend inwards to the sub-retinal and sub RPE spaces
Retinal pigment epithelium	Retinal pigment epithelium is the pigmented cell layer lying outside the neurosensory retina and, with Bruch's membrane,

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Glossary of terms and abbreviations used in this guideline	
	separates the retina from the choroidal circulation. It is also the site of the outer blood-retinal barrier.
Teleophthalmology	Teleophthalmology is a part of telemedicine that involves digital medical equipment or technology to deliver eye care or service.
Triamcinolone acetonide	A synthetic corticosteroid and a broad-spectrum antibiotic, and it is used typically in the treatment of inflammatory conditions.
Visual acuity	Visual acuity is used to measure the clarity or sharpness of a person's vision, and describe how well the person see small details with one's central vision. It is a measure of the smallest object that the eye can resolve under optimal conditions. It is measured using the Snellen or log MAR scales (charts), which consists of a number of rows of letters that get smaller as the person reads down the chart.

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