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Commissioning Guidance

Age Related Macular Degeneration Services: Evidence Base

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1. Abbreviations and Glossary

Abbreviation	Explanation
AHP	Allied Health Professional
AMD	Age-related macular degeneration
Anti-VEGF	Drugs that block the action of Vascular Endothelial Growth Factor. They are effective in the treatment of choroidal neovascularisation
AREDS	Age Related Eye Disease study
CBS	Charles Bonnet Syndrome
CoO	College of Optometrists
COS	Community Ophthalmology Services Commissioned locally by ICBs. These may involve the assessment and management of patients whose eye conditions are at low-risk of deterioration who are either referred by primary care for further assessment or discharged from secondary care for monitoring (Primary Eye Care, Community Ophthalmology and General Ophthalmology 2019)
CFP	Colour Fundus Photo
CI	Credible Interval
CVI	Certificate of Vision Impairment
DICOM	Digital and Imaging Communications in Medicine - the international standard for medical images and related information
DNA	Did Not Attend
ECLO	Eye Clinic Liaison Officer or Eye Care Liaison Officer
Endophthalmitis	Infection that involves the internal structures of the eye. It usually poses a serious threat to the visual function of the eye and is a rare complication of intravitreal injection.
eRS	Electronic Referral System
ETDRS	Early Treatment Diabetic Retinopathy Study
FFA	Fundus Fluorescein Angiography
GA	Geographic Atrophy
GOS	General Ophthalmic Services
HCP	Health Care Professional. In this document, the term HCP refers to nurses, optometrists, and orthoptists. Each profession is regulated by a different

	regulatory body (respectively the Nursing and Midwifery Council, General Optical Council and Health Care Professions Council)
HES	Hospital Eye Service
ICB	Integrated Care Boards
ICG	Indocyanine Green Angiography
IOI	Intraocular Inflammation
LOCSU	Local Optical Committee Support Unit
LVA	Low Vision Assessment
MNV	Macular neovascularisation
MDT	Multidisciplinary Team
MSVI	Moderate to Severe Visual Impairment (presenting visual acuity <6/18 to 3/60 inclusive)
nAMD	Neovascular or "wet" AMD
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NPSA	National Patient Safety Agency
OCT	Optical Coherence Tomography
OCTA	Optical Coherence Tomography Angiography
OMP	Ophthalmic Medical Practitioner
OPT	Ophthalmic Practitioner Training
PAS	Patient Administration System
PCV	Polypoidal Choroidal Vasculopathy
PDT	Photodynamic therapy
PED	Pigment Epithelial Detachment
Primary Care	First contact eye care is mainly delivered by optometrists and opticians in primary care. GPs and pharmacists can provide non-specialist eye care including initial assessment and treatment of common low-risk conditions not requiring specialist expertise or equipment (e.g., conjunctivitis), but first contact eye care is a small part of their routine workload. (Primary Eye Care, Community Ophthalmology and General Ophthalmology 2019)
RAP	Retinal angiomatous proliferation
RPE	Retinal pigment epithelium
SAS Doctors	Staff and Associate Specialist Doctors
SD	Standard Deviation

SDD	Subretinal Drusenoid Deposits
SI	Sight Impairment
SMH	Sub-Macular Haemorrhage
SSI	Severe Sight Impairment (presenting visual acuity < 3/60)
TREX or T&E	Treat and Extend
UI	Uncertainty interval
VA	Visual Acuity

2. Introduction

The macula is the centre of the retina that is responsible for high quality central vision. Age related macular degeneration (AMD) is a chronic progressive degenerative disease of the macula typically affecting people over the age of 50 years. There are two types of advanced forms of the disease, geographic atrophy and neovascular AMD. Whilst geographic atrophy is a slowly deteriorating condition, exudation from neovascular AMD (wet AMD) usually presents acutely and needs both urgent and long-term treatment. These advanced forms of AMD may co-exist.

Advanced AMD is the most common cause of visual impairment in the older population significantly affecting their quality of life and independence. Other than the cost incurred by social services, the cost of providing care for advanced forms of AMD is very high due to the cost of the drugs and the service provision to monitor and treat these conditions over several years. Although the treatment of geographic atrophy is not available, the treatment burden of this condition is anticipated to be similar or higher than for neovascular AMD. In addition, treatment for exudative neovascular AMD must be initiated urgently, and so fast-track services need to be implemented to diagnose and treat this condition promptly. The demand for this service is projected to rise as the ageing population increases, highlighting the need to continually plan the capacity to meet the growing need. New and existing drugs for neovascular AMD are being evaluated to reduce treatment burden, whilst ensuring cost effectiveness and optimal outcomes. As new drugs are anticipated for the management of geographic atrophy, further needs assessments are required to incorporate this service into current intravitreal injection and monitoring services.

People with both forms of advanced AMD require low visual aids, counselling on coping with their vision, advice on available support and have associated conditions and risk of falls that may require treatment. Most patients with AMD are elderly, and many have other chronic diseases and mobility issues. Therefore, transport needs for these patients should be considered, and services should be readily accessible in terms of location, parking, public transport, and hours of opening. Stable treated AMD patients may be evaluated in the community by optometrists or in diagnostic hubs linked to teleophthalmology services provided robust referral pathways for prompt treatment is incorporated into these services as current audits suggest that 25-30% of presumed stable patients show recurrence on OCT within the first year. Psychological counselling regarding the loss of vision is also required. Eye Clinic Liaison Officers (ECLOs) are essential throughout a patient journey and a considerable proportion of affected individuals need the help of family/friends to attend appointments. Timely and effective referral/signposting to patient support organisations and early referral to low vision is required.

A patient focused approach should be the overarching principle when designing local pathways. New ways of delivering care need to be discussed with patients and patient choice offered. In some areas, a move to a single point access for multiple referral routes is being evaluated to benefit the patient, NHS, and wider society. A transformative national strategy for eye care is being scoped. Meanwhile, several re-design and transformation plans are already being developed and best practice and lessons learned will be shared. It is important that duplication of efforts to transform are avoided.

2.1 Purpose of this guidance

This guidance is intended for use by commissioners/ integrated care boards, providers, social care, and users of the AMD services, including their families and carers.

The guidance sets out the principles and recommended minimum standards of care for AMD to decrease variations of care across AMD services in England and Wales. This is based on best practice, the latest available evidence and is in line with published NICE guidance including NG 82 and associated Technology Appraisals[1].

The guidance provides information that can:

- support the current and future capacity planning of AMD services.
- enable the review of services, treatment options and patient pathways to meet the changing needs of the population with due consideration for cost-effectiveness, clinical evidence, and best practice research.
- be adapted locally based on available resource, existing infrastructure, and service demands.

The introduction of Integrated Care Systems with health and care services working closer together will enable AMD services to work closely with system partners including charitable organisations and primary eye care / optometry community services. Cost improvement opportunities described in this document can free up valuable resource which can in turn be reinvested back into services to improve access, quality standards and ensure a patient centred approach to care. Elective NHS services including AMD treatments are also being commissioned and provided by the independent sector. The guidance in this document is applicable to all types of providers.

2.2 Evidence base for this guidance

The guidance follows the RCOphth guidance development process and is based on best available evidence obtained from systematic review of the literature (see appendix A) and is compliant with the National Institute for Health and Care Excellence (NICE) Clinical Guideline on AMD NG82 dated 23-01-2018[1]. NICE quality standard QS180 (standards 3 and 4) dated February 2019 has also been considered in compiling this statement[2]. The commissioners should refer to the cost-effective analysis in NICE NG82 Appendix J to address the cost-effectiveness of service provisions recommended in this guidance. This should consider therapy choices and pathway redesign. Evidence from research published post-NICE Clinical Guideline on AMD NG82 in 2018 are also considered. Practice will improve, evidence will emerge, and innovative technology will be developed. Therefore, this guidance will have a cyclical review to reflect continuously evolving towards current best practice.

3. Background

There are several classification systems that describe the disease progression in AMD. The staging of severity of AMD is important because visual impairment increases with severity of AMD. The NICE guidance NG82 dated 23-01-2018 is the most recent classification of AMD. However, the frequently used terminologies to describe the various stages are based on previous classifications. Table 1 describes the NICE criteria for classification of AMD progression as set out in NICE, *Age-related macular degeneration NICE guideline* [NG82]

(2018): 25-27. It is compared to the more commonly used terminology used to describe the changes.

Table 1: NICE guidelines-based classification of Age related macular degeneration[1]

AMD Classification in NICE Guidance	Definition in NICE Guidance	Frequently Used Terminology
Normal Eyes	No signs of age-related macular degeneration (AMD) Small ('hard') drusen (less than 63 micrometres) only	No AMD
Early AMD	Low risk of progression: • medium drusen (63 micrometres or more and less than 125micrometres) or pigmentary abnormalities Medium risk of progression: • large drusen (125micrometres or more) or • reticular pseudodrusen (subretinal drusenoid deposits or • medium drusen with pigmentary abnormalities High risk of progression: • large drusen (125 micrometres or more) with pigmentary abnormalities or • reticular pseudodrusen (subretinal drusenoid deposits 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	Early AMD or Age-related maculopathy Intermediate AMD
Late AMD (indeterminate)	Retinal pigment epithelial (RPE) degeneration and dysfunction (presence of degenerative AMD changes with subretinal or intraretinal fluid in the absence of detectable neovascularisation) Serous pigment epithelial detachment (PED) without neovascularisation	

Table 1: NICE guidelines-based classification of Age related macular degeneration continued[1]

AMD Classification in NICE Guidance	Definition in NICE Guidance	Frequently Used Terminology
Late AMD (wet active)	Classic choroidal neovascularisation (CNV) – Type 2 Occult (fibrovascular PED & serous PED with neovascularisation – Type 1 Mixed (predominantly or minimally classic CNV with occult CNV) Retinal angiomatous proliferation (RAP) – Type 3 Polypoidal choroidal vasculopathy (PCV)	Neovascular AMD (nAMD) or wet AMD
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	Advanced dry AMD / Geographic atrophy
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)	Advanced wet AMD/ Disciform scar
Do not refer to late AMD (wet inactive) as 'dry AMD'.		

4. Epidemiology of AMD

4.1 Global prevalence of AMD

The global prevalence of AMD is projected to increase from an estimated 196 million (95% CrI, 140-261) in 2020 to 288 million (95% CrI, 205-399) in 2040[3]. Between the ages of 45-85 years, the worldwide prevalence is any AMD 8.7% [95% credible interval (CrI), 4.3–17.4], early AMD 8.0% (95% CrI, 4.0–15.5), and late AMD 0.4% (95% CrI, 0.2-0.8)[4-6]. The prevalence of AMD increases with age. Typical AMD disease characteristics are more prevalent in people of European ancestry with estimated prevalence of early or intermediate AMD being 25.3% and advanced AMD 2.4% in people aged 60 years or older. [7] The prevalence of AMD is less in Asians and Africans but the rates of polypoidal vasculopathy is higher in these ethnic groups. There is no gender predilection for AMD.

4.2 Global prevalence of visual impairment due to AMD

AMD is a common cause of visual impairment in the elderly. Globally, in 2010, the total number of persons with severe sight impairment (SSI; historically termed blind registered, presenting visual acuity < 3/60) was 32.4 million. A further 191 million people had moderate to severe vision impairment (MSVI; presenting visual acuity < 6/18 to 3/60 inclusive). Of these, 2.1 million [95% uncertainty interval (UI), 1.9–2.7] were blind/SSI and 6.0 million (95% UI, 5.2–8.1) MSVI due to macular disease [8-11]. With longer life expectancy and increase in population age universally, early diagnosis and timely management of treatable AMD is of utmost priority to decrease the proportion of people with avoidable irreversible visual loss.

4.3 Prevalence of AMD in the UK

In 2012, it was estimated that there were 513K cases of late AMD, 276,000 cases of geographic atrophy (GA), and 263,000 cases of neovascular AMD (nAMD) in the UK. When these figures are applied to updated 5 yearly population estimates for the UK, published by the United Nations for males and females combined, for years 2020 and 2050, the prevalence in 2020 is estimated to be 645,000 cases of late AMD, 354,000 cases of GA and 339,000 cases of nAMD. In 2050, these figures are projected to increase to 1.3 million late AMD, 720,000 GA and 683,000 nAMD (Personal communication with Dr Alicja R Rudnicka and Professor Christopher G Owen)[12, 13].

4.4 Prevalence of visual impairment in the UK due to AMD

In 2013, it was estimated that 1.93 (95% CI 1.58 to 2.31) million people had MSVI and blindness in the UK, representing 3.0% (2.5% to 3.6%) of the population[14]. This included about 255,000 (208,100 to 304,800), or 13.2% who are severely sight impaired (blind). From 2013 to 2050, sight loss and blindness from AMD is projected to increase from 23.1% to 29.7%, more than doubling from 445,809 (363,900 to 532,800) people to 1.23 (1.01 to 1.47) million people. Analysis of certificates of visual impairment (CVI) show that approximately 50% of people registered SI or SSI are due to degeneration of the macula and posterior pole[14].

4.5 Incidence of AMD in the UK

Based on the estimations made in 2012 from the 2007-2009 UK population data, the annual incidence per year of new cases of late AMD was 71 000, equating to 4.1 cases per 1000 women and 2.6 per 1000 men. The incidence of GA was 44,000, that is 2.4 per 1000 women and 1.7 per 1000 men. For nAMD, these figures were 40,000 that equates to 2.3 per 1000 women and 1.4 per 1000 men[12]. When these figures are applied to updated 5 yearly

population estimates for the UK, published by the United Nations for males and females combined, for years 2020 and 2050, the incidence in 2020 is estimated to be 83,000 cases of late AMD, 51,000 cases of GA and 46,000 cases of nAMD. In 2050, these figures are projected to increase to 157,000 late AMD, 97,000 GA and 88,000 nAMD (Personal communication with Dr Alicja R Rudnicka and Professor Christopher G Owen)[12,13]. Increasing age, white ethnicity and smokers are risk factors that affect the incidence of AMD.

4.6 Cost of visual impairment and treatment

The Time to Focus report by Fight for Sight in 2020 revealed that the annual societal costs of AMD related visual impairment is £2.6 billion, of which 47% of costs fall within the health and social care sector. The estimated costs include £1.2billion on healthcare; £0.036 billion on devices; £0.14 billion on productivity; £0.002 billion on welfare; £0.5 billion on informal care and £0.69 billion on intangible costs. It was also estimated that more than 11,000 new cases of late AMD already have at least moderate visual impairment. Overall, the total lifetime costs for this cohort were estimated at almost £818 million with an average cost per patient of £73,350[15].

Total lifetime costs of the cohort of cases with late AMD in the context of the NHS budget over the same period and growth in spending needs to be factored in service provision. Costs have significantly increased since the introduction of the new nAMD treatments: since receiving funding direction from NICE in 2008/09, new nAMD drugs costs have increased from 0% to 2.74% of the total NHS drugs budget and by 2016/17 both featured in the top five highest cost items in the NHS drugs budget (across both hospital and primary care). Over the same period (since 2009/10), the NHS budget has received year on year funding increases of approximately 1.2%. New intravitreal therapies for GA are anticipated. This therapy and treatment burden need to be considered in planning the next NHS budget.

5. Risk factors for development and progression of AMD

This includes all stages of AMD.

5.1 Non-modifiable risk factors	
Increasing drusen area and volume	Patients with a drusen volume over 0.03 mm3 in the 3mm circle of the macula centred at the fovea has a greater than 4-fold increased risk for developing late AMD compared with those with lower drusen volumes [16,17].
Subretinal Drusenoid Deposits (SDD)	Subretinal Drusenoid Deposits (also known as reticular pseudodrusen) are an independent risk factor for AMD development progression [18,19].
Genetics	Although 52 genetic variants have been identified for AMD, almost 15% of patients with AMD have no risk variants [20,21]. Additionally, no genetic score has been defined to assess risk for AMD [22].
Fellow eye of wet AMD eyes	There is a 10% per year risk of developing wet AMD in the fellow eyes in people with unilateral wet AMD [23,24]. The risk if higher in eyes with non-exudative macular neovascularisation.

5.2 Modifiable risk factors for progression to more advance forms of AMD	
Smoking history	Smoking is an established strong modifiable risk factor for AMD [25]. Being a current smoker quadruples the risk of progression to late AMD [26,27]. A synergistic effect has been documented between smoking and genetic factors [28]. Current smokers develop late wet AMD at an average of 5.5 years younger than those who never smoked and 4.4. years younger than past smokers [29]. The risk of AMD goes back to that of a non-smoker wth 10 years of quitting, therefore smoking cessation should be recommended to these patients [30].
Body Mass Index	A higher body mass index (BMI) (>30) increases the risk for progression to advanced AMD (RR 2.35). A wider waist circumference is associated with a two-fold increased risk for progression[31]. There is a direct association with higher BMI leading to higher risk of AMD[32].
Nutrition	A diet low in omega-3 and -6 fatty acids, antioxidant vitamins, carotenoids and minerals are a risk factors for AMD. Adherence to a Mediterranean diet is associated with a 41% reduced risk of incident late AMD. The effect is due to the increased consumption of fruits and diet rich in antioxidants that aid in prevention of AMD[33]. A diet of 200 grams per day of vegetables, fruit two times per day, and fish two times per week is associated with a significantly reduced risk of AMD[34]. The original Age-Related Eye Disease Study (AREDS) showed that supplements containing vitamin C, vitamin E, beta carotene, and zinc reduced the 5-year likelihood of developing late AMD by an estimated 25% in at risk individuals[35]. These individuals were those with bilateral large drusen or fellow eyes with large drusen with late AMD in the first eye. The primary analysis of Age-Related Eye Disease Study 2 (AREDS 2) showed no additional value of adding lutein and Zeaxanthin, omega-3 long-chain polyunsaturated acid or the combination on the progression to advanced AMD or changes in visual acuity compared with placebo. However, secondary exploratory analyses suggest that due to the risk in smokers lutein/zeaxanthin is more appropriate than beta carotene in the AREDS supplementation[36]. These supplements may be obtained over the counter; and is an item not routinely prescribed in primary care (NHS England, *Items which should not be routinely prescribed in primary care: Guidance for CCGs* (2019).
Sunlight exposure	Meta-analysis on the association between sunlight exposure and AMD indicated no relationship between exposure to sunlight and increased risk of AMD[37].

6. Associations of AMD

Systemic comorbidities in patients with AMD may present a challenge for on-going care of this long-term condition due to difficulties in accessing care and maintaining compliance. Key co-morbidities include hearing loss, poorer cognitive function, established dementia, Alzheimer's disease, depression, and anxiety related to both the diagnosis and therapy for AMD[38,39].

Charles Bonnet syndrome (CBS) is a clinically significant effect of AMD that cause a negative outcome in a third of people with visual impairment and can be of prolonged duration. CBS is characterised by the occurrence of chronic visual hallucinations, not attributable to other neurologic causes such as Alzheimer's disease, or use of drugs and the patients are aware of the unreality of these images[40]. The prevalence of CBS in nAMD patients ranges from 11% to as high as 40% and mainly affects older individuals with poor visual acuity[41,42]. It is useful to make this condition known to all patients with visual impairment. Misdiagnosis in patients with mental health issues is also a concern.

7. Diagnostic modalities of AMD

7.1 Clinical Examination

Clinical examination should include recording symptoms of AMD, smoking and family history, visual acuity assessment, fundoscopy, and examination of both eyes. Visual acuity should ideally be measured using a LogMAR chart and recorded in Early Treatment Diabetic Retinopathy Study (ETDRS) letters for all cases of AMD. Treatment response must be monitored using ETDRS letters. Snellen visual acuity is acceptable if ETDRS is not available during the first consultation, however conversion of Snellen visual acuity to LogMar should be avoided due to high level of inaccuracy[43].

7.2 Optical Coherence Tomography (OCT)

OCT is the first diagnostic test for patients with AMD[44]. OCT is a non-invasive test that provides information on the structure of the retina. OCT has high sensitivity and specificity in detecting late AMD. In the indeterminate form of late AMD, it may identify subretinal or intraretinal fluid or serous pigment epithelial detachment (PED) without detectable macular neovascularisation (MNV). These cases require regular monitoring with multimodal imaging as they are at increased risk of developing nAMD. OCT should be acquired in both eyes. Fellow eyes of unilateral nAMD patients under treatment are at risk of conversion to nAMD and the progression of disease is best captured on OCT as patients may be asymptomatic at point of conversion. OCT is also the most sensitive tool to assess response to treatment including reactivation of nAMD. Although OCT may be used to diagnose GA, monitoring change in GA enlargement on OCT needs further research.

7.3 Optical coherence tomography –angiography (OCT-A)

OCT-A has recently become more widely accepted as a rapid, sensitive, and non-invasive imaging test used for detection and management of nAMD[45]. When the structural OCT shows features suggestive of the nAMD, evidence of macular neovascularisation on OCT-A is considered adequate evidence to initiate therapy. However, the technique requires high specification computers for data storage, analysis, and expert interpretation of scans due to presence of artefacts (such as motion, blink, and projection). A negative OCT-A scan

however does not exclude the diagnosis of MNV. In such cases, when the structural OCT suggests the nAMD, but OCT-A imaging does not confirm the presence of MNV, invasive tests may need to be performed to confirm nAMD. Fundus fluorescein angiography (FFA) is the recommended invasive test but indocyanine angiography (ICG) may add value to the interpretation especially when there is a suspicion of polypoidal choroidal vasculopathy[46,47].

7.4 Fundus Fluorescein Angiography (FFA)

Traditionally the diagnosis of nAMD was made using FFA. With the advent of structural OCT and OCT-A, FFA is less widely used for clinical diagnosis at present. However, FFA is a useful tool that aids in accurate diagnosis in indeterminate cases. FFA in combination with ICG is indicated specifically in cases with equivocal scans on OCT-A, partial or poor responders to anti-VEGF therapy and in patients where any other retinal signs might be confounders.

7.5 Indocyanine green angiography (ICGA)

Further confirmation of diagnosis with ICGA may be required at baseline or at some point in the pathway to confirm the diagnosis of polypoidal vasculopathy PCV), retinal angiomatous proliferation (RAP) and to re-evaluate the diagnosis mainly in poor or non-responders. For this procedure there should be a senior ophthalmologist/consultant guiding the decision. Centres that do not have ICGA facility may need to refer to other centres with this facility.

7.6 Fundus autofluorescence (FAF)

Diagnosis and monitoring enlargement of GA is best defined by FAF. Average growth rate of GA on FAF is 1.75mm^2/year (95% CI 1.46 to 2.02). Fast-progressors are medium sized GA, multifocal GA, GA in eyes with SDD, non-foveal GA.

7.7 Recommendations

1. The order of examination is shown above and most diagnosis of nAMD can be made by clinical examination, OCT and OCT-A.
2. OCT can be employed as sole investigation to detect nAMD in rare scenarios:
    a. when there is no ready access to confirmatory tests such as OCTA or FFA to avoid delay in receiving first treatment within 2 weeks of diagnosis; **or**
    b. due to patient factors such as difficulty in obtaining informed consent, allergy or contraindication to fluorescein dye or inconclusive OCTA and/or FFA.
3. FFA in combination with ICG is indicated specifically in cases with equivocal scans on OCT-A, partial or poor responders to anti-VEGF therapy and in patients where any other retinal signs might be confounders.
4. Centres that do not have ICG facility may need to refer to those with services.

8. Care Pathway

8. 1 General Recommendations for all AMD patients

1. Advice on smoking cessation services and the information must be made available to patients by local services.
2. Nutrition and supplements – A healthy diet, rich in fresh fruit, vegetables, eggs, and oily fish is recommended. Licensed formulations of multivitamin supplements containing the AREDS2 formulation are not available on prescription within the NHS. Patients may choose to source these over-the-

counter supplements independently. The original AREDS formulation consisting of vitamins C, E, beta-carotene, and zinc reduced the 5-year risk of developing late AMD in persons at risk by an estimated 25%. These include those with either bilateral large drusen or large drusen in one eye and late AMD in the fellow eye. The AREDS 2 study corroborated these findings and recommended switching beta-carotene to lutein and zeaxanthin in former smokers.

3. Genetic screening is not recommended[48,49].
4. Need for low vision aids should be assessed in those who meet the definition of low vision at any point throughout the patient journey in primary or secondary care. The definition of 'low vision' applies when a person's vision affects their daily lives and cannot be improved with spectacles or contact lenses. Referral to low vision services is recommended. Timely and effective referral/signposting to patient support organisations and early referral to low vision is recommended.
5. Prescription for health –All eye care professionals including ophthalmologists, ECLO, ophthalmic nurses, optometrists, dispensing opticians, and GPs support is required to promote health-seeking behaviour, physical activity, and signposting to other services where considerable range of support is available from the third sector. Social prescribing is recommended.
6. Screening of fellow eyes - Monitoring of fellow eyes with 4-monthly OCT should be done while the affected eye is undergoing treatment or is being monitored (NICE Quality Standard QS180)[2].
7. Whilst patients are undergoing treatment or are being monitored, continued attendance at their regular optometrist should be encouraged. This allows early identification of co-morbidities and correction of refractive errors.
8. Information on natural history and risk factors should be provided to patients (please see section 5 for some examples).
9. Written information leaflets either locally developed or sourced from national organisations such as RCOphth, CoO or patient support charities are recommended. Both information and support are provided by third sector. In signposting patients to support outside the clinic, wherever in the pathway this occurs or whoever does it, it is important to make sure that the signposting is effective. In a recent Macular Society survey only 17% of patients had recall of being signposted to support organisations. Referral to support services should be made at more than one point in the pathway and by all staff involved in the patient pathway need to be alert to the facts that the patient might not have been signposted or have not acted on the previous signposting.
10. Information about psychological counselling services should be made available to those who need it, especially support from ECLOs in all eye clinics. There is evidence that ECLO services contribute to better outcomes for patients but also improve the efficiency of clinics themselves[50]. ECLO services should be commissioned for every clinic. Where this is not done, commissioners need to be clear who will be providing these essential services, for example:

    - Provision of emotional support for the patient and family
    - Rapid referral to counselling or to medical care for depression/anxiety
    - Early falls intervention
    - Consistent and timely referral for CVI
    - Timely referral to low vision support

- Signposting to services outside the clinic such as further information and advice, peer support, free services provided by third sector organisations.

11. When patients are discharged to primary care for ongoing monitoring it is essential that they are discharged with a report of the last findings at discharge, thorough communication between practitioners is essential to ensure patients receive safe and appropriate care.

8.2 Early AMD

The population with early AMD at any risk of progression may be diagnosed and managed by within the core skills of primary care optometrists working in the community in enhanced primary eye care where these have been commissioned locally as part of their routine practice. As minimal pre-requisites, diagnosis should be based on history, symptoms, visual acuity assessment and fundus assessment. OCT can be helpful if available. In suspected cases of nAMD, the patients must be referred to secondary eye care if suspicion is high. If diagnosis is uncertain in an eye with suspected nAMD, the patient can be referred to primary care/community eye services (LOCSU) or diagnostic hubs with OCT facilities within one day. Discussion with HES/HES virtual review of images may be required to determine action to be taken.

8.2.1 Recommendations for early AMD

1. Do not refer to secondary care when the diagnosis is confirmed as early AMD.
2. If confirmed as early AMD within secondary care, patients can be discharged and advised to have regular sight tests with their primary care optometrist (see section 11.1). General ophthalmic services (GOS) funds sight tests whenever clinically necessary (although. usually on a one- or two-year cycle depending on the age and risk factors of the patient). It is imperative therefore that the primary care optometrist is kept updated of the diagnosis and management. This will allow for improved referrals and lower likelihood of unnecessary re-referrals.
3. Self-monitoring with Amsler chart is often recommended but has very low sensitivity. Patients need to report if they notice distortion, sudden drop in vision or scotoma in central visual field. However, the diagnostic accuracy of Amsler chart or self-reported change in visual function is inferior to OCT screening. Any move towards routine OCT monitoring would require additional infrastructure and resources. However, it is the most accurate monitoring test. For example, in Wales, there is already a pathway for the assessment of sudden change in vision. Many optical practices already have OCTs, and health boards are moving to either remote triage (Consultant Connect) or Optometric Diagnostic and Treatment Centres type assessment centres (Newport Friars Walk). None of the visual function tests are as sensitive as OCT.
4. Subthreshold nanosecond laser is not recommended for early AMD.
5. Novel approaches referred to as “photobiomodulation” have reported some benefit that at the time of writing requires further evaluation.
6. General recommendations for AMD patients apply (see section 8.1).

8.3 Late dry AMD (Geographic Atrophy)

Currently, there are no treatment options for this condition. However, new treatments for GA are anticipated.

8.3.1 Recommendations for Late dry AMD

1. General recommendations for AMD patients apply (see section 8.1).
2. If patients with late dry AMD develop nAMD (wet active), they should be treated as late nAMD (wet active) unless there is no potential for visual improvement (see section 8.4.8).
3. Depending on the visual acuity of both eyes, consider refraction, low visual aids or CVI and providing information on DVLA standards for driving eligibility.
4. Ophthalmic nursing support, trained health care professionals (HCP) and ECLO services are highly recommended as they play a useful, key role in terms of supporting, providing education, and making appropriate MDT and/or third sector referrals for these patients.
5. Optometrists and Dispensing Opticians in primary care practice are also able provide these support services where these are commissioned locally.
6. Considerable support is provided by third sector and cover both visual and psychological challenges faced by individuals with this condition including those with Charles Bonnet Syndrome.
7. These patients may also be offered any clinical research on new treatments for late dry AMD that are run in hospital eye service (HES). Clinical research into new treatments for late dry AMD is needed. Clinical trials to follow due process and adhere to local policies.
8. In anticipation of new treatment for GA, identifying fast progressors may be useful.

8.4 Late wet AMD (neovascular AMD /nAMD)

8.4.1 Population to whom care pathway applies

This population is defined as the group of patients with nAMD in one or both eyes who will be at risk of rapid decline in vision in the affected eye, if not treated promptly and efficiently. Early diagnosis, prompt referral and protocol-based treatment help to stabilise visual function in many cases. However, the main issue faced by providers is a lack of adequate capacity in the face of increasing numbers of affected patients (due to increasing age of the population) who need prompt initiation of treatment and ongoing therapy over several years. For commissioners, the increasing cost of ongoing therapy is a growing concern.

8.4.2 Referral from initial referring source

Patient suspected with nAMD must be directly referred within 1 working day to an NHS commissioned specialist AMD service, if suspicion is high. The specialist AMD service needs to be under the oversight of a consultant ophthalmologist specialised in medical retina beyond core-training and is actively engaged in the assessment, diagnosis, and treatment of patients with medical retina diseases. If diagnosis is uncertain in an eye with suspected nAMD, the patient can be referred to primary care/community eye service or diagnostic hub with OCT facilities within one day. Discussion with HES/HES virtual review of images may be required to determine action to be taken[1]. Whichever route is followed the time from suspicion to treatment must be no longer than two weeks. There needs to be a dedicated

robust rapid access referral system, either via direct referral to the HES (face to face or virtual clinics) or via a referral refinement system through primary care optometrists (optometrist decision maker or virtual opinion by HES on the optometrist collected data may be an option).

For triage of possible nAMD referrals, it is highly desirable for HES medical retina team to be able to review a complete OCT and colour photo for both eyes at the point of referral for possible nAMD (with a DICOM compatible OCT file attached to the referral). Services should aim to develop such an approach by electronic referral directly from the community optometrists to the hospital eye service. In some areas, a single point of access for such referrals are commissioned to streamline the process and to avoid delays. This means that people who do have signs of nAMD can be directed straight to one-stop treatment clinics if appropriate. Moreover, remote opinions on the OCT scans can then be given, which could avoid many unnecessary repeat OCT scans and hospital visits for patients. It is anticipated that a high proportion such referrals would be dealt with by remote opinion and feedback to the referring optometrist and patient based on the OCT scans and colour photos, without the patient needing to visit the hospital eye service as well. This will also provide educational opportunities for the community optometrists. The software systems should ideally be developed to link into the hospital administrative PAS systems and any ophthalmic electronic patient record system in use, and that a full record of any remote clinical opinions, feedback, and OCT scans should be stored by the HES.

To allow equity of access to OCT scans in the community for all patients, it would be anticipated that a fee for such referrals to include the full DICOM compatible OCT files should be given. That fee would be locally negotiated with the ICB. At present, in many places, OCTs are only performed in community optometric practices if the patient can pay the practice for this themselves. Setting up a contracting process for the optometrists to receive timely payment for that activity would be a very important factor in the success of such an approach. Please refer to the standard clinical specification provides for a Community Minor and Urgent Eye Care Service (LOCSU and the Clinical Council for Eye Health Commissioning (CCEHC)).

The principles around enhancing joint working and better communication between community optometry and the HES should involve the potential for two-way communication of the full OCT images, colour photos and clinical information.

The delivery of more specialised eye health services by, or in partnership with community optometry will increase patient choice and improve access in terms of location and time with many community optometrists offering extended days and 7-day services. Delivering services in a community setting will help some patients to normalise the management of their eye health issues and participate in self-care and proactive monitoring and management during their regular activities in the community. The shared care model and integrated pathways will also support improved collaboration between primary care, community optometry and specialist services.

Shared training and development will result in improvements in the quality of referrals, discharges to primary eye care, shared care, and patient outcomes.

8.4.3 Sources of referral

1. Primary care Optometrists refer directly to the commissioned rapid access clinics.
2. As a minimum referral, letters should include history and symptoms, visual acuity and fundoscopy findings. It is recommended that a DICOM compatible OCT file is attached to the referral to reduce false positive referrals and for prompt treatment of nAMD. However, the ophthalmology and primary eye care sectors have only recently begun to seek to move towards the adoption of DICOM standards for OCT so this recommendation will take some years to implement. This is compounded by the ongoing lack of NHS connectivity between primary eye care, primary medical care, and hospital eye services.
3. Referral from GP should have history and symptoms indicating a suspicion of nAMD as a minimum. Optional referral to optometrists may be made first for diagnostic confirmation of nAMD prior to referral to rapid access clinic but this should not delay treatment.
4. Self-referral to eye casualty: patients may notice distortion or central visual impairment and these patients should be fast-tracked for OCT evaluation to rule out nAMD.
5. Referral from diabetic retinopathy services should have minimum standards of colour fundus photograph findings and visual acuity record.
6. Referral may also be from other ophthalmologists and emergency services.
7. Telemedicine and virtual retinal clinics or other non-medical retinal clinics run in HES may diagnose nAMD by reviewing visual acuity, OCT +/-colour fundus photograph. Timely referral of these patients within 1 working day is required for prompt evaluation and treatment.
8. Monitoring of second eye must be done at all visits while the first eye is being treated or monitored by OCT. Asymptomatic fellow eyes with active disease defined as new macular haemorrhage and/or OCT features of nAMD should be referred for treatment.

8.4.4 Method of referral

1. Referral methods may include a dedicated phone line for urgent referrals, or a secure email service approved for information transfer of clinical information. If the option is available and compatible with local rapid access services, eRS helps optimise dialogue and feedback. Images may also be sent by email however a single OCT scan as part of an imaging dataset may not be adequate to prioritise timely review. It is recommended that a DICOM compatible OCT file is attached to the referral where this is possible.

8.4.5 Booking of referrals in HES

1. Dedicated referral route – a fast track or rapid access assessment service should be available for these patients.
2. Direct booking by administrative team into the Rapid Access clinic or virtual clinic (see referral refinement for rapid access in section 8.4.7) as soon as the patient presents.
3. If nAMD is suspected, a rapid access route for evaluation and treatment needs to be available. These clinics may be face-to-face or virtual and provided by medical staff or allied health professionals, under the supervision of a medical retina consultant (see section 16).

4. It is advisable to send AMD information or links to NHS England decision support tool for wet AMD with the initial letter (https://www.england.nhs.uk/publication/decision-support-tool-making-a-decision-about-wet-age-related-macular-degeneration/)

8.4.6 Assessment within Rapid Access Clinic in HES

Minimum standards to be met:

1. Medical retina consultant led service providing governance structure.
2. History and symptoms: medical history should include medication and allergies.
3. Visual acuity assessment preferably in ETDRS letters
4. Imaging: OCT for initial assessment. If clinical examination and OCT confirms no nAMD, the pathway stops, and patients may be discharged back to the referring optometrist.
5. OCT findings confirmed by OCT-A and/or FFA/ICG if OCT shows signs of nAMD.
6. Assessment and offer of treatment within 2 weeks of date of referral after discussing the pros and cons of the treatment regimen.

8.4.7 Referral refinement of rapid access

Referral refinement for rapid access requires an OCT as standard. OCT is becoming more widely available in primary care and commissioners should work with providers to agree a clear pathway to include electronic direct referral with an attached OCT file, meeting DICOM standards when this becomes possible, to avoid duplication of care.

Until NHS OCT scanning is commissioned consistently in primary eye care, referral for OCT and further diagnostics is to be expected. Not all primary care optometrists have access to OCT scanning so in cases with a lower suspicion of wet AMD but a need to rule this out with OCT, triaging or referral refinement approach therefore remains an option and commissioners need to plan for this provision.

Methods include:

- Tele-ophthalmology where visual acuity and an OCT file (DICOM compatible when this is possible) is attached to the referral may be sent to the HES for further grading and refinement. Its application to the service would require additional IT support and infrastructure[51-53].
- Virtual clinics where health care professionals document the visual acuity and obtain OCT images of both eyes for grading by retina trained HCP delegated to manage this clinic under the guidance of retinal specialists.
- Traditional HES Face to face retinal clinic where decision is made on the outcome of the referral by medical or non-medical trained HCP.
- Services for referral refinement should be developed with device agnosticism so that all primary care providers are able to refer into the service.

8.4.8 Referral outcomes

1. Outcome is no AMD: Discharge
2. Outcome is early AMD: Follow recommendation for AMD in section 8.2.1.

3. Outcome is late indeterminate AMD: Monitoring with visual acuity and OCT assessment under secondary care oversight; treatment initiated if nAMD is confirmed.
4. Outcome nAMD present and symptomatic presenting VA better 6/96 or better: Follow recommendation for anti-VEGF in nAMD in section 10.
5. Outcome nAMD with or without disciform scar and poor visual potential (presenting visual acuity Snellen 6/96 or worse or ETDRS letters less than 25 letters): Clinicians' discretion to initiate treatment or monitor. NICE guidance advises to only consider treatment if the patient's visual function could improve e.g., if the better seeing eye is affected. Discharge if no treatment is expected.
6. For those eyes that present with active nAMD and visual acuity better than 6/12, waiting for the visual acuity to decrease to Snellen 6/12 or worse as recommended by NICE results in delayed treatment and poorer outcomes. NICE criteria were based on clinical trials with strict eligibility criteria of 6/12 to 6/96 but there is sufficient real-world evidence that shows early diagnosis and prompt treatment is associated with better visual outcome.Local funding agreement may need to be arranged.
7. Outcome is geographic atrophy (Late dry AMD): Recommendations see section 8.3.1.
8. Outcome non-AMD causes of fluid at macula: Referral to Medical or Surgical Retina Service for diagnosis confirmation and appropriate treatment.
9. Other pathology: refer to subspecialty depending on pathology identified.
10. Feedback on referral to be sent to the referring optometrists or OMP and copied to the GP.

9. Pharmacological management of nAMD (late wet active AMD)

9.1 Anti- VEGF therapy

The currently available anti-VEGF agents are ranibizumab biosimilars and originator, aflibercept 2mg and 8mg, faricimab, brolucizumab and bevacizumab. Bevacizumab is not licensed for this indication and its off-label use requires pre-requisites to be met (see section 9.1.1). Ranibizumab biosimilars are less costly than currently licensed agents. However, given that the drying effect of ranibizumab biosimilars is not as effective as aflibercept 2 or 8mg or faricimab, more patients would need to be monitored at shorter intervals and injected and so the overall cost-savings are unlikely to be significant especially when long-acting agents are available such as faricimab and 8mg aflibercept that show that about 70% of patients require only 12-weekly or longer interval between injections after the loading phase in clinical trial settings. There is a lack of comparative data on treatment burden between the existing biosimilars and newer agents such as faricimab and 8mg aflibercept in an NHS setting. Patient and caregiver burden also need to be considered when evaluating cost. Full detail of the evidence on currently available agents are in Appendix B. With rapid advances in therapeutics for this condition, an updated guidance may be required soon as real-life data on more durable agents become available. Currently, Port Delivery Systems are anticipated.

9.2 Verteporfin photodynamic therapy (vPDT)

vPDT is a treatment option for patients with polypoidal choroidal vasculopathy (PCV), that are not responding to anti-VEGF.

9.3 Non-pharmacological agents

Currently, there is insufficient evidence that any form of photobiomodulation using any wavelength is effective for any stages of AMD[58]. There is also no evidence of the benefits of applying laser for drusen disappearance or for treating subfoveal choroidal neovascularisation. There is no evidence to date on the role of radiotherapy for nAMD. [59].

10. High-value management pathway for nAMD

Given the large number of follow-up examinations and treatment required for the significant and increasing number of people with nAMD, a high value care pathway will need to include medical and other suitably trained and experienced non-medical HCPs in the hospital, and primary care optometry settings. A significant number of injections are provided by HCPs especially nurses. Development of current and future services necessitates identifying the population eye health needs, capacity, and demand tools, use of electronic medical records, robust information technology (IT) support with secure clinical data and communication systems and strong infrastructure across the system.

Some patients may also have good visual acuity in the early stages of nAMD and these patients are likely to have a better than average long-term prognosis if treated early[60-63]. So, close monitoring is recommended.

10.1 Initiation of anti-VEGF therapy

Patients should be provided sufficient information to assist them to reach an informed decision about anti-VEGF therapy and to give informed consent.

10.1.1 Information and consent

1. The patient information specified in NICE guidelines should be explained to the patient by all HCPs involved in the care of the patients and opportunities should be provided to discuss all aspects of the AMD pathway. For non-English speaking patients, use of interpreters and/or translation of patient leaflets and letters are recommended. Important information on making a decision about wet AMD is also provided by Decision Support Tool developed by NHS England. In addition, clinicians should use real-world data on expected outcomes and the treatment burden so that patients can make an informed choice about starting treatment, especially when baseline acuity is poor.
2. Topics to be covered include:
    a. what is AMD and its prevalence; types of AMD;
    b. causes of AMD; smoking cessation and other lifestyle advice;
    c. progression and complications of AMD;
    d. the possibility of developing visual hallucinations associated with retinal dysfunction (CBS) including signposting support services;
    e. vision standards for driving; required tests and investigations;
    f. treatment options, including possible benefits and risks;
    g. importance of probable repeated injections should be discussed; the likely frequency at which these will be required, and long-term nature of therapy.

h. who to contact for practical and emotional support including signposting third sector organisations;
i. where the person's appointments will take place;
j. which healthcare professionals will be responsible for the person's care;
k. expected wait times for consultations, investigations and treatments and transport requirements;
l. treatment options and licensing status;
m. benefits of CVI and local authority registration when sight impaired or severely sight impaired;
n. when, where and how to seek help with vision changes;
o. consideration should be given to the needs of family and care givers.

3. Time should be allocated to discuss the patient's concerns about their diagnosis, treatment, long term nature of treatment and prospects for their vision. Ophthalmic nurses and ECLO are well-placed to identify and respond to the patient's emotional needs and refer as appropriate for support. Covering these topics is a lot for patients to take in under what may be a stressful situation for the patients. Provision should be made to enable patients to return to the HES or contact the HES via telephone, email etc to gather more information and with questions when they are ready and able to process the information.
4. The information provided in writing is subject to the NHS Accessible information Standard, so the information needs to be available in a format accessible to the individual patient.

5. Pre injection consultation should cover the following aspects: the importance of treatment; the treatment options, differences in terms of burden and durability of each option; why the intravitreal (IVT) procedure is appropriate for the patient; what the treatment involves/what to expect/what the risks are; who is likely to give the injection; risks to vision if patient non-compliant with treatment advice. If appropriate, the patient should be advised of off-label treatment and that they are entitled to request an alternative licensed therapy; patient should be given sufficient information to make an informed choice based on a patient and clinician discussion. Potentially serious risks quoted in relation to IVT should include endophthalmitis, retinal detachment, vitreous haemorrhage, central retinal artery occlusion, and rarely cataract and corneal abrasions. Additional risks should be explained for such as anti VEGF therapy and the theoretical risk of thrombo-embolic events and retinal pigment epithelial rips. Floaters may occur following IVT and silicone floaters from syringes.
6. The information should be provided in accessible formats for people with AMD at their first appointment, and then offered again on return to clinic or whenever asked for. The information should cover the information about AMD and treatment pathways, including likely timescales, key contact details; 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.
7. Patient's priorities should be assessed when making management decisions. ECLO support as a supplementary role to assess patient's situation holistically.

8. Additional peer support often facilitated by third sector organisations should be promoted particularly for people who are beginning intravitreal injections, as they may feel reassured by discussion with someone who has previously had the same treatment. Third sector organisations also provide expert advice free and professional emotional support services (counselling).
9. Valid consent must be obtained from the patient prior to first IVT procedure; this will normally suffice for a series of treatments over several months when the drug is licensed for IVT as per RCOphth guidance (https://www.rcophth.ac.uk/resources-listing/intravitreal-injections-consent-and-checklist-recommendations/). However, it is recommended that local hospital consent policies are consulted for the period a consent form for a course of treatment is considered valid. If consent is taken in advance, before every injection the patient must be asked about any changes to their medical condition and consent should be briefly re-confirmed. The information provided in writing is subject to the NHS Accessible information Standard, so the information needs to be available in a format accessible to the individual patient. The cognitive status should be assessed at each injection visit and change in consent form is recommended if/when patient assessment suggests that they do not have the capacity and capability to proceed with treatment.
10. Repeat written consent to be taken in the following scenarios:
    - If there is a change to the treatment plan; drug used; the clinical condition and/or the perceived benefit/risk to the patient.
    - If the drug used is unlicensed for this condition.

10.1.2 Recommendations on initiation of treatment

1. Offer treatment within 2 weeks of referral (an audit standard for AMD service). Treatment on same day of diagnosis is an option especially if the better-seeing eye is affected.
2. Minimum standards to be met: visual acuity recorded in ETDRS letters and utilising OCT to diagnose and treat patients. Treatment is recommended in patients with a visual acuity of 6/96 (logMAR 1.20, 25 ETDRS letters) or higher. In patients with advanced disease, senior retinal specialist assessment is required of the degree of structural damage and potential benefit from treatment especially if the patient has excellent vision in the unaffected eye and is unlikely to gain functional benefit. In patients with visual acuity worse than 6/96, treatment may be considered only if it is the only functional or better seeing eye.
3. Initiate anti VEGF therapy: Mandatory loading dose monthly depending on the summary of product characteristics,
4. Patient choice of anti-VEGF: aflibercept 2mg, aflibercept 8mg, faricimab, ranibizumab (ranibizumab biosimilars) or brolucizumab may be used as first line therapy. However, patients should be counselled on the higher rate of severe intraocular inflammation with brolucizumab compared to other anti-VEGF agents.
5. Monitoring of fellow eyes: Fellow eyes should be monitored with OCT while the patient is being treated or monitored for unilateral nAMD. However, there is an unmet need to explore continued access to regular OCT monitoring for patients who have been discharged from HES.
6. Blood pressure measurement may be done before first injection and then only if deemed appropriate.

7. Intraocular pressure needs to be recorded before and about 30 minutes after first injection and then once a year. In eyes with glaucoma, it is advisable to reduce the pre-injection intraocular pressure with iopidine and if necessary, with oral acetazolamide and post-injection pressure check is advisable and management of any increase in pressures be done immediately in the treatment visit. Referral to glaucoma team may be considered to plan future injections.
8. Individual level discussion on benefits and risks of IVT may need to be discussed with patients who have a history of a recent infection or are on antibiotics and those with active blepharitis during the course of therapy.
9. If a patient has a cardiovascular event or stroke, anti-VEGF injection needs to be deferred until a systemic workup has been done by the patients' physician and risk factors managed. Due to the theoretical risk associated with anti-VEGF therapy and cardiovascular risk, a temporary pause in treatment may be required, followed by an informed decision to proceed after weighing the risks of vision loss.

10.2 Medicines management

Liaise closely with your local pharmacy department to ensure that an adequate supply is maintained. Recognise that obtaining a timely supply is balanced against ensuring that relevant patient information is collated to enable adequate payment. This may include but is not limited to keeping the relevant medication as stock and using an electronic record, implementing an automated dispensing system, investing in the pharmacy team to help manage supplies.

10.3 Treatment regimen

1. A loading phase of injections based on the summary of product characteristics of each anti-VEGF agent.
2. A treat and extend regimen based on visual acuity and OCT is recommended (see appendix B).
3. Extend by 2 – 4 weeks to a maximum of 12-16 weeks based on disease activity and drug posology.
4. Option to monitor and extend if dry macula after maximum extension is reached and maintained at this interval for a further 2-3 visits. Patients may be kept on OCT monitoring which may be most efficient within virtual review clinics within HES or the community depending on local infrastructure (see section 11 and 16).
5. nAMD is a lifelong disease and approximately 25-30% can reactivate and so the patients can very rarely be discharged from monitoring unless disease has been stable without requiring injections for at least two years[64].
6. Some patients may require IVT indefinitely at an individualised treatment interval to sustain the initial VA gains[65].

10.4 Stability

Stable disease is defined clinically as 2-3 visits at maximal extension based on posology of the drug used (12 or 16 weeks) with dry retina and stable VA. However, this is subject to clinician discretion and varies with individual patient. After a treatment free monitoring interval of 12 months 25-30% of patients will still reactivate and need to restart treatment in the subsequent 12 months of further monitoring[66]. Self-monitoring using Amsler chart is not a sensitive tool. Home monitoring devices utilising visual function are not validated in the NHS yet [67]. Meanwhile, OCT is the only sensitive monitoring tool for assessing reactivation. Monitoring of stable patients:

1. Monitoring must be done with visual acuity and OCT: These may be done in virtual clinics or face to face clinic (see 11.3). Although there is no data on length of monitoring period required, there is consensus that patients should be monitored for at least 2 years after stability is achieved. Monitoring with visual acuity assessment or visual function devices alone is not appropriate. Changes in OCT precede visual function tests.
2. Monitoring using visual acuity and OCT may be done closer to home by optometrists in optometry practices to avoid burden on hospitals, where these services are locally commissioned, but the optometrists will need access to training to identify reactivation if they do not have the relevant higher qualification. Community follow-up of these by trained optometrists with medical retina Consultant-led governance supported by fast-track referral to hospital, ophthalmology advice and guidance will enable quality assured joined up care to increase overall capacity. However, these monitoring provisions in community would require OCT and a pathway re-design (see section 11.3).
3. Although not matured at the time of writing, continuing development may in future enable monitoring using artificial intelligence.
4. If reactivation occurs, re-treatment should be initiated as soon as possible on pro re nata or a treat and extend protocol or re-initiate on loading dose until stability criteria is met. The choice of treatment regimen is based on clinician discretion and individualised per patient as currently, there is no robust evidence comparing these approaches in treating re-activation.

10.5 Treatment discontinuation

The NICE guidelines indicate that it is appropriate to stop anti-VEGF treatment if an eye met the defined criteria of late AMD wet inactive (defined in section 3, Table 1), and/or if it was determined that there was no prospect of visual improvement because of continued treatment. Inefficient treatment, for example provided too infrequently, might cause a loss in visual acuity that leads to treatment discontinuation. However, treatment should be given as recommended in the guideline prior to determining whether it should be discontinued. These patients may be discharged from the HES. Fellow eyes of unilateral nAMD that have discontinued treatment due to wet inactive disease need to be monitored.

Premature treatment discontinuation and inefficient treatment are important causes of visual loss and should be avoided. On an average, a patient initiated on treatment would require 6 injections in the first year and 5 injections in the second year. From the third year, an average of 5 injections are required to prevent decrease in vision due to inadequate treatment. However, individualised care is recommended with some requiring more and others requiring fewer injections.

10.6 Non responder

Suboptimal response is defined as intraretinal fluid or subretinal fluid on OCT, other anatomic features of active or worsening disease (e.g., new SRHM or new haemorrhage), or unchanged (≤5-letter improvement)/reduced VA due to nAMD, after three consecutive monthly intravitreal injections.

1. The diagnosis should be re-evaluated as very few patients with active wet AMD do not respond to anti-VEGF therapy. This may require additional imaging with FFA and/or ICG angiography where applicable.
2. The most likely reason for non-response is inadequate therapy due to protocol deviations. Therefore, to avoid further loss, adhere strictly to a re-loading

followed by treat and extend protocol[68]. Failsafe admin processes should be available to track patients with poor compliance due to co-morbidities.

3. Switch to another therapy for disease control may be required for suboptmal response after the loading phase or at any other point due to resistance to current agent (refractory cases). Treatment-resistant nAMD generally defined as persistent retinal fluid on OCT despite continued intravitreal anti-VEGF injections over a 12-month period [.
4. A switch to another anti-VEGF agent is also recommended in cases of allergy or presumed tachyphylaxis. In a small minority, a patient may require a switch back to previous agent or to another agent if disease worsens after the initial switch. There are practical reasons for switching regimens. For example, it may be easier to switch to a fixed regimen rather than a treat and extend protocol in some individuals to aid adherence to treatment.

10.7 Switch to another agent to reduce treatment burden

As new treatments emerge it would be worth evaluating the effectiveness based on efficacy (improved visual or anatomical outcomes) or decrease in treatment burden. Agents with a reduced treatment burden are particularly helpful for patients with co-morbidities affecting compliance and are also useful to allow timely service delivery of care. It may also help with cost pressures by reducing the requirement for out of hours additional clinics.

A switch to another agent may be considered for individuals who respond to treatment but for whom treatment interval cannot be extended beyond 7 weeks with the current agent. These cases may need a loading dose of the new agent before extension. Careful monitoring is required at this phase as these are difficult to treat cases and interval may need to be shortened after having failed at least two extended interval attempts.

Switch to another agent may be considered in those managed on longer intervals (8 or more weeks) to reduce treatment burden. These cases may be switched on a matched treatment interval and then a treat and extend interval post-initial dose. This approach may be easier for patients, but it is not known whether loading these patients may increase the chances of further extension so reload may also be offered.

10.8 Special clinical scenarios

10.8.1 Submacular haemorrhage

Some eyes may present with submacular haemorrhage with poor visual acuity.

The current evidence is to initiate on anti-VEGF therapy on a monthly basis until the haemorrhage improve or futility to treatment is established[69]. An FFA/ICG is recommended as PCV is more likely to bleed compared to active MNV.

An urgent referral to vitreo-retinal team is recommended for possibility of pneumatic displacement and/or recombinant tissue plasminogen activator (tPA). Some patients may benefit from vitrectomy with subretinal tPA and air tamponade[70,71].

10.8.2 Polypoidal choroidal vasculopathy (PCV)

PCV may occur anywhere in the fundus. Peripapillary PCV may cause fluid to track to the macula and cause visual impairment. PCV may also present at the macula and is usually associated with visual impairment. These eyes need to be Initiated on anti VEGF monotherapy if macula is affected by fluid due to PCV. PDT may be offered if there is insufficient response to anti-VEGF.

10.8.3 Retinal Pigment Epithelium (RPE) rip

RPE rips may occur in patients with large pigment epithelial detachments at the time of diagnosis or any time point during therapy or in untreated eyes due to natural history. Intravitreal injections need to be continued unless there is foveal involvement of rip with no potential for visual acuity improvement as per decision of the treating clinician.

10.9 Complications

In services where an HCP has been delegated by a named consultant Ophthalmologist or SAS doctor with autonomous practice rights to deliver intravitreal agents, it is essential that the HCP always has immediate access to advice from an ophthalmologist whilst giving injections and an appropriately trained clinician is available on site to deal with any very urgent complications[72].

10.9.1 Endophthalmitis

The risk of endophthalmitis after anti-VEGF therapy is approximately 0.02-0.09% from randomized controlled trial data whereas real-world evidence from large cohorts suggests 0.028%[73-77]. The cumulative risk per individual increases with increasing number of injections.

1. The precautions to avoid endophthalmitis include use of topical Povidone Iodine 5% pre-injection as the most effective step, supported using surgical hand disinfection with sterile gloves (changed for each injection) and a “no lid touch” technique. The use of a lid speculum and face mask are advised. A sterile drape over the patient’s face may also be helpful or a “no-talking” technique whilst the injection is performed. Additionally, there are also injector devices available which may combine the functions of drape, caliper and speculum. Bilateral cases can be treated but separate equipment must be used for each eye and preferably different drug batches. Peri-operative or take-home topical antibiotics are not recommended. Intravitreal injections should be performed in a designated clean room compliant with RCOphth standards[72]. Iodine disinfection is key and can be applied on a cotton bud to injection site in all cases, even in those with perceived iodine hypersensitivity induced corneal reaction. Chlorhexidine may be used to clean the lashes as an alternate disinfection in exceptional cases of true hypersensitivity to iodine.
2. Services should report each endophthalmitis case to the service risks management team as part of an incident reporting system so that early recognition of clusters of cases is undertaken[78]. Collective annual incidence should also be reported as part of an audit pathway.

10.9.2 Cataract

Patients undergoing anti-VEGF may have increased risk of age-related cataract with frequent injections. A very rare complication is iatrogenic cataract.

Cataract surgery should preferably be avoided in the first 6 months after initiation of anti-VEGF injections as complications are maximum then[79]. Zonular dehiscence is more common in people with repeated anti VEGF injections and extra caution should be taken[79,80]. Iatrogenic cataract is best managed by the vitreo-retinal team.

10.9.3 Glaucoma

There is a risk of ocular hypertension with increasing number of injections[81]. Eyes with ocular hypertension or glaucoma should have controlled IOP prior to injections. Post injection all patients get an initial spike in IOP, however only a small percentage may get sustained rise in IOP requiring treatment. The initial pressure spike may be reduced to a small degree in higher risk patients with the use of apraclonidine before injection. Pre-operative oral acetazolamide may be required.

1. Patients with persistent ocular hypertension should be referred to the glaucoma team for further management.
2. Routine IOP testing post injection is not recommended but annual IOP monitoring is required to identify sustained IOP rise from repeated injections.
3. However, patients with glaucoma with established field defects need to be monitored with IOP assessment and appropriate treatment before and after IVT.

10.9.4 Central Retinal Artery Occlusion (CRAO)

Immediate care such as anterior chamber paracentesis, acetazolamide and digital massage within minutes is indicated if there is a potential for vision improvement as determined by the clinician[72].

10.9.5 Intraocular inflammation (IOI)

Intraocular inflammation is a known adverse event of anti-VEGF agents. A close watch for signs of inflammation is recommended. Patients must be warned to report immediately if they have any symptoms of inflammation such as pain, visual impairment, floaters. Signs may range from mild iritis to vasculitis and loss of vision. These eyes require urgent management for the inflammation. Treatment for nAMD with another anti-VEGF may be commenced after control of inflammation to control nAMD disease activity.

11. Monitoring

11.1 General Recommendations

Do not routinely monitor people with early AMD or late dry AMD at hospital eye services unless in clinical research.

Patients with late dry AMD, or people with AMD who have been discharged from hospital eye services should:

- Self-monitor their AMD -but please note that utilising visual function changes to monitor new or recurrent disease is not sufficiently sensitive.
- consult their hospital eye-care professional as soon as possible if their vision changes.
- continue to attend regular sight-tests with their primary care optometrist.
- OCT is the most sensitive monitoring tool. For community provision, OCT should be used to monitor patients that are at high risk of new wet AMD or being monitored for stable wet AMD.
- be provided information about sources of support for living with sight loss including local and national charities.
- be made aware of the local ECLO service, and how to re-access emotional and practical support. This would include advice on Certification and Registration.

For people being monitored for late AMD (wet active), both eyes should be assessed at their monitoring appointments.

11.2 Self monitoring

Patients with AMD should be advised by a trained HCP regarding the strategies available. Patients should be reminded that none of the strategies for home monitoring of visual function are currently sufficiently sensitive to detect disease recurrences and that OCT is the most sensitive detection tool. Patients with AMD should report any new symptoms or changes regarding their central vision to an eye-care professional as soon as possible:

- blurred or grey patch in their vision
- straight lines appearing distorted
- objects appearing smaller than normal

Local commissioning arrangements may be put in place with primary eye care to support patients who identify new symptoms following self-monitoring.

It is essential to encourage and support patients with AMD who may lack confidence to self-monitor their symptoms. They should be advised to seek assistance from peer support groups or supporting organisations such as the Macular Society.

If patients are not able to self-manage their AMD, AMD monitoring techniques should be discussed with their family members or carers (as appropriate). Local commissioning arrangements may be put in place with primary eye care to facilitate monitoring for this cohort.

11.3 Monitoring nAMD

1. Patients with nAMD (wet active) should be offered ongoing monitoring with OCT for both eyes.
2. Offer fundus examination or colour photography if OCT appearances are stable, but:
    a. there is a decline in visual acuity or
    b. the patient reports a decline in visual function.
3. Consider FFA to identify unrecognised neovascularisation if OCT appearances are stable, but:
    a. there is a decline in visual acuity or
    b. The person reports a decline in visual function.
4. If OCT results suggest macular abnormalities but the abnormalities are not responding to treatment, consider alternate diagnosis.
5. This service should be provided in the HES while on active management of the disease. Once stability is achieved, for instance, those who have not required treatment in either eye for more than 1 year require monitoring. These patients may be monitored in HES or in the community where relevant services are commissioned. The HES/ICB could decide to commission community follow-up for certain patients who had been on an AMD treatment pathway that could be a) an ‘ imaging-only’ appointment at a local optometric practice, with uploading of the full OCT images for the hospital eye service to review, or b) if the community optometrists have appropriate training, the optometrist could review the OCTs and only refer back if there were new concerns. It would be essential for the community optometrists to have access to the last OCT that was performed when they were last seen by the

hospital eye service for future comparison. There should be appropriate commissioning arrangements with a fee for such a review with OCT negotiated by the ICB as appropriate.

11.4 Monitoring co-existent ocular pathology

1. Diabetic retinopathy: Patients with co-existent diabetes should continue attending their diabetic retinopathy screening appointment.
2. Glaucoma: Patients with co-existent glaucoma should continue their management with the glaucoma team.

11.5 Support services

11.5.1 Low Vision Aid (LVA) service

1. Patients with late AMD usually have trouble with visual impairment and ought to maintain regular sight tests. Patients should have access to low vision aid appointments at the earliest opportunity. Leaving referral late can delay a patient's ability to use and adapt to low vision aids.
2. Patients may benefit from low visual aids especially for reading and should have access to low vision aid appointments. Option of electronic devices as LVA should be presented to the patient as well.
3. Those who qualify for local authority visual impairment registration should be informed about this eligibility and should be registered in a timely manner if they so choose.
4. Some patients may benefit from eccentric viewing training, and this should be encouraged in the LVA setting itself.
5. Group based rehabilitation programme is also recommended.
6. Patients who do not meet the requirements to hold a driving license due to their visual impairment should be informed that they must inform the DVLA and stop driving pending DVLA evaluation.
7. National LVA service that is primary care based free at the point of access has been proven successful in Wales. Practitioners providing this service are able to make appropriate social care and third sector referrals and support local authority registration where patients choose this.
8. Referral to third sector organisations such as Macular Society, RNIB, SeeAbility etc provide support and advice on technology. For example, information about RNIB's Tech for Life Service can help with both simple and complex technology queries and issues offering information, advice and guidance over the phone, over email or through setting up a volunteer request. Other national and local charities also provide similar services. Local charities may also provide support, for example, N-Vision. Blackpool, Fylde, and Wyre Society for the Blind.

11.5.2 Eye Clinic Liaison Officer

All ophthalmic departments providing AMD services should have at least one ECLO to provide on-going holistic support for these patients and signposting to other services. Large services may require more than one ECLO to deal with the volume of patient assessments required. ECLO support should be provided to all patients with AMD and especially those with co-morbidities to improve patient engagement, help ensure timely treatment and follow-up and support registration and information provision. ECLO support may be needed at multiple time points during the care pathway of an individual patient. ECLO should also

link into community-based AMD services. It is important the ECLO service adhere to the UK Ophthalmic Alliance Patient Standard/ Royal National Institute of Blind People (RNIB) Quality Framework to ensure a quality service is provided, that effectively meets the needs of patients and provides the right care in the AMD pathway (see section 8.1)[50].

11.5.3 Allied health professional (AHPs) with specialist role

We recommended that stable patients be monitored via stable virtual review clinics. Primary care optometrists and AHPs (including ophthalmic nurses and orthoptists) may undergo or lead on training of staff and the development of such services, working alongside medical staff at all stages of the patient pathway. Their involvement is particularly necessary with the volume of patients anticipated in the future. The RCOphth "Ophthalmic Common Clinical Competency Framework" may be used to guide training and development of relevant staff. (See Section 14).

11.5.4 Charles Bonnet syndrome

Patients with CBS should be offered the opportunity to access psychological support. These patients require referral by GP, optometrist, ophthalmic nurse, or ophthalmologist to the local low vision service for an assessment and support from trained ophthalmic nurses and ECLOs. All patients with AMD should be provided with dedicated literature from and signposted to contacts with high quality information and support e.g., NHS choices, the Macular Society and Esme's Umbrella (a campaign group to build awareness around CBS and NHS choices) have information and advice on CBS[82]. The Macular Society provides a free counselling service for people affected by their CBS either one to one or in groups of CBS patients providing both professional and peer support. Optometrists and dispensing opticians providing low vision services should also be able to provide this.

11.5.5 Depression and anxiety

All patients experiencing depression and anxiety should be referred to psychological support services. Supporting patients to adapt to their sight loss and their AMD diagnosis can have a profound impact on improving patient's wellbeing. These patients may require support from ophthalmic nurse counsellors and ECLO and referral to their GP for further management. Low vision services in primary care are also a valid resource for access to help and advice regarding depression and anxiety. RNIB and the Macular Society both provide free professional short-term counselling, as do some local sight loss charities.

11.5.6 People with learning disabilities

Reasonable adjustments in eye care, treatment and surgery should be instituted. This includes good communication such as easy read information and proper consideration of capacity and consent issues and Best Interest meetings. They also need regular eye care and visits to the optometrists due to higher prevalence of refractive errors and co-morbid ocular conditions. Referral for treatment should be no different to people without learning disabilities.

12. Governance and administrative structure for an Anti VEGF service

The service requires dedicated administrative staff available for booking patients, answering telephone calls, changes in appointments, tracking down patients who fail to attend clinic appointments. Patients value the opportunity to book their next appointment before they leave the clinic, it gives patients a sense of reassurance and helps people plan their lives. There should be senior fail-safe administrative support available within the remit of the medical retina services. Governance of the service should be led by a Consultant Ophthalmologist with Medical Retina expertise or a nominated SAS doctor with similar expertise and autonomous practice in this area. Services need to review regularly to ensure the pathway is patient focussed with efficient use of resources.

13. Auditing and quality assurance

Both the 2018 AMD Feasibility Audit, commissioned by the Healthcare Quality Improvement Partnership, and the National Ophthalmology Database AMD Audit, identified significant variation in baseline characteristics, care processes and clinical outcomes between NHS providers. As a result, providers are encouraged to compare key care processes, visual acuity and safety outcomes against local and national benchmarks via clinical audit. (Where possible, visual acuity outcomes should be adjusted to take account of baseline ocular and patient characteristics.) The results of clinical audit should be shared at least annually with local commissioners and neighbouring units. This will help identify if local outcomes are in keeping with available benchmarks or if elements of the AMD care pathway require attention and improvement.

Electronic medical records are vital for high-quality clinical audit. Standardised data sets e.g. the National Ophthalmic Database AMD Audit Dataset and high data quality are also vital. Participation in the UK AMD Audit should be mandatory for all providers of NHS-funded AMD treatment. Data quality was variable in both the year 1 and 2 reports of the UK AMD Audit. Participation is strongly encouraged and providers of treatment need to work with electronic medical records providers to ensure that data quality is as high as possible, especially for recording the date of referral from primary care, baseline visual acuity and the planned follow-up interval.

The primary outcome measures for the NOD AMD Audit include:

- Percentage of patients with confirmed Late AMD (wet active) starting treatment (or being offered treatment) within 14 days of referral from primary care.
- The proportion of eyes completing the initial, loading phase of three-monthly injections within 10 weeks or 4 loading phase within 16 weeks for faricimab.
- The proportion of eyes with more than 1 follow-up delay of at least 14 days within the first 12 months of treatment.
- Visual acuity change from baseline to 12 months, both crude and adjusted (taking account of age and visual acuity at the start of treatment).
- The proportion of eyes with “good” visual acuity (≥ 70 ETDRS letters) after one year of treatment.

- The incidence of intraocular inflammation or presumed infectious endophthalmitis within 42 days of a prior intravitreal injection.

Secondary measures include:

- Data quality
- Baseline visual acuity and the proportion of eyes with “good” vision at the start of treatment (better than Snellen 6/12).
- The median number of injections in the first 12 months of treatment
- Follow-up to months 12 and 24 (Persistence with treatment)

In addition, providers are encouraged to collect data relating to patients’ experiences of local AMD treatment. Results should also be shared with commissioners and neighbouring providers. Suggested topics include:

- Percentage of patients with Late AMD given written, accessible information at their first appointment and whenever requested on the disease, treatment options and pathways, key local contacts, and available supports.
- Percentage of patients with AMD offered CVI as soon as they become eligible, even if they are still receiving active treatment.
- Percentage of patients with access to an ECLO during their treatment pathway
- Monitoring of “did not attend” (DNA) and appointment cancellation rates at yearly intervals.

Additional information on service quality from the following should also be made available to staff involved in the service provision:

- Friends and family Test
- Complaints and compliments
- Feedback from the Macular Society, RNIB and local patient groups
- Patient satisfaction questionnaires are also recommended

14. Workforce Development and Training

Non-medical healthcare professionals (HCPs) are subject to statutory regulation. As registered practitioners, they are responsible and accountable for practising within their personal scope of practice and competence at any one time. They are responsible for the decisions and actions that they take (including decisions not to act), and for engaging in continuing education and professional development to maintain and update their knowledge and skills.

HCPs must be enabled by their employer to engage in education and training that supports them to perform required activities and develop in their job role. Opportunities for development should align with changing workforce deployment and service delivery needs, while supporting HCPs to fulfil their professional regulatory responsibilities and adhere to local clinical governance arrangements.

All HCPs should have the appropriate theoretical knowledge of anatomy and physiology, assessment and examination, disease, investigations, and management. Their individual education and training needs will vary, subject to the following:

- their specific contribution to managing patient caseload within a particular service set-up and multi-disciplinary team (including the team's skill mix and job role configuration)
- their profession's education and scope of practice
- their personal scope of practice, post-registration professional experience and opportunities for professional development to date.
- Primary care Optometrists are involved in the diagnosis and management of early AMD, as well as referral refinement of suspect nAMD and work autonomously within their core skills and without supervision, see the qualification and competency table (login required).

Core competency optometrists should be able to participate in the service so long as the appropriate clinical governance. The oversight of activity delegated to HCPs in secondary care rest with the Medical Retina Lead of the service to ensure national standards are met. Each commissioned service should have a Medical Retina Consultant or Speciality Doctor with medical retina experience who holds autonomous sign-off responsibility.

For HCPs involved in treatment decisions within components of patient pathways managed within Hospital Eye Services that require to identify their level of competencies, the Ophthalmic Practitioner Training (OPT) programme (based Ophthalmic Common Clinical Competency Framework can help to identify both their existing professional competence (gained and demonstrated through their pre- and post-registration education and professional experience) and their individual areas of learning need.

The OPT defines three levels of competence in the following aspects of care: ophthalmic history taking, ophthalmic examination, investigations, management and interventions, ability to deal with the needs of ophthalmic patients, teaching and education and personal development.

Ophthalmic supervisors can use the OPT with individual HCPs to establish their existing capability against the OPT competencies; give due recognition to their established, current competence (including through the appropriate recognition of prior learning and evidenced capability); and identify areas for supported professional development.

For HCPs involved in the diagnosis, referral and management of stable patients, accredited medical retina courses are available (although not required) to support and recognise their professional development and competence. These include the CoO higher qualifications, delivered under CoO accreditation by universities. OPT recognition of HCPs' successful completion of CoO higher qualifications, and other relevant HEI provision, is currently being pursued (supported by Health Education England). Other training options may be arranged locally.

The UK Ophthalmic Alliance has devised a policy document detailing the operating procedures for HCPs undertaking intravitreal injections.

ECLOs should adhere to, and be trained in accordance with, the RNIB ECLO Quality Framework, and have completed the Eye Clinic Support Studies course accredited by City University.

In summary:

- HCPs should have the appropriate underpinning clinical knowledge and skills to undertake assessments, investigations, and management safely and effectively,

with due recognition of their personal scope of practice and current competence.

- HCPs are responsible and accountable for practising within their current scope of practice and competence, and engaging in continuing education and CPD, in line with their professional role and to fulfil statutory regulatory requirements.
- Professional development opportunities should be provided to meet individual and service delivery needs, drawing on the OPT and accredited qualifications.
- Employers are responsible for ensuring that individual practitioners are supported to engage in learning and development to meet workforce, service delivery and patient care needs and to maintain the currency of their competence to fulfil their job role.

15. Information and Support

15.1 Links to patient information

Name	Published	Link
Wet AMD clinical decision support tool	NHS England	https://www.england.nhs.uk/publication/decision-support-tool-making-a-decision-about-wet-age-related-macular-degeneration/
Royal National Institute of Blind People	RNIB	https://www.rnib.org.uk/eye-health/eye-conditions
NHS Choices conditions information	NHS	https://www.nhs.uk/conditions/age-related-macular-degeneration-amd/
Understanding Macular Disease	Macular Society	https://www.macularsociety.org/
Moorfields patient information	Moorfields Eye Hospital NHS Foundation Trust	https://www.moorfields.nhs.uk/content/patient-leaflets

15.2 Links to clinical information, clinical guidelines, decision support tools

Name	Published	Link
The Way Forward for AMD Services	The Royal College of Ophthalmologists	https://www.rcophth.ac.uk/standards-publications-research/the-way-forward/
NICE Serious Eye Disorders Quality Standard	NICE	https://www.nice.org.uk/guidance/qs180
Commissioning Standards	The Royal College of Ophthalmologists	https://www.rcophth.ac.uk/standards-publications-research/ophthalmic-services-guidance-2/
Quality Standard for Medical Retina Disease Services	The Royal College of Ophthalmologists	Quality Standard for Medical Retina Disease Services
SAFE - Systems and Assurance Framework for Eye health	Clinical Council for Eye Health Commissioning	https://www.college-optometrists.org/clinical-council-for-eye-health-commissioning#tab-informationandguidance-4420b169
NHS England Eye Care Restoration and Transformation project resources	NHS England	https://future.nhs.uk/connect.ti/ECDC/view?objectId=22317360 Registration required to access
Eye Care Support Pathway	RNIB	https://www.rnib.org.uk/your-eyes/the-eye-care-support-pathway/

16. Service Model Options

16.1 Artificial Intelligence

Artificial intelligence has shown great promise in classifying two-dimensional photographs and OCTs of some common diseases and typically relies on databases of millions of annotated images. The technology has not been implemented in clinics yet.

16.2 Virtual clinics

The use of the term “Virtual clinic” with respect to the management of AMD refers to a process where acquisition of data from the patient (e.g., visual acuity measurements and OCT images (including colour fundus photographs) occurs at a separate point in time to the assessment of that data to formulate a plan for treatment within secondary care including their diagnostic hubs. Acquisition of data for these virtual clinics assessments are often done by HCP in a high-throughput clinic in secondary care and is then commonly followed by a

later asynchronous assessment of the data by trained clinicians, again facilitating the review of high volumes of patient data without interacting directly with the patient.

Clinics which have taken this approach have reported higher patient throughput, at least double the number of patients' data could be reviewed and management plans made compared to the number of patients assessed in a traditional face-to face clinic format. It is also recommended that the virtual clinics should have HCP or ECLO with appropriate training available to support a patient with additional questions or concerns to ensure that patient needs are met and avoid them having to make many different appointments and delaying patient access to support.

In 2015 the Royal College project "The Way Forward" reported that virtual clinics for AMD had already been implemented in 60% of services and the expectation is that in 2019 this percentage will be higher give the drive to optimize capacity in over-stretched Ophthalmic services.

An additional advantage of virtual clinics is that the data acquisition element can be often delivered outside of routine working hours when equipment such as OCT scanners and VA charts lie unused so that other types of patient care episodes can be prioritized during normal working hours. This is beneficial to services where clinic infrastructure is inadequate to meet demand.

Virtual clinics are a very effective way of increasing throughput in assessment clinics for nAMD disease activity status without compromising quality of care in terms of decision making on hospital eye services.

A similar approach for new patient referrals increases throughput in the same way and ensures that the true positive diagnoses of nAMD can be fast-tracked into the rapid access clinic whilst false positive patients (e.g., with late dry AMD) can still be seen within a service but in a lower priority timescale. This is necessary as historical audits have shown that ~ 50% of nAMD referrals are less urgent pathology and without triage many patients will be booked for an urgent appointment within 2 weeks as per NICE guidelines where more routine assessment would be suitable.

Despite these positive impact on service provision, these clinics do often compromise patient care, in that a holistic face-to-face clinical interaction between patient and clinician does not occur at every single patient episode. It is also not possible to give patients a treatment plan and next appointment on the day of their attendance.

New true positive nAMD patients should ideally be seen in a face-to-face clinic for their first consultation. Virtual clinics assessment of true positive cases should be done with caution. An important point to consider is that patients are often distressed when receiving news of their diagnosis. Whilst a face-to-face clinical interaction at this point is best practice, training and guidance on 'breaking bad news' to all HCPs should be in place if new suspected AMD patients triaged to be true positive are seen in a in a virtual setting. Points on information and consent in section 10.1.1 should be included in for each virtual consultation.

17. Summary

As with NICE Clinical Guidelines generally, this commissioning guidance is intended to apply to 80% of patients on 80% of occasions and this recommendation provides details of the optimum pathway for patient benefit. In clinical medicine, there will always be exceptions and uncertainties. This guidance sets out principles and the minimum standards of care, to be moderated by well-informed clinical judgement and common sense for individual patient situations.

Patients with no or early low risk AMD do not require any monitoring or treatment and can be discharged to routine review by primary care optometrists.

Patients with medium or high-risk AMD should be advised to stop smoking, encouraged to have a healthy diet, with plenty of greens and monitor themselves for any central visual disturbances and report if they experience any visual symptoms. It is recommended that they be advised that OCT is the most sensitive tool to diagnose conversion. Visual symptoms or apps to monitor visual function or using Amsler charts are not sensitive measures to identify conversion to nAMD.

Genetic testing is not advocated at present.

Indeterminate AMD is challenging and best reviewed regularly in secondary care either face-to-face or in virtual clinics with imaging facilities or directly in the medical retina clinics. These are challenging cases and require secondary care oversight. Advanced AMD is associated with visual impairment and increased likelihood of depression, falls and cognitive impairment. Timely initiation and prompt repeated intravitreal anti-VEGF therapy is the first line evidence based cost-effective treatment option for active wet AMD. Access to this treatment should not be denied in eyes that meet NICE criteria.

Photodynamic therapy may be used in combination with anti-VEGF in the variant of AMD polypoidal vasculopathy.

A typical care pathway for anti-VEGF treatment is described in the document but this must be personalised to the patient and adaptable for patients with specific needs. Auditing of high value anti-VEGF pathway for nAMD should include time from referral to first injection, delays in planned assessments and treatments, and change in visual outcome over time stratified by baseline visual acuities, occurrence of significant complications should be recorded routinely, and the data should be available to care providers and commissioners and regional eye care working groups.

Information required for the UK minimum dataset should be routinely collected locally for annual audit of the services and clinical outcomes (see Section 13).

Currently, treatment for GA is anticipated. Patients with poor VA due to Late AMD should be offered visual rehabilitation such as low visual aid assessment. If eligible, subject to willingness, these patients should also be informed about the provision of CVI.

18. Guidance development group

A commissioning guidance development group was established to review and advise on the content of this commissioning guide. This group met on three occasions, with additional interaction taking place via email.

Name	Job title	Role/representing
Sobha Sivaprasad (Chair)	Consultant Ophthalmologist, Moorfields Eye Hospitals NHS Foundation Trust	The Royal College of Ophthalmologists
Clare Bailey	Consultant Ophthalmologist, Bristol Eye Hospital	The Royal College of Ophthalmologists
Beth Barnes	Head of Professional Support	The Royal College of Ophthalmologists
Priya Boparai	Medicines Information and Ophthalmology Pharmacist Sheffield Teaching Hospitals NHS Foundation Trust	UK Ophthalmic Pharmacists Group
Matt Broom	Volunteer	Vision UK (until June 2020) and The Royal College of Ophthalmologists' Lay Advisory Group
Krishnachandran Chandra	Operational Manager	University Hospitals Southampton NHS Foundation Trust
Shruti Chandra	Ophthalmology Specialist registrar and NIHR Academic Clinical Fellow	Trainee representative
Roxanne Crosby-Nwaobi	Lead Nurse for Research/NIHR ICA Clinical Lecturer, Moorfields Eye Hospitals NHS Foundation Trust	The Royal College of Nursing, Ophthalmic Nursing Forum
Louise Downey	Consultant Ophthalmologist, The Hull and East Yorkshire Eye Hospital	The Royal College of Ophthalmologists
Sara Fletcher	Head of Reform for Delivery	Greater Manchester Integrated Care Board
Sajjad Mahmood	Consultant Ophthalmologist, Manchester Royal Eye Hospital (until Summer 2020) then Optegra Manchester	The Royal College of Ophthalmologists

Aleksandra Mankowska	Optometrist and lecturer in the Bradford School and Vision Science	College of Optometrists
Martin McKibbin	Consultant Ophthalmologist, Leeds Teaching Hospitals NHS Foundation Trust	The Royal College of Ophthalmologists
Zoe Richmond	Optometrist and Clinical Director	Local Optical Committee Support Unit
Elizabeth Wick	Volunteer	The Royal College of Ophthalmologists' Lay Advisory Group
Cathy Yelf	Chief Executive	Macular Society (from September 2020)

18.1 Funding statement

The development of this commissioning guidance is funded by the following source:

- The Royal College of Ophthalmologists

18.2 Conflict of interest statement

Individuals involved in the development and formal peer review of commissioning guidance completed a conflict-of-interest declaration. It is noted that declaring a conflict of interest does not imply that the individual has been influenced by his or her interest, it is intended to ensure interests (financial or otherwise) are transparent and to allow others to have knowledge of the interest.

The following interests have been declared by the Group:

- Sobha Sivaprasad has received grant funding from Abbvie, Bayer, Boehringer Ingleheim, Optos, consultancy fees from AbbVie, Amgen, Apellis, Bayer, Biogen, Boehringer Ingelheim, Novartis, Eyebiotech, Eyepoint Phamaceuticals, Janssen Pharmaceuticals, Ocular Therapeutix, Kriya Therapeutics, OcuTerra, Roche, Stealth Biotherapeutics. Sanofi; travel fees from Roche and Bayer and Trial steering committee or data monitoring committee member for Nova Nordik and Bayer.
- Priya Boparai has attended Roche Diabetic Eye Disease and neovascular AMD advisory board meetings.
- Louise Downey has been the Principal Investigator for sponsored clinical trials with Bayer, Novartis, Allergan, Roche and Alimera. She has also received fees for speaking at meetings from Bayer and Novartis and sponsorship for attending a meeting from Novartis, Bayer, and Allergan.
- Zoe Richmond, the Local Optical Committee Support Unit provides advice on services to primary care providers and commissioners. Zoe is also the Clinical Director for LOCSU. She provides advice and support to National Eye Care Recovery and Transformation program. Specifically, the Pathway improvement workstream as Optometry lead. She has received consultancy fees from Santen

to support in the development of a report exploring current challenges in implementing new pathways for DED in the UK.
- Cathy Yelf, the Macular Society has received grants from the following companies: Alcon, Allergan (AbbVie), Apellis, Bayer, Novartis, OKKO health, Oxsight, Roche, Vision Express. It has also received consultancy fees from Novartis and an honorarium for her attendance at meetings of the Roche global Retina Patient Forum
- Sajjad Mahmood has been the Principal Investigator for sponsored clinical trials with Bayer, Novartis and Roche. He has also received honoraria for lecturing and travel grants for meetings from Bayer, Novartis and Roche.
- Roxanne Crosby-Nwaobi has received an honorarium from Bayer for attending a Bayer Ophthalmology Masterclass event.

18.3 Past Guidance Development Group Members

- Tessa Barrett – Director of Services, Macular Society until September 2020
- Kenny Li - Deputy Director and Head of Medicines Optimisation for Manchester Health and Care Commissioning and provides sessional commissioning support to other NHS organisations.

18.4 Reviewers

With thanks to the reviewers of the document prior to full consultation and the update.

- Romi Chhabra, Consultant Ophthalmologist
- Pardip Grewal, Senior Service Manager Ophthalmology, ENT and Oral Surgery
- RCOphth Quality and Standards Committee

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ROYAL COLLEGE OF OPHTHALMOLOGY

Report of guidelines search and record categorisation

I. Abbreviations

CDSR Cochrane Database of Systematic Reviews

CENTRAL Cochrane Central Register of Controlled Trials

CRD Centre for Reviews and Dissemination

DARE Database of Abstracts of Reviews of Effects

HTA Health Technology Assessment

NHS EED NHS Economic Evaluation Database

RCO Royal College of Ophthalmologists

II. Search Methodology

a. Search strategy

A literature search was designed to identify evidence on age related macular degeneration. The draft search strategy was discussed with the Royal College of Ophthalmologists. The final MEDLINE and Embase search was run in Embase via Dialog.

Table 2.1: Databases and information sources searched

Resource	**Interface/URL**
MedlineALL and Embase	Dialog
Cochrane Central Register of Controlled Trials	Cochrane Library / Wiley
Database of Abstracts of Reviews of Effect	https://www.crd.york.ac.uk/CRDWeb/
Health Technology Assessment Database	https://www.crd.york.ac.uk/CRDWeb/

Resource	Interface/URL
NHS Economic Evaluation Database	https://www.crd.york.ac.uk/CRDWeb/
Cochrane Database of Systematic Reviews	Cochrane Library / Wiley
NHS Evidence guidelines	https://www.evidence.nhs.uk/
ERCI	https://guidelines.ecri.org/

a. Search results

The searches identified 9,327 records. Table 2.2 shows the number of results by database.

Table 2.2: Number of records returned by the searches

Resource	Number of records identified
MedlineALL and Embase	8593
Cochrane Central Register of Controlled Trials	702
Database of Abstracts of Reviews of Effect	0
Health Technology Assessment Database	0
NHS Economic Evaluation Database	0
Cochrane Database of Systematic Reviews	31
NHS Evidence guidelines	N/A
ECRI	1
Total number of records retrieved	**9327**

Appendix A: Search Strategies

A. 1.: Source: MedlineALL/Embase
Interface / URL: Dialog interface
Database coverage dates: 2019 July 04 to 2023 October 12
Search date: 12/10/2023
Retrieved records: 8593
Search strategy:

S1 emb.explode(macular degeneration)

S2 emb(subretinal neovascularization)
S3 emb(drusen)
S4 ti(maculopath* or drusen*) or ab(maculopath* or drusen*) or if(maculopath* or drusen*)
S5 ti((macula* or retina* or “sub-retina*” or choroid* or wet or dry) PRE/2 degener*) or ab((macula* or retina* or “sub-retina*” or choroid* or wet or dry) PRE/2 degener*) or if(“macula* degener*” or “macula* retina*” or “sub-retina* degener*” or “choroid* degener*” or “wet degener*” or “dry degener*”)
S6 ti((macula* or retina* or “sub-retina*” or choroid*) N/2 (neovascula* or “neo-vascula*” or exudative or nonexudative or “non-exudative” or vasculo* or proliferat* or telangiect*)) or ab((macula* or retina* or “sub-retina*” or choroid*) N/2 (neovascula* or “neo-vascula*” or exudative or nonexudative or “non-exudative” or vasculo* or proliferat* or telangiect*)) or if((macula* or retina* or “sub-retina*” or choroid*) N/1 (neovascula* or “neo-vascula*” or exudative or nonexudative or “non-exudative” or vasculo* or proliferat* or telangiect*))
S7 Ti((macul* or geographic*) PRE/2 atroph*) or ab((macul* or geographic*) PRE/2 atroph*) or if(“macul* atrophy*” or “geographic* atroph*”)
S8 ti(macul* PRE/2 (lutea* or syndrome)) OR ab(macul* PRE/2 (lutea* or syndrome)) OR if(“macul* lutea*” or “macula* syndrome”)
S9 ti(wAMD or GAMD or ARMD or wARMD) or ab(wAMD or GAMD or ARMD or wARMD) or if(wAMD or GAMD or ARMD or wARMD)
S10 Ti(“retina* pigment* epithelium*” or “disciform* scar”) or ab (“retina* pigment* epithelium*” or “disciform* scar”) or if(“retina* pigment* epithelium*” or “disciform* scar”)
S11 emb(charles bonnet syndrome)
S12 Ti(“Charles bonnet”) or ab(“Charles bonnet”) or if(“Charles bonnet”)
S13 ((S12 OR S11 OR S10 OR S9 OR S8 OR S7 OR S6 OR S5 OR S4 OR S3 OR S2 OR S1)) and (pd(>20161231))
S14 Emb(animal or animal experiment or animal model or animal tissue or nonhuman) not emb.explode(human)
S15 dtype(conference abstract or conference paper or conference proceeding or conference review or editorial) or ti(“case report”)
S16 S13 NOT (S14 or S15)

A. 2.: Source: CENTRAL
Interface / URL: The Cochrane Library
Database coverage dates: Issue 10 of 12, October 2023
Search date: 12/10/2023
Retrieved records: 702
Search strategy:

#1 MeSH descriptor: [Macular Degeneration] explode all trees
#2 MeSH descriptor: [Choroidal Neovascularization] this term only
#3 MeSH descriptor: [Retinal Drusen] this term only
#4 (maculopath* or drusen*)
#5 ((macula* or retina* or (sub NEXT retina*) or choroid* or wet or dry) NEAR/2 degener*)
#6 ((macula* or retina* or (sub NEXT retina*) or choroid*) NEAR/2 (neovascula* or (neo NEXT vascula*) or exudative or nonexudative or non-exudative or vasculo* or proliferat* or telangiect*))
#7 ((macul* or geographic*) NEAR/2 atroph*)
#8 (macul* NEAR/2 (lutea* or syndrome))

#9 (wAMD or GAMD or ARMD or wARMD)
#10 (retina* NEXT pigment* NEXT epithelium*) or (disciform* NEXT scar)
#11 "charles bonnet"
#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 with Publication Year from 2019 to 2023, with Cochrane Library publication date from Jan 2019 to present (12/10/2023), in Trials

A. 3.: Source: CDSR
Interface / URL: The Cochrane Library
Database coverage dates: Issue 10 of 12, October 2023
Search date: 12/10/2023
Retrieved records: 31
Search strategy:

#1 MeSH descriptor: [Macular Degeneration] explode all trees
#2 MeSH descriptor: [Choroidal Neovascularization] this term only
#3 MeSH descriptor: [Retinal Drusen] this term only
#4 (maculopath* or drusen*)
#5 ((macula* or retina* or (sub NEXT retina*) or choroid* or wet or dry) NEAR/2 degener*)
#6 ((macula* or retina* or (sub NEXT retina*) or choroid*) NEAR/2 (neovascula* or (neo NEXT vascula*) or exudative or nonexudative or non-exudative or vasculo* or proliferat* or telangiect*))
#7 ((macul* or geographic*) NEAR/2 atroph*)
#8 (macul* NEAR/2 (lutea* or syndrome))
#9 (wAMD or GAMD or ARMD or wARMD)
#10 (retina* NEXT pigment* NEXT epithelium*) or (disciform* NEXT scar)
#11 "charles bonnet"
#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 with Cochrane Library publication date from Jan 2019 to present (12/20/2023), in Cochrane Reviews, Cochrane Protocols

A. 4.: Source: HTA/DARE/NHS EED
Interface / URL: https://www.crd.york.ac.uk/CRDWeb/
Database coverage dates: The Centre for Reviews and Dissemination (CRD) databases are no longer included in the Cochrane Library, from 7th August 2018. CRD is maintaining versions of the Database of Abstracts of Reviews of Effects (DARE) and the NHS Economic Evaluation Database (NHSEED) until at least 2021, when the current process will be reviewed.
The Centre for Reviews and Dissemination is no longer adding records to the Health Technology Assessment (HTA) database. The International Network of Agencies for Health Technology Assessment (INAHTA) will be taking over production and the next phase of the database development. Updating and addition of new records will resume on their new platform, when it is ready.
The three databases were accessed via **www.crd.york.ac.uk/CRDWeb**
Search date: 12/10/2023
Retrieved records: 0
Search strategy:

1 MeSH DESCRIPTOR Macular Degeneration EXPLODE ALL TREES 247
2 MeSH DESCRIPTOR Choroidal Neovascularization
3 MeSH DESCRIPTOR Retinal Drusen
4 ((maculopath* or drusen*))
5 ((macula* or retina* or sub-retina* or choroid* or wet or dry) NEAR2 degener*)
6 ((macula* or retina* or sub-retina* or choroid*) NEAR2 (neovascula* or neo-vascula* or exudative or nonexudative or non-exudative or vasculo* or proliferat* or telangiect*))

7 ((macul* or geographic*) NEAR2 atroph*)
8 (macul* NEAR2 (lutea* or syndrome))
9 (wAMD or GAMD or ARMD or wARMD)
10 ("retina* pigment* epithelium*" or "disciform* scar")
11 ("charles bonnet")
12 (degener* NEAR2 (macula* or retina* or sub-retina* or choroid* or wet or dry))
13 ((neovascula* or neo-vascula* or exudative or nonexudative or non-exudative or vasculo* or proliferat* or telangiect*) NEAR2 (macula* or retina* or sub-retina* or choroid*))
14 (atroph* NEAR2 (macul* or geographic*)
15 ((lutea* or syndrome) NEAR2 macul*)
16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17 * FROM 2019 TO 2023
18 * WHERE LPD FROM 01/01/2019 TO 12/10/2023
19 #17 OR #18
20 #16 AND #19

A. 5.: Source: NHS Evidence - Guidelines
Interface / URL: https://www.evidence.nhs.uk/. The evidence search service is now closed. Bibliographic databases now to be accessed from the providers' websites. For example:

- Medline
- Embase

Database coverage dates: N/A
Search date: N/A
Retrieved records: N/A
Search strategy: N/A

A. 6.: Source: ERCI
Interface / URL: https://guidelines.ecri.org/
Database coverage dates:
Search date: 12/10/2023
Retrieved records: 1
Search strategy:

The following search terms were searched individually and the results were screened by the IS.

- Macular
- Choroidal

- Retinal drusen
- Retinal
- Geographic atrophy
- Maculopathy
- AMD
- Lutea

Appendix B Review of Clinical Trials on anti-VEGF in wet AMD

This summary is based on NICE, Age-related macular degeneration NICE guideline [NG82] (2018) and added newer evidence since NG82.

Ranibizumab

Ranibizumab (Lucentis, Novartis, Basel) is a humanised monoclonal antibody fragment against all isomers of VEGF-A formulated for intravitreal injections.

It received its marketing authorisation for nAMD from the European Medicines Agency on 22nd January 2007[1]. It is available as single use pre-filled syringes or vials and the dose delivered intravitreally is 0.5mg/0.05ml.

Current posology for ranibizumab for nAMD is that it is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. Initially, three or more consecutive, monthly injections may be needed [2]. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters. If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, ranibizumab should be discontinued. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g., OCT or FFA). If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity and/or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for nAMD, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened accordingly.

Landmark trials on Ranibizumab

The pivotal trials for ranibizumab were the ANCHOR and MARINA studies [3,4] . The MARINA trial on ranibizumab randomised 716 patients with subfoveal occult choroidal naeovascularisation due tAMD 1:1:1 to ranibizumab 0.3 mg or 0.5 mg or sham injections monthly. At 1-year, mean VA scores increased by 6.5 and 7.2 letters in the 2 ranibizumab groups, respectively, and decreased by 10.4 letters in the sham group with improved anatomical outcomes also observed in the ranibizumab arms. The ANCHOR trial enrolled 423 patients with treatment naïve sub foveal predominantly classic choroidal neovascularisation due to neovascular AMD and randomised to verteporfin photodynamic therapy (PDT) or antiangiogenic drugs. Patients were randomized 1:1:1 to monthly verteporfin PDT, 0.3 mg ranibizumab, or 0.5 mg ranibizumab arms. At 2 years, there was significant VA benefit in the

ranibizumab arms compared to PDT. Ranibizumab biosimilars are now available and has largely replaced ranibizumab in the management of nAMD.

Aflibercept

Aflibercept (Eylea, Bayer, Germany) is a recombinant fusion protein that inhibits VEGF-A, VEGF-B and PIGF and is formulated for intravitreal use.
It received its marketing authorisation for neovascular AMD from the European Medicines Agency on 21st November 2012[5]. It is available as single use pre-filled syringes or vials and the dose delivered intravitreally is 2 mg/0.05ml.

The current posology for aflibercept treatment is that it is initiated with one injection per month for three consecutive doses. The treatment interval is then extended to two months [6].

Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at two months or further extended using a treat-and-extend dosing regimen, where injection intervals are increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

There is no requirement for monitoring between injections. Based on the physician's judgement the schedule of monitoring visits may be more frequent than the injection visits.

Treatment intervals greater than four months or shorter than 4 weeks between injections have not been studied.

Landmark Trials on Aflibercept

The licensing Phase 3 clinical trials for aflibercept 2mg were the VIEW1 and 2 non-inferiority randomised controlled trials run in parallel that compared the outcomes of aflibercept and ranibizumab [7]. A total of 2419 patients in both trials were randomised to 4 weekly ranibizumab or 4 weekly 0.5mg aflibercept or 4 weekly 2 mg aflibercept or 8 weekly aflibercept after 3 loading doses of the respective interventions. Compared to ranibizumab, aflibercept arms were statistically noninferior and clinically equivalent for the primary endpoint of loss of less than 15 letters at 96 weeks [8].

PULSAR (NCT04423718) is a double-masked, active-controlled pivotal trial evaluating non-inferiority of aflibercept 8 mg 12-week (n=335) and 16-week (n=338) dosing regimens compared to an 8-week dosing regimen for aflibercept 2 mg Injection (n=336). All patients received three initial monthly doses. 83% of all aflibercept 8 mg patients were on a ≥12-week dosing interval at 48 weeks and 77% of aflibercept 8 mg patients maintained 16-week dosing intervals. Visual gains and safety of aflibercept 8 mg remained consistent with the established profile of EYLEA® (aflibercept) 2 mg Injection.

Brolucizumab

Brolucizumab (Beovu, Novartis, Basel) is a humanized single-chain antibody fragment that inhibits all VEGF-A isoforms. It is a small molecule (26 kDa) with potent inhibition of, and

high affinity to, all VEGF-A isoforms. It received its marketing authorisation for neovascular AMD from the European Medicines Agency on 13th February 2020[9]. The NICE Technology Appraisal of this agent was published on 3rd February 2021. It is available as pre-filled syringes and the dose delivered intravitreally is 6 mg/0.05ml.

The current posology is that this drug is administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters [10]. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered. The physician may further individualise treatment intervals based on disease activity. If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, Beovu should be discontinued.

Landmark Trials on Brolucizumab

The HAWK and HARRIER phase 3 multicentre non-inferiority studies compared brolucizumab with aflibercept on 1817 patients with neovascular AMD [11]. After 3 loading injections, the eyes treated with brolucizumab were injected every 12 weeks, but this interval could be adjusted to 8 weeks if disease activity was present. Aflibercept group received 8 weekly fixed dosing after the loading phase. The noninferiority margin in mean best-corrected visual acuity change from baseline to Week 48 was 4 letters. Non-inferiority of best corrected visual acuity outcomes was achieved at 48 weeks with better anatomic macular fluid outcomes in the brolucizumab arm. Approximately 50% of patients were maintained on 12 weekly dosing. Most adverse events were similar between arms. However, although the numbers were small, there were higher incidences of intraocular inflammatory events in the brolucizumab arm, mainly in the HAWK study. Since the launch of brolucizumab, post marketing safety surveillance has revealed sight threatening adverse drug reactions associated brolucizumab treatment - retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation. It is important that clinicians should be aware of this potential adverse event, and potential patients consented appropriately

Bevacizumab

Bevacizumab (Avastin, Roche) is a full-length monoclonal antibody against all isomers of VEGF-A and is approved for use in systemic cancers but is used off-label for nAMD.
The drug is formulated for intravenous use. The Summary of Product Characteristics (SPC) for Bevacizumab states “Avastin is not formulated for intravitreal use” [12].
Landmark Trials on Bevacizumab

The CATT trial was a non-inferiority US trial that compared outcomes of ranibizumab and bevacizumab administered monthly or as needed (pro re nata [PRN]) on 1,208 patients with neovascular AMD [13]. Based on noninferiority margin of 5 letters, the change in visual acuity outcomes were statistically equivalent for ranibizumab and bevacizumab when given monthly or when given as needed. However, monthly monitoring is required to achieve these outcomes.

The IVAN trial was a multicentre, factorial randomised controlled trial conducted in the UK NHS that evaluated the non-inferiority of ranibizumab versus bevacizumab and continuous versus discontinuous regimens with these agents [14]. A total of 610 participants were

allocated and treated (314 ranibizumab, 296 bevacizumab; at 3 months, 305 continuous, 300 discontinuous). After 2 years, bevacizumab was neither non-inferior nor inferior to ranibizumab [-1.37 letters, 95% confidence interval (CI) -3.75 to +1.01 letters] and discontinuous treatment was neither non-inferior nor inferior to continuous treatment (-1.63 letters, 95% CI -4.01 to +0.75 letters) based on a non-inferiority margin of 3.5 letters. Discontinuing treatment and restarting when required resulted in slightly worse efficacy. Safety was worse with discontinuous treatment, although new GA developed more often with continuous treatment.

The LUCAS study is a multicentre non-inferiority randomised controlled trial that compared bevacizumab and ranibizumab on a treat and extend protocol on 441 participants with neovascular AMD with a noninferiority limit of 5 letters [15]. Monthly injections were given until inactive disease was achieved. The patients were then followed with a gradual extension of treatment interval by 2 weeks at a time up to a maximum of 12 weeks. If signs of recurrent disease appeared, the treatment interval was shortened by 2 weeks at a time. Bevacizumab was equivalent to ranibizumab in terms of best corrected visual acuity at 1 year. However, a higher number of injections and follow-up visits were required with bevacizumab.

Faricimab

TENAYA and LUCERNE were randomised, double-masked, non-inferiority trials (TENAYA NCT03823287 and LUCERNE NCT03823300). Treatment-naive patients with nAMD aged 50 years or older were randomly assigned (1:1) to intravitreal faricimab 6·0 mg up to every 16 weeks, based on protocol-defined disease activity assessments at weeks 20 and 24, or aflibercept 2·0 mg every 8 weeks. The primary endpoint was mean change in best-corrected visual acuity (BCVA) from baseline averaged over weeks 40, 44, and 48 (prespecified non-inferiority margin of four letters), in the intention-to-treat population. Across the two trials, 1329 patients were randomly assigned between TENAYA n=334 faricimab and n=337 aflibercept, and LUCERNE n=331 faricimab and n=327 aflibercept. BCVA change from baseline with faricimab was non-inferior to aflibercept in both TENAYA (adjusted mean change 5·8 letters [95% CI 4·6 to 7·1] and 5·1 letters [3·9 to 6·4]; treatment difference 0·7 letters [-1·1 to 2·5]) and LUCERNE (6·6 letters [5·3 to 7·8] and 6·6 letters [5·3 to 7·8]; treatment difference 0·0 letters [-1·7 to 1·8]). Rates of ocular adverse events were comparable between faricimab and aflibercept (TENAYA n=121 [36·3%] vs n=128 [38·1%], and LUCERNE n=133 [40·2%] vs n=118 [36·2%]).

The current posology is as follows:
The recommended dose for Vabysmo is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks for the first 4 doses.

Thereafter, treatment may be individualised using a treat-and-extend approach following an assessment of the individual patient's anatomic and visual outcomes. The dosing interval may be extended up to every 16 weeks, and extensions in increments of up to 4 weeks should be considered, based on the physician's judgement of the individual patient's anatomic and/or visual outcomes. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reductions of up to 8 weeks may be implemented if deemed necessary. Treatment intervals shorter than 21 days between injections have not been studied.

Table: Clinical Trials on anti-VEGF in wet age-related macular degeneration

Study	Drug	Sample size	Mean change in VA at 12 months	Estimated no. of visits by 12 months	No. of injections by 12 months	Mean change in VA at 24 months	Estimated no. of visits by 24 months	No. of injections by 24 months
Fixed Dosing Regimen (4-weekly unless otherwise noted)								
ANCHOR[3,16]	Ranibizumab	140	11.3	12	11.2	10.7	24	21.3
BRAMD[17]	Bevacizumab	161	5.1	12	12	N/A	N/A	N/A
BRAMD[17]	Ranibizumab	166	6.4	12	12	N/A	N/A	N/A
CANTREAT[18,19]	Ranibizumab	258	6.0	12	11.8	6.0	24	23.5
CATT[13,20]	Bevacizumab	286	8.0	12	11.9	7.8	24	23.4
CATT[13,20]	Ranibizumab	301	8.5	12	11.7	8.8	24	22.9
GEFAL[21]	Bevacizumab	191	4.82	12	6.8	N/A	N/A	N/A
GEFAL[21]	Ranibizumab	183	2.93	12	6.5	N/A	N/A	N/A
HARBOR[22,23]	Ranibizumab	275	10.1	12	11.3	9.1	24	21.4
IVAN[14,24]	Bevacizumab	149	4.66	12	12	4.1	24	23
IVAN[14,24]	Ranibizumab	157	6.32	12	12	4.9	24	23
MARINA[4]	Ranibizumab	240	7.2	12	12	4.9	24	23
TREX AMD[25,26]	Ranibizumab	8.020	9.2	12	13	10.5	24	25.5
TREND[27]	Ranibizumab	327	8.1	12	11.1	N/A	N/A	N/A
VIEW[7,8]	Aflibercept 2mg	304	9.3	12	12	7.6	24	16.0
VIEW[7,8]	Ranibizumab	303	8.7	12	12	7.9	24	16.5

Study	Drug	Patient Nos.	Mean change in VA at 12 months	Estimated no. of visits by 12 months	No. of injections by 12 months	Mean change in VA at 24 months	Estimated no. of visits by 24 months	No. of injections by 24 months
HAWK[11, 28]	Aflibercept 2mg (8 weekly)	369	6.8	8	6.8	5.3	13	12.3*
HAWK[11, 28]	Brolucizumab (8-12 weekly)	360	6.6	NK	6.2	5.9	NK	10.8*
HARRIER[11.28]	Aflibercept 2mg (8 weekly)	369	7.6	8	6.9	6.6	13	12.6*
HARRIER[11.28]	Brolucizumab (8-12 weekly)	370	6.9	NK	6.4	6.1	NK	11.3*
VIEW[7,8]	Aflibercept 2mg (8 weekly)	306	8.4	8	7.5	7.6	20	11.2
TENAYA/LUCERNE[29]	Aflibercept (8 weekly)	664	5.9	8	9.0	4.3	13	15**
PULSAR[30]	Aflibercept 2mg (8 weekly)	336	7.0	NK	6.9	6.6	NK	12.8
PULSAR[30]	Alibercept 8mg (12 weekly)	335	6.1	NK	6.1	5.6	NK	9.7
PULSAR[30]	Aflibercept 8mg (16 weekly)	338	5.9	NK	5.2	5.5	NK	8.2
*Mean number of active injections weighted by number of days on the study **Pooled data from TENAYA and LUCERNE								
Pro-re-nata Dosing Regimen								

CATT[13,20]	Bevacizumab	300	5.9	12	7.7	5.0	24	14.1
CATT[13,20]	Ranibizumab	298	6.8	12	6.9	6.7	24	12.6
HARBOR[22,23]	Ranibizumab	275	8.2	12	7.7	7.9	24	13.3
IVAN[14,24]	Bevacizumab	145	5.1	12	NK	3.5**	24	13
IVAN[14,24]	Ranibizumab	155	5.1	12	7	3.5**	24	13
MANTA [31]	Ranibizumab	163	4.1	12	8.8	N/A	N/A	N/A
MANTA [31]	Bevacizumab	154	4.9	12	9.1	N/A	N/A	N/A
**Pooled discontinuous data from IVAN								
Study	Drug	Sample size	Mean change in VA at 12 months	Estimated no. of visits by 12 months	No. of injections by 12 months	Mean change in VA at 24 months	Estimated no. of visits by 24 months	No. of injections by 24 months
Treat & Extend Dosing Regimen								
CATT[13,20]	Bevacizumab	300	5..9	12	7.7	5.0	24	14.1
HARBOR[22,23]	Ranibizumab	298	6.8	12	6.9	6.7	24	12.6
HARBOR[22,23]	Ranibizumab	275	8.2	12	7.7	7.9	24	13.3
IVAN[14,24]	Bevacizumab	145	5.1	12	NK	3.5**	24	13
IVAN[14,24]	Ranibizumab	155	5.1	12	7	3.5**	24	13
MANTA [31]	Ranibizumab	163	4.1	12	8.8	N/A	N/A	N/A
MANTA [31]	Bevacizumab	154	4.9	12	9.1	N/A	N/A	N/A
**Pooled discontinuous data from IVAN								
Treat & Extend Dosing Regimen								
ALTAIR[32]	Aflibercept 2mg 2w extension	123	9	NK	7.2	7.6	NK	10.4
ALTAIR[32]	Aflibercept 2mg 4w extension	123	8.4	NK	6.9	6.1	NK	10.4

ARIES[33]	Aflibercept 2mg (late T&E)	136	10.2	NK	7.1	7.9	NK	12
ARIES[33]	Aflibercept 2mg (early T&E)	135	7.8	NK	8.0	4.3	NK	13
ATLAS[34]	Aflibercept 2mg	27	7.2	NK	8.0	2.4	NK	14.5
CANTREAT[18,19]	Ranibizumab	268	8.4	NK	9.4	6.8	NK	17.6
LUCAS[15,35]	Bevacizumab	213	7.9	8.9	8.9	7.4	18	18.2
LUCAS[15,35]	Ranibizumab	218	8.2	8.0	8.0	6.6	16	16
TREX AMD[25,26]	Ranibizumab	40	10.5	NK	10.1	8.7	NK	18.6
TREND[27]	Ranibizumab	323	6.2	NK	8.7	N/A	N/A	N/A
TENAYA/LUCERNE[29]	Faricimab	665	6.2	NK	7.0	4.4	NK	10*
*Pooled data from TENAYA and LUCERNE								

Biosimilars

Study	Drug	Patient No.	Dose	Mean change in VA at 8 weeks	Mean change in VA at 24 weeks	Adjusted treatment difference between groups (letters)
NCT03150589	SB11 (Byooviz)[36]	351	Monthly fixed	6.2	8.6	-0.8 [90% CI, -1.8 to 0.2] at8 weeks
NCT03150589	Ranibizumab[36]	353	Monthly fixed	7.0	NK	-0.8 [90% CI, -2.0 to 0.5] at24 weeks
COLUMBUS-AMD	FYB201 (Ongavia)[37]	238	Monthly fixed	5.1	+6.9	-0.4 [90% CI -1.6 to 0.9] at 8 weeks
COLUMBUS-AMD	Ranibizumab[37]	239	Monthly fixed	5.6	+7.1	-0.0 [90% CI, -1.6 to 1.5] at 24 weeks

Verteporfin photodynamic therapy (vPDT)

Landmark Trials on Photodynamic Therapy

The Treatment of age-related macular degeneration with photodynamic therapy (TAP) study showed that vPDT is effective in stabilising visual acuity in eyes with sub foveal predominantly classic choroidal neovascularisation compared to placebo [38]. However, the ANCHOR study showed that ranibizumab was superior to vPDT and resulted in gain in VA compared to vPDT eyes that showed a mean loss of VA.
The EVEREST II trial is a 24-month multicentre study of 322 Asian participants that compared the monotherapy of ranibizumab with combination therapy of ranibizumab and vPDT [39]. Photodynamic therapy was performed at baseline along with 3 monthly ranibizumab injections followed by treatment on a PRN basis. The combination arm showed a mean gain of 8.3±1.0 ETDRS letters compared to the monotherapy arm that showed a mean gain of 5.1±1.1 ETDRS letters at the end of 12 months. Median number of ranibizumab injections required in the combination group was 6 compared to 12 in the monotherapy. The median PDT treatments was 2 in the combination arm.

In the PLANET study, on the other hand, a loading phase of aflibercept followed by a treat and extend regimen was compared to a combination therapy of aflibercept and deferred vPDT after 3 months in participants recruited from Asia-Pacific and Europe [40]. The VA gain with aflibercept monotherapy was 10.7±11.3 ETDRS letters compared to a mean of 10.8±10.7 letters in the combination arm.

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